CARL WEINER
CATALIN BUHIMSHI

Drugs for Pregnant and Lactating Women

Second Edition

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Notice

Knowledge and best practice in this field are constantly changing. As new research and experience broaden our knowledge, changes in practice, treatment and drug therapy may become necessary or appropriate. Readers are advised to check the most current information provided (i) on procedures featured or (ii) by the manufacturer of each product to be administered, to verify the recommended dose or formula, the method and duration of administration, and contraindications. It is the responsibility of the practitioner, relying on their own experience and knowledge of the patient, to make diagnoses, to determine dosages and the best treatment for each individual patient, and to take all appropriate safety precautions. To the fullest extent of the law, neither the Publisher nor the Editors assumes any liability for any injury and/or damage to persons or property arising out of or related to any use of the material contained in this book.

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Preface

Thousands of pregnant and breast-feeding women take a prescription or over-the-counter drug each day. Though for the most part safe, a small percentage of these actions will have unintended adverse consequences for either mother or child. An additional percentage proves ineffective, due in part to the unique physiology of pregnancy or breastfeeding. And while an unnecessary drug should never be given to the pregnant or breast-feeding woman, an important therapy should never be withheld because of her status. Health care givers are now accustomed to routinely checking the FDA classification of a drug before prescribing it. Unfortunately, this classification system, though simple in concept, is dated, rarely revised as new information becomes available, and too simplistic to account for the physiology and health care needs of pregnant and breast-feeding women. Few drugs are approved by the FDA for use during pregnancy, and even oxytocin is a Category X agent. The important information provided by the manufacturer is often couched in protective legalese and never focuses on the needs of the obstetrical health care provider. Prior attempts to provide the caregiver the needed information have proven dense and filled with descriptions of studies, but not their implications. As a result, they are used in practice as a source of the FDA pregnancy category.

So much has changed since the publication of the first edition. I would like to thank the many healthcare providers who provided valuable feedback now incorporated into the second edition. In addition to the several hundred new drugs added since the first publication, I have attempted to further enhance the value of the text by adding **International Names** and relevant **Drug Interactions**. The text continues its user-friendly format available in both electronic and hardcopy media.

The purpose of this text remains to provide a user-friendly, pregnancy-lactation-focused reference for the use of the concerned health care provider. Do not use this as a reference when prescribing for a man. And though we recommend consulting a more complete reference before prescribing an unfamiliar agent, the information provided will aid the safe prescribing of drugs familiar to the physician. The number of new drugs released over the last decade is great, and their known impact on pregnancy and lactation, and vice versa often limited to absent. This is indeed a living text, coupled to a convenient, user-friendly hand-held electronic version that will be updated and expanded on a regular basis. Conflicts in FDA class with existing knowledge are pointed out, and recommendations made wherever possible based on medical evidence. Over the next few years, the FDA has embarked on a new and more detailed classification of drug safety during pregnancy. It is my intent to include this information wherever possible into the updates provided free to the electronic version.

We encourage readers to contact us at Technical.support@elsevier.com with any requests, errors, or conflicts.

Carl P. Weiner
January 25, 2009

Foreword to the First Edition

The study of medication use in pregnancy is one of the least developed and most neglected areas of clinical pharmacology and drug research. Although pregnancy is widely regarded as a special population due to both the unique maternal physiology and the vulnerability of the developing fetus, researchers and pharmaceutical companies have been reticent to evaluate optimal modalities of treatment for this group. The issue is compounded by the enormous number of medications women are exposed to during pregnancy. Epidemiological surveys indicate nearly two thirds of all pregnant women use four to five drugs during pregnancy through delivery. Women with medical conditions such as epilepsy, diabetes, and hypertension must continue therapy while pregnant. In some cases, due to a justified or unjustified concern for the developing fetus, the medication prescribed is either withheld, inadequate to treat the maternal condition, or not monitored closely enough as pregnancy progresses for needed adjustments in dosing. The result is a double negative, that of fetal exposure without maternal or fetal benefit. The lack of Food and Drug Administration obstetric labeling and the near universal off-label use of drugs are the direct result of the paucity of research and clinical trials in this special population. The public concern stems from the use of drugs in pregnancy based on an empiric approach rather than a scientific basis, and does not take into account the many alterations in pregnancy.

There are profound physiologic changes in pregnancy involving the mother, placenta and fetus that may alter absorption, distribution and elimination of drugs. For example, there is a decrease in gastric emptying and an increase in intestinal transit time, both of which may alter gastrointestinal absorption of drugs. Similarly, the physiologic increase in pulmonary blood flow, hyperventilation, or increased tidal volume during pregnancy may increase the absorption of inhalants. The dramatic increase in blood volume with subsequent dilutional hypoalbuminemia, especially in the third trimester, can be associated with a decreased drug binding capacity and may profoundly affect the distribution of many drugs during pregnancy. These are but a few of the many examples of the complex changes in pregnancy that affect the type, dosing, and effectiveness of medications in this special population

Daily advances in therapeutics dramatically increase the number and types of medications available more rapidly than textbooks can be updated. This new text by Weiner and Buhimschi, Drugs for Pregnant and Lactating Women, helps fill the void. It is a comprehensive resource addressing the unique needs of this special population. Each drug entry includes the generic and trade names, drug class, indication(s) (on and off label), mechanism(s) of action, dosage, maternal and fetal considerations, breastfeeding safety, references, FDA pregnancy and lactation categories, and a summary. Wherever possible, evidence-based recommendations are made. This unique reference combines the printed word with an electronic version updated quarterly to allow for the incorporation of the new therapeutics. This design is user friendly for the busy clinician and includes prescribing information as well as a review of the published experience with the drug in pregnancy and lactation. As the first of its type, Drugs for Pregnant and Lactating Women will simplify the clinician's ability to maintain updated information on medications in pregnancy and facilitate the incorporation of more rigorous study into the use of medications in the pregnant and lactating populations.

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Foreword to the Second Edition

This is a dream come true for all of those who care for pregnant and non-pregnant women. There is nothing like this in medical literature. In the past, I have been involved in the publications of several texts on drugs and pregnancy. This new text is on the leading edge of science and knowledge for women and drugs, with more than 720 generic drugs with their 1500 trade names listed in alphabetical order to make identification easy for each drug. Over-the-counter drugs are also included. The information provided in both hard text and electronic versions is very extensive, concise, and user friendly. Its availability as an electronic version for hand-held computer devices, that will be updated for the life of the edition, is particularly exciting. This will not only benefit all health care workers in the field of obstetrics and gynecology, but will also allow instantaneous access to drug related questions.

Included in text and electronic versions are the following headings:

Name
Class
Indications
Dosage with Qualifiers
Maternal Considerations
Fetal Considerations
Breastfeeding Safety
References
Summary

Additionally, there are lists of known teratogens, pregnancy drug registries, AHA endocarditis guidelines, FDA category definitions, and the percent of drugs assigned to them also included.

Thanks go to Dr. Weiner for his ingenuity in taking a complicated problem and making it straightforward and simple for those who care for pregnant and non-pregnant women.

This effort is the first to simultaneously embrace text and an electronic version for hand-held computers. The combination of Elsevier–the world's largest health sciences publisher–and Dr. Weiner–an individual who has a long-term interest in female reproduction and especially high-risk obstetrics–assures success of the project.

This is the new frontier in medical publishing and we will look forward to additions and revisions in the electronic format.

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Acknowledgment

The second edition turned into a predominantly solo journey. I want to recognize and thank Carol, who spent many evenings and weekends alone while I worked on the text. Your support is central. Thank you. I also want to acknowledge the important contributions of my good friend Dr. Catalin Buhimschi.

Carl P. Weiner

Introduction

Frustrated by the absence of a comprehensive resource that recognizes the uniqueness of medical needs during pregnancy and lactation, we created Drugs for Pregnant and Lactating Women as an easy-to-use, reader friendly resource containing the key information required by caregivers to make prescribing decisions. Too often, we check only the FDA Pregnancy Category before making a decision to prescribe or discontinue a medication. Unfortunately, few of us have read these definitions (TABLE 1), understand their limitations, and realize the assigned category is essentially stagnant, based predominantly on information available when the drug was approved in the United States, and only occasionally officially updated to reflect advancing knowledge. Two-thirds of all drugs sold in the United States are classified Category C, and less than 1% Category A. With the benefit of added experience, we learn that many Category X drugs are not absolutely contraindicated during pregnancy, and several Category C or D drugs are either clear human teratogens or have frequent and serious adverse fetal effects. These facts are highlighted by a study comparing the categorization of same drugs by the appropriate agencies in the United States, Australia, and Sweden (Addis A, Sharabi S, Bonati M. Drug Saf 2000; 23:245-53). Only 25% of the 236 drugs common to all 3 systems were placed into the same risk factor category. Nor does the categorization inform the provider how either pregnancy or lactation may alter the patient's response to therapy compared to the nonpregnant state. The FDA is well aware of these limitations and is actively considering revision. Lastly, increasingly busy health care providers are often dependent on either the advertisements in trade journals or the pharmaceutical house detail people for up-to-date information on new drugs. Yet, a recent study observed that promotional claims are frequently misleading and the cited studies were either unretrievable or failed to back-up the particular claim (Villanueva P, Peiro S, Libero J, Pereiro I. Lancet 2003; 361:27-32). This is not a new problem (Wilkes MS, Doblin B, Shapiro M. Ann Intern Med 1992; 116:912-19).

This text seeks to reduce the aforenoted limitations by using brief descriptions to summarize the current level of knowledge. New for the second edition, the information on each drug is divided into 12 sections. Those who purchase the electronic version can search by subgroups or names in each of these sections.

The first section of the text lists the generic Name followed by trade names used in the United States. Some drugs have a half dozen or more trade names, and are difficult to remember if you do not use them regularly.

New for the second edition, the second section lists the common International Trade Names. It is our intent for this to be an international resource for obstetric caregivers.

The third section is the drug Class, such as antibiotic (type), nonsteroidal anti-inflammatory (NSAID), anticonvulsant, antihypertensive, etc. This makes it easier to sort drugs in search of alternative or complementary agents when necessary.

The fourth section lists the Indications for the drug. In most, though not all instances, this list is confined to FDA approved indications. Popular off-label uses are typically reviewed in a subsequent section.

The fifth section is the known or presumed Mechanism of Action. This is frequently either unknown, or while several activities of the drug are known, it is unclear whether they are responsible for the disease-directed action of the drug. Knowledge of the mechanism of action is important for the selection of complementary drugs and the prediction of adverse effects.

The sixth section contains the Dose by specific indication. Also included in this section are most relevant Contraindications and Cautions. This information is mostly derived from manufacturer-provided material, but tailored for women. You will not find erectile dysfunction or benign prostatic hypertrophy as either an indication or a

contraindication for a particular drug, though they certainly might be listed in a general drug text. Also frequently removed from the list are typical corporate liability comments on pregnancy that are not substantiated by either animal or human experience. The dose advice provided has been checked multiple times by at least 3 individuals. However, the very design of this text assumes the prescriber has previously familiarized him- or herself with the contents of the package insert. The details provided under Dose are a suitable refresher, but not a substitute. We strongly recommend you confirm the dose when using an unfamiliar drug. Further, we have adopted the approach of simply noting when a dose modification must be considered, rather than trying to be all things for all situations. The standard 'NOTE' mentions the need for either renal or hepatic dosing. This means that, in the face of compromised renal or hepatic function, the physician must take into account altered clearance of the drug. The formulas are usually contained in the package insert or may be discussed with the dispensing pharmacist.

The seventh and eighth sections form the unique core of the text. In the seventh, titled Maternal Considerations, we review how the drug impacts pregnancy and vice versa. We summarize the published experience during pregnancy, highlighting any known problems. Off-label uses are detailed, as is the evidence for efficacy if it exists. We also note applications that have proved unsuccessful. The sad reality is that many drugs used during pregnancy are either ineffective or poorly effective for their most common uses—the tocolytic agents being prime examples. Specific evidence-based recommendations are made wherever possible. It is in this section we also detail the known drug Side Effects, again focusing on mother and child. Priapism and impotence may be important side effects in some populations, but not in the one our envisioned reader provides care.

The eighth section is titled Fetal Considerations. Here, the impact of the drug on the human fetus is reviewed, information on placental transfer presented (e.g., the fetal umbilical vein: maternal vein ratio), and any adverse effects summarized. The possible applications of a drug for fetal therapy and an appraisal of its efficacy will also be found here. Animal data are presented when human experience is missing. Rodent teratogenicity studies are summarized, where available, recognizing there are well-known human teratogens, which were not teratogens in rodents (e.g. thalidomide). Of potential relevance is the dose at which the adverse effects are seen in rodents (in terms of multiples of the maximum recommended human dose), and the presence or absence of maternal toxicity that may be the proximate cause of the noted effect. Much of this information is published in peer-reviewed articles, but in some instances, the only source of this information is the manufacturer. It is frightening to us, as practitioners, to find how little is known about many commonly used drugs during pregnancy and lactation. It is our hope readers will be encouraged when confronted with the facts to try and fill in the missing information with quality studies. It is of at least equal concern the number of drugs withheld from women during pregnancy or lactation because of unsubstantiated or, at times, past but refuted theories.

New for the second edition, the ninth section is entitled Drug Interactions. Here, the more common or dangerous drug:drug interactions are noted. This is an ever growing risk in this era of polypharmacy.

The tenth section is Breastfeeding. We note whether the drug enters human breast milk, and the kinetics of its excretion, if known. The ideal information includes the weight-corrected percent of the maternal dose ingested by the unsupplemented 3kg-newborn and the resulting neonatal blood levels. The number of times the ideal is achieved can be counted on the hands of a single individual. When this information is not known, a milk:plasma (M:P) ratio or concentration is given. This information provides limited information, and may indeed mislead the reader. When no human data are available, animal (typically rodent) is proffered, wherever available. Some of this information is published in peer-reviewed articles, and some by the manufacturer. Occasional conflicts are noted, and wherever possible, specific evidence-based recommendations made. For example, many drugs are used for a limited period or even one-time use. When the patient wishes to continue breastfeeding, but there is reasonable doubt of safety, we will recommend the patient pump her breasts for a period of time before resuming breastfeeding. In other instances, the drug may be safe, but the mother not, for example, the woman with HIV.

Section eleven contains salient References. Most are directed at source material, but some are reviews. This information is rarely in packaged inserts (which comprise, for example, the PHYSICIANS DESK REFERENCE) and, cover maternal, fetal, and lactational issues.

The final section, section twelve, is entitled Summary. In this section, the reader will find the FDA category as published in the package insert and a code assigned by the editors for breast-feeding safety (S, safe; NS, not safe; and U, unknown). Often there is some but not enough information for a particular conclusion. In these situations, we have placed a question mark next to the selected code (e.g., S?).

The final comments always reflect the need to balance risk. This is a patient-specific process and not given to absolutes. In many instances, the reader is informed there are other alternatives for which there are more experience in pregnancy and lactation. We strongly suggest that wherever possible, the reader seek and use those agents. Pregnancy is not the occasion to be a pioneer, if unnecessary. If there is a post-marketing registry, the telephone number is listed in the Appendix. These registries have the potential to identify important but unusual outcomes.

This text has always been designed as a living resource. New print editions will be frequent, and those readers with the electronic version will receive periodic updates when they re-synchronize their hand-held computers. There are already several hundred new drugs in the second compared to the first edition, and all have been subject in the second edition to a literature search. Also new is a growing number of popular herbal remedies with which the obstetrical caregiver will be confronted during the normal course of practice. Readers are encouraged to contact the editors with comments, concerns, and criticisms.

Acarbose—(Precose)

International Brand Names—Glibose (Taiwan); Glicobase (Italy); Glucobay (Argentina, Austria, Bangladesh, Belgium, Brazil, Bulgaria, Chile, Colombia, Costa Rica, Czech Republic, Denmark, Dominican Republic, Ecuador, El Salvador, England, Germany, Greece, Guatemala, Honduras, Hungary, India, Israel, Italy, Japan, Korea, Malaysia, Mexico, Netherlands, Nicaragua, Norway, Pakistan, Panama, Peru, Poland, Portugal, Spain, Sweden, Switzerland); Gluconase (Philippines); Glumida (Spain); Prandase (Canada, Israel); Rebose (India)

Drug Class	α-Glucosidase inhibitor; Antidiabetic agents; Oral hypoglycemics
Indications	Diabetes mellitus, type II
Mechanism	An oral pancreatic α-amylase and intestinal α-glucoside hydrolase inhibitor that delays bowel carbohydrate metabolism, slowing the postprandial rise in glucose
Dosage with Qualifiers	Diabetes mellitus, type II—begin 25mg (50mg if >60kg); thereafter, 50-100mg PO ac tid based on glucose levels • **Contraindications**—hypersensitivity to drug or class, DKA, cirrhosis, intestinal obstruction or malabsorption syndromes • **Caution**—renal dysfunction
Maternal Considerations	**Acarbose** is the subject of a large ongoing trial to determine whether its use can reduce or delay the onset of type II diabetes in patients with impaired glucose intolerance. The preliminary results indicate benefit. There are no adequate reports or well-controlled studies of **acarbose** in pregnant women. There is a single report of 6 pregnant women with impaired glucose tolerance treated with **acarbose**. Glucose levels returned to normal, and the pregnancies were reportedly uncomplicated. ***Side effects*** include intestinal discomfort consisting of pain, diarrhea, flatulence, elevated LFTs, and jaundice.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. Only 2% of the oral dose is absorbed. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses almost 10× higher than those used clinically.
Breastfeeding Safety	There is no published experience in nursing women. It is unknown whether **acarbose** enters human breast milk. A single rat study suggests **acarbose** might alter the composition of breast milk by inhibiting lipogenesis. Less than 2% of **acarbose** is bioavailable. It is unlikely any would be excreted into the milk and or absorbed by the neonate.
Drug Interactions	Some drugs tend to produce hyperglycemia. They include thiazides and similar class diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, **phenytoin**, **nicotinic acid,** sympathomimetics, calcium channel–blocking drugs, and **isoniazid**. Women taking both **acarbose** and one of these drugs should be monitored closely for loss of glucose control. Discontinuation of such drugs may lead to hypoglycemia. Intestinal adsorbents (e.g., charcoal) and digestive enzyme such as **amylase** and **pancreatin** may reduce the effect of **acarbose** and should not be taken together. **Acarbose** may alter **digoxin** bioavailability when they are co-administered.

■ **References** ····· Hanefeld M, Schaper F, Koehler C. Cardiovasc Drugs Ther 2008; 22:225-31.
Mercer SW, Williamson DH. Biochem J 1987; 242:235-43.
Product information. Precose, Bayer Corp., 1997.
Zarate A, Ochoa R, Hernandez M, Basurto L. Ginecol Obstet Mex 2000; 68:42-5.

■ **Summary** ·····

Pregnancy Category: B
Lactation Category: S (likely)

- Insulin and diet regulation remain the standard treatments for glucose intolerance during pregnancy.
- There is a growing interest in the use of oral hypoglycemic agents during pregnancy, and **acarbose** is a candidate for future study in this area.

Acebutolol—(ACB; Alol; Beloc; Diasectral; Espesil; Lupar; Neptal; Rhotral; Sectral; Sectral LP; Wesfalin)

International Brand Name—ACB (New Zealand, Singapore); Acecor (Italy); Diasectral (Denmark, Finland); Espesil (Finland); Flebutol (Venezuela); Grifobutol (Chile); Monitan (Canada); Prent (Germany, Italy, Portugal); Rhotral (Canada); Sectral (Belgium, Bulgaria, Canada, Czech Republic, England, France, Hong Kong, Ireland, Italy, Malaysia, Netherlands, Poland, South Africa, Spain, Switzerland, Taiwan); Sectral LP (France)

■ **Drug Class** ····· Antiarrhythmics, class II; Antiarrhythmics, ventricular; Antihypertensives; β-Blocker

■ **Indications** ····· Chronic hypertension, ventricular arrhythmias

■ **Mechanism** ····· Cardioselective partial β-adrenoceptor antagonist

■ **Dosage with Qualifiers** ····· Hypertension—begin 400-800mg PO qd; max 1200mg/d
Ventricular arrhythmia—begin 200-400mg/d; typical dose, 600-1200mg/d

- **Contraindications**—hypersensitivity, CHF, heart block, hypotension, pulmonary disease
- **Caution**—diabetes mellitus, hepatic or renal dysfunction

■ **Maternal Considerations** ····· There are no adequate reports or well-controlled studies of **acebutolol** in pregnant women. **Acebutolol** was significantly less successful than either **labetalol** or **α-methyldopa** in controlling chronic arterial hypertension >90mmHg in one small randomized trial. The rates of pregnancy complications among the 3 groups of women were similar.
Side effects include CHF, bronchospasm, fatigue, dizziness, headache, constipation, and diarrhea.

■ **Fetal Considerations** ····· There are no adequate reports or well-controlled studies in human fetuses. **Acebutolol** and its main metabolite, ***N*-acetylacebutolol,** cross the placenta with a 0.6:0.8 M:F ratio. A prospective study of **acebutolol's** hemodynamic and renal impact on neonates after chronic *in utero* exposure found hemodynamic failure in 5/11 children delivered of treated mothers. Exposed neonates had significantly less early neonatal diuresis, absence of a significant rise in the GFRs, and reduced sodium and calcium balances. The direct effect of the drug on the glomerular and tubular functions and/or the renal arteriolar vasomotoricity could explain these effects.

Breastfeeding Safety

Acebutolol and ***N*-acetylacebutolol** are concentrated in breast milk (M:P ratios 2:9 for **acebutolol** and 2:25 for ***N*-acetylacebutolol**), though symptoms of neonatal β-blockade are rarely reported. A neonate might receive pharmacologically active amounts of **acebutolol** if the daily maternal dosage exceeds 400mg and/or renal function in the mother is impaired. However, the American Academy of Pediatrics considers **acebutolol** permissible with breastfeeding.

Drug Interactions

Catecholamine-depleting drugs, such as **reserpine,** may have an additive effect when given with β-blockers.
Women treated with both **acebutolol** and catecholamine depletors should be observed closely for bradycardia or hypotension that may present as vertigo, syncope/presyncope, or orthostatic hypotension without compensatory tachycardia.
Women receiving β-blockers should be warned that hypertensive responses may follow the combined use of β-blockers and α-adrenergic agonists, including those in OTC cold remedies and vasoconstrictive nasal drops.
NSAIDs may blunt the antihypertensive effect of β-blockers.

References

Boutroy MJ, Bianchetti G, Dubruc C, et al. Eur J Clin Pharmacol 1986; 30:737-9.
Committee on Drugs, American Academy of Pediatrics. Pediatrics 1994; 93:137-50.
Lardoux H, Blazquez G, Leperlier E, Gerard J. Arch Mal Coeur Vaiss 1988; 81(Spec No):137-40.
Yassen H, Boutroy MJ, Monin P, Vert P. Arch Fr Pediatr 1992; 49:351-5.

Summary

Pregnancy Category: B (1st trimester), **D** (2nd and 3rd trimesters)
Lactation Category: S

- There are alternative agents for which there is more experience during pregnancy and lactation.
- Consider withholding oral **acebutolol** therapy for 12h prior to the anticipated delivery to minimize the risk to the neonate.

Acetaminophen—(APAP; Acephen; Aceta; Acetaminophen Uniserts; Anapark; Apacet; Asidon; Calip; Dapacin; Ed-Apap; Feverall; Genapap; Genebs; Mapap; Maranox; Neopap; Oraphen-PD; Panadol; Redutemp; Ridenol; Silapap; Tapanol; Tempra; Tylenol; Uni-Ace)

International Brand Name—Abenol (Canada); Acamol (Chile, Israel); Acamoli Forte suppositories for Kids (Israel); Acet (Malaysia, Philippines); Acetalgin (Switzerland); Acetam (Peru); Acetamol (Italy); ACET suppositories (Singapore); Adorem (Colombia); Afebrin (Hong Kong, Indonesia, Philippines); Algiafin (Chile); Alphagesic (Indonesia); Alvedon (Sweden); Amol (Israel); A-Mol (Thailand); Anaflon (Germany); Analgiser (Israel); Apirex (France); Arfen (Malaysia, South Africa); Atamel (Peru); Benuron (Japan); Ben-U-Ron (Belgium, Germany, Portugal, Switzerland); Biogesic (Indonesia, Philippines, Thailand); Biogesic Suspension (Hong Kong); Bodrex (Indonesia); Brenal (Philippines); Calapol (Indonesia); Calodol (Philippines); Calpol (India, Ireland, Israel, Japan, Puerto Rico, South Africa, Thailand); Causalon (Argentina); Cemol (Thailand); Christamol (Hong Kong); Claradol (Morocco); Clocephen (Philippines); Crocin (India); Daga (Thailand); Datril (Mexico, Venezuela); Depyretin (Taiwan); Dirox (Argentina); Dismifen (Mexico); Dolex (Uruguay); Dolex 500 (Colombia, Uruguay); Doliprane (France, Morocco); Dolitabs (France); Dolofen (Colombia); Dolomol (Israel); Dolorol (South Africa); Dolotemp (Mexico); Doltem (Peru); Drilan (Philippines); Dymadon (Australia); Efferalgan 500 (Costa Rica, Dominican Republic, El Salvador, Guatemala, Honduras, Israel, Nicaragua, Panama); Efferalganodis (France); Eraldor (Ecuador); Expandol (France); Fervex (Brazil); Flurinol (Philippines); Fortolin (China); Gelocatil (Spain); Geluprane 500 (France); Gunaceta (Indonesia); Kamolas (Indonesia); Kyofen (Colombia); Lemgrip (Belgium); Lotemp (Thailand); Malidens (India); Mebinol (Peru); Meforagesic (Philippines); Metagesic (Philippines); Mexalen (Austria, Czech Republic, Hungary); Milidon 500 (Singapore); Minopan (Korea); Mypara (Thailand); Nalgesik (Indonesia); Napa (Singapore); Napamol (South Africa); Naprex (Indonesia); NEBS (Japan); Nektol 500 (Philippines); Nilapur (Indonesia); Pacemol (Brazil, Singapore); Pacimol (India); Pamol (Denmark, New Zealand); Panadol (Belgium, Brazil, Bulgaria, Chile, England, Finland, France, Greece, Hong Kong, Indonesia, Ireland, Italy, Korea, Netherlands, South Africa, Switzerland, Taiwan, Thailand, Uruguay); Panadol Actifast (Malaysia, Singapore); Panamax (Australia); Panodil (Denmark, Norway, Sweden); Paracet (Norway); Parageniol (Paraguay); Paragin (Thailand); Paralgin (Australia); Paralief (Ireland); Paramidol (Peru); Paramol (Israel, Taiwan); Parapaed (Germany); Parapaed Junior (New Zealand); Parapaed Six Plus (New Zealand); Paratabs (New Zealand); Parvid (Philippines); Paximol (Singapore); Pedipan (Korea); Penral-Night (Korea); Pinex (Norway); Poro (Malaysia); Predimol (India); Puernol (Italy); Raperon (Korea); Rapidol (Chile); Reliv (Sweden); Remedol (Puerto Rico); Revanin (South Africa); Rhinapen elixir (Korea); Roxamol Gelcaps (Israel); Salzone (South Africa); Saridon (Colombia); Serimol (Hong Kong); Setamol (Australia); Sinedol (Dominican Republic); Taganopain (Korea); Tamifen (Ecuador); Tempra (Belgium, Canada, Costa Rica, Ecuador, El Salvador, Greece, Guatemala, Honduras, Indonesia, Japan, Mexico, Nicaragua, Panama, Spain, Thailand); Tempte (Taiwan); Temzzard (Mexico); Termofren (Costa Rica, Dominican Republic, El Salvador, Guatemala, Honduras, Nicaragua, Panama); Turpan (Indonesia); Tylenol (Australia, Austria, Brazil, Bulgaria, Canada, China, France, Germany, Hong Kong, Israel, Japan, Korea, Mexico, Philippines, Portugal, Spain, Switzerland, Thailand, Venezuela); Tylenol Extra Fuerte (Paraguay, Peru); Tylex (Costa Rica, Dominican Republic, El Salvador, Guatemala, Honduras, Nicaragua, Panama); Winadol (Colombia, Venezuela); Winasorb (Costa Rica, Dominican Republic, El Salvador, Guatemala, Honduras, Nicaragua, Panama); Xebramol (Thailand); Zetifen (Philippines); Zolben (Venezuela); Zydinol (Philippines)

Drug Class	Analgesics, non-narcotic; Antipyretics; NSAID
Indications	Mild pain, fever, menstrual cramps, osteoarthritis, tension headache
Mechanism	Nonspecific cyclooxygenase inhibitor
Dosage with Qualifiers	Pain and/or fever—650-1000mg PO/PR q4-6h; max 4g/d *NOTE: included in many combinations.* • **Contraindications**—hypersensitivity to drug or class • **Caution**—hepatic or renal dysfunction, chronic alcohol use, G6PD deficiency, PKU
Maternal Considerations	**Acetaminophen** is component of a long list of OTC medications. It is metabolized in the liver and excreted by the kidneys. During the 1st trimester, the mean t/2 is significantly lower and oral clearance is significantly higher compared to nonpregnant control subjects. Only during pregnancy is weight related to clearance,

suggesting the dose may need to be adjusted in obese women. **Ibuprofen** provides more rapid relief of perineal pain after vaginal delivery. Up to ⅔ of pregnant women ingest **acetaminophen** some time during gestation. In one recent RCT, **acetaminophen** plus **oxycodone** was superior to patient-controlled **morphine** for the relief of post-cesarean pain. There are no obvious differences in clearance at term. Chronic abuse and overdose are the most common problems. The damage appears secondary to free radical toxicity with consumption of glutathione. ***N*-acetylcysteine** is the treatment of choice for acute overdose. In one prospective case-control study, use of prenatal **ibuprofen, naproxen,** and **aspirin,** but not **acetaminophen,** increased the risk of spontaneous abortion by 80% (adjusted hazard ratio 1.8 [95% CI 1.0-3.2]). The association was stronger if the initial use occurred around conception or if the use lasted more than a week.

Side effects include hepatotoxicity, nephrotoxicity, agranulocytosis, pancytopenia, hemolytic anemia, pancreatitis, rash, angioedema, and urticaria.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. **Acetaminophen** crosses the human placenta, reaching steady state in the isolated perfused model within 1h. The F:M ratio for **acetaminophen** approximated 0.12 in the pregnant ewe, and neither sulfate or glucuronide metabolites crossed. **Acetaminophen** use during labor to treat the fever of chorioamnionitis is associated with improved fetal umbilical blood gases, presumably by reducing fetal oxygen demand as the maternal core temperature declines. Although it was previously suggested that exposure to **acetaminophen** was associated with clubfoot and digital abnormalities, these reports are not sustained in large series. However, there appears to be a link between it and gastroschisis and small bowel atresia, but not cardiac ventriculoseptal defects. Unlike aspirin, **acetaminophen** has no antiplatelet activity and does not pose a hemorrhagic risk to the fetus.

Breastfeeding Safety

Acetaminophen is excreted in low concentrations into breast milk. The amount of the drug administered to the mother estimated to be available to the neonate ranges from 0.04% to 0.23%, and it is generally considered compatible with breastfeeding.

Drug Interactions

Tramadol may increase the risk of **acetaminophen** toxicity. Local anesthetics may increase the risk of methemoglobinemia.

References

Beaulac-Baillargeon L, Rocheleau S. Eur J Clin Pharmacol 1994; 46:451-4.

Cleves MA, Savell VH Jr, Raj S, et al; National Birth Defects Prevention Study. Birth Defects Res Part A Clin Mol Teratol 2004; 70:107-13.

Committee on Drugs, American Academy of Pediatrics. Pediatrics 1994; 93:137-50.

Davis KM, Esposito MA, Meyer BA. Am J Obstet Gynecol 2006;194:967-71.

Kamandetdecha R, Tanninandorn Y. J Med Assoc Thai 2008; 91:282-6.

Kirshon B, Moise KJ Jr, Wasserstrum N. J Reprod Med 1989; 34:955-9.

Li DK, Liu L, Odouli R. BMJ 2003; 327:368-73.

Rayburn W, Shukla U, Stetson P, Piehl E. Am J Obstet Gynecol 1986; 155:1353-6.

Wang LH, Rudolph AM, Benet LZ. J Pharmacol Exp Ther 1986; 238:198-205.
Weigand UW, Chou RC, Maulik D, Levy G. Pediatr Pharmacol (New York) 1984; 4:145-53.
Werler MM, Mitchell AA, Hernandez-Diaz S, Honein MA. Am J Obstet Gynecol 2005;193:771-7.
Werler MM, Sheehan JE, Mitchell AA. Am J Epidemiol 2002; 155:26-31.

Summary

Pregnancy Category: B
Lactation Category: S

- **Acetaminophen** is used throughout pregnancy for analgesia and to reduce fever.
- Like most drugs, it should be used during the 1st trimester only when clearly necessary.

Acetazolamide—(Acetadiazol; Acetamide; Azomid; Dehydratin; Diamox; Diamox Sequels; Diamox Sodium; Ederen; Glauconox; Inidrase; Nephramid; Oratrol)

International Brand Name—Acetadiazol (Mexico); Albox (Japan); Apo-Acetazolamide (Malaysia); Carbinib (Portugal); Cetamid (Philippines); Defiltran (Germany); Diamox (Argentina, Bangladesh, Brazil, Bulgaria, Canada, Chile, Czech Republic, Ecuador, Germany, Greece, Hungary, Korea, Mexico, Pakistan, Peru, Poland, Portugal, Slovenia, South Africa, Turkey, Venezuela); Diamox Sustets (Colombia); Diluran (Czech Republic); Diural (Uruguay); Diuramid (Germany, Poland); Edemox (Spain); Genephamide (Peru); Glaucomed (Colombia); Glaucomide (New Zealand); Glaupax (Denmark, Ireland, Japan, Netherlands, Norway, Sweden, Switzerland, Thailand); Huma-Zolamide (Hungary); Ledamox (Japan); Lediamox (Portugal); Ledimox (Japan, Portugal); Stazol (Paraguay)

Drug Class

Carbonic anhydrase inhibitors; Diuretics

Indications

Glaucoma, open and closed angle; altitude sickness, prevention and treatment; epilepsy; CHF; drug-induced edema; urinary alkalinization

Mechanism

Carbonic anhydrase inhibitor

Dosage with Qualifiers

Glaucoma—125-250mg PO/IV bid to qid
Altitude sickness—250-500mg PO bid beginning 48h before ascent
Epilepsy—375-1000mg (8-30mg/kg/d) PO qd if sole agent; begin 250mg qd if with other agents
Congestive heart failure—250-375mg PO/IV qd (for best results, take on alternate days)
Drug-induced edema—250-375mg PO/IV qd (for best results, take on alternate days)
Urinary alkalinization—5mg/kg PO/IV bid or tid to maintain alkaline urine pH

- **Contraindications**—hypersensitivity to drug or class, hyponatremia, hypokalemia, depressed respiratory function, cirrhosis, hyperchloride acidosis, adrenocortical insufficiency
- **Caution**—hepatic and/or renal dysfunction

Maternal Considerations

There are no adequate reports or well-controlled studies of **acetazolamide** in pregnant women. Pregnancy is not known to alter the impact, efficacy, and dosing of **acetazolamide**.
Side effects include aplastic anemia, Stevens-Johnson syndrome, toxic epidermal necrolysis, fulminant hepatitis, paresthesias, loss of appetite, taste changes, dyspepsia, and polyuria.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. **Acetazolamide** apparently crosses the human placenta. There is no suggestion of teratogenicity in humans despite a long clinical experience. A single case report documents a preterm infant whose mother was treated for glaucoma throughout pregnancy with oral **acetazolamide**. When renal tubular acidosis developed, **acetazolamide** was detected in the child's serum, confirming transplacental passage. In some rodents, **acetazolamide** is teratogenic (skeletal abnormalities consisting variably of ossification defects or some form of postaxial forelimb ectrodactyly in rats, urinary malformations in mice when combined with **amiloride**). The prevalence of defects is enhanced when combined with **ibuprofen**.

Breastfeeding Safety

Acetazolamide is not concentrated in the milk, and the neonatal exposure is <0.5% of the maternal dose. It is generally considered compatible with breastfeeding.

Drug Interactions

Acetazolamide may modify **phenytoin** metabolism and increase serum level of **phenytoin**. By decreasing the GI absorption of **primidone,** it may decrease serum concentrations of **primidone**. **Acetazolamide** reduces urinary excretion of **quinidine** and may enhance its effect. It increases **lithium** excretion. **Acetazolamide** may elevate **cyclosporine** levels.

References

Academy of Pediatrics. Pediatrics 1994; 93:137-50.
Lee GS, Liao X, Cantor RM, Collins MD. Birth Defects Res A Clin Mol Teratol 2006;76:19-28.
Nakatsuka T, Komatsu T, Fujii T. Teratology 1992; 45:629-36.
Ozawa H, Azuma E, Shindo K, et al. Eur J Pediatr 2001; 160:321-2.

Summary

Pregnancy Category: C
Lactation Category: S

- **Acetazolamide** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Acetohexamide—(Dimelin; Dimelor; Dymelor; Gamadiabet; Ordimel; Toyobexin)

International Brand Name—Dimelin (Japan); Dimelor (South Africa, Taiwan); Toyobexin (Japan)

Drug Class

Carbonic anhydrase inhibitors; Oral hypoglycemics; Sulfonylureas

Indications

Diabetes mellitus, type II

Mechanism

Acutely stimulates the release of pancreatic insulin and thus requires islet activity

Dosage with Qualifiers

Diabetes mellitus, type II—begin 250mg/d before breakfast in women not receiving another hypoglycemic agent; increase by 250-500mg every 5-7d until desired control

- **Contraindications**—hypersensitivity to drug or class, ketoacidosis, type I diabetes mellitus
- **Caution**—pregnancy

Maternal Considerations

There are no adequate reports or well-controlled studies of **acetohexamide** in pregnant women, and no publications within the last 3 decades. Some oral hypoglycemic drugs are associated with an increased risk of CV death compared to diet and insulin control of glucose.
Side effects include hypoglycemia, cholestatic jaundice, GI upset, allergic skin reactions, SIADH, hemolytic anemia, various cytopenias, and hepatic porphyria.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. Although **acetohexamide** apparently crosses the placenta, there are no reports of teratogenicity in humans. Prolonged neonatal hypoglycemia associated with hyperinsulinism is reported. Differences in the extent of the placental transport of various sulfonylureas are reported. Embryotoxicity is noted in rodent studies.

Breastfeeding Safety

There is no published experience in nursing women. It is unknown whether **acetohexamide** enters human breast milk as other sulfonylureas do.

Drug Interactions

The hypoglycemic action of sulfonylureas can be enhanced by some drugs, including NSAIDs and other drugs that are highly protein bound, salicylates, sulfonamides, **chloramphenicol, probenecid,** coumarins, MAOIs, and β-blockers. Women treated with both should be observed closely for hypoglycemia.
Thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, **phenytoin, nicotinic acid,** sympathomimetics, calcium channel blockers, and **isoniazid** tend to produce hyperglycemia and may lead to loss of control or hypoglycemia when withdrawn.
Severe hypoglycemia was reported following concurrent use of oral **miconazole** and oral hypoglycemic agents. It is not known whether this interaction occurs with IV, topical, and vaginal preparations of **miconazole**.

References

Kemball ML, McIver C, Milner RD, et al. Arch Dis Child 1970; 45:696-701.

Summary

Pregnancy Category: C
Lactation Category: U

- Insulin and diet regulation remain the standard treatments for glucose intolerance during pregnancy.
- There is growing interest in the use of oral hypoglycemic agents during pregnancy, and **acetohexamide** might be a candidate for future study. If a patient is maintained on **acetohexamide** during pregnancy, she should be switched to insulin 1-2w prior to delivery in hopes of reducing the risk of neonatal hypoglycemia secondary to hyperinsulinism.

Acetylcysteine—(Acetyst; Alveolux; Bromuc; Mucomyst; Mucosil; Mucosol; Mukosil; Respaire)

International Brand Name—ACC (Mexico); Acerac (Korea); Acetain (Korea); Acypront (Hong Kong); Alveolex (Ireland); Bromuc (Brazil); Cetilan (Korea); Drenaflen (Ecuador); Ecomucyl (Switzerland); Eloamin (Czech Republic); Encore (Taiwan); Exomuc (France, Hong Kong); Fabrol (Austria, England, Finland, Greece, Ireland, Sweden); Flemex-AC (Thailand); Fluimicil (Germany, Hungary, Switzerland); Fluimucil (Brazil, China, Colombia, Ecuador, France, Hong Kong, Indonesia, Italy, Morocco, Netherlands, Peru, Singapore, Spain, Taiwan, Thailand); Fluimucil A (Malaysia); Flutafin (Taiwan); Hidonac (Philippines); Libramucil (Ecuador); M.C.T. (Korea); Menaxol (Costa Rica, Dominican Republic, El Salvador, Guatemala, Honduras, Nicaragua, Panama); Mucidin (Korea); Mucofillin (Japan); Mucolator (Malaysia); Mucolitico (Chile); Mucomiste (Portugal); Mucomyst (Australia, Austria, Belgium, Canada, Denmark, France, Netherlands); Mucoserin (Korea); Mucosof (China); Mucosten (Korea); Mucoza (Singapore, Thailand); Mukolit (Indonesia); Muteran (Korea); Parvolex (Canada, Philippines); Parvolex DBL (Malaysia); Reolin (Israel); Siran 200 (Israel); Solmucol (Singapore); Spatam (Singapore); Stecin (Korea); Zifluvis (Colombia)

Drug Class	Antidotes; Antioxidants; Mucolytics
Indications	Treatment of **acetaminophen** or *Amanita phalloides* toxicity; mucolytic in patients with cystic fibrosis
Mechanism	A glutathione precursor that breaks disulfide bonds caused by oxidation
Dosage with Qualifiers	Acetaminophen toxicity—begin 140mg/kg PO by NG tube; thereafter, 70mg/kg PO q4h ×15-20 doses Mucolytic—1 nebulizer ampule q6-8h; alternatively 2-5ml of 10% solution or 600mg in 3 divided doses • **Contraindications**—hypersensitivity to drug or class • **Caution**—severe respiratory failure, asthma
Maternal Considerations	***N*-acetylcysteine** is a prototype antioxidant presently used nearly exclusively during pregnancy for the treatment of maternal drug toxicity associated with free radical excess such as that occurring with **acetaminophen**. There are no adequate reports or well-controlled studies of ***N*-acetylcysteine** in pregnant women. It has been used for the treatment of **acetaminophen** toxicity during pregnancy. ***N*-acetylcysteine** or another like compound may have a role in the treatment of several disorders associated with excess free radical generation, including preterm labor and preeclampsia. For example, its administration reduced maternal hypertension after uterine artery ligation in rats. ***Side effects*** include bronchospasm, anaphylaxis, N/V, stomatitis, rhinorrhea, urticaria, and rash.
Fetal Considerations	***N*-acetylcysteine** crosses the placenta, reaching equilibrium with maternal sera. In laboratory studies, it reduces embryo toxicity associated with hyperglycemia, hypoxia, and sepsis. In other studies, it reduces the adverse fetal effects of maternal inflammation by in part blocking the inflammation-stimulated release of cytokines. More recently, it has been shown to prevent neuronal loss in chronically hypestemic guinea pig fetuses.
Breastfeeding Safety	There is no published experience in nursing women. It is unknown whether ***N*-acetylcysteine** enters human breast milk. It is unlikely short-term administration for an acute problem would pose a risk to the nursing infant.
Drug Interactions	***N*-acetylcysteine** should not be mixed in solution with **tetracycline, oxytetracycline,** and **erythromycin lactobionate**.

■ **References**

Beloosesky R, Gayle DA, Ross MG. Am J Obstet Gynecol 2006; 195:1053-7.
Bisseling TM, Maria Roes E, Raijmakers MT, et al. Am J Obstet Gynecol 2004; 191:328-33.
Boyer JC, Hernandez F, Estorc J, et al. Clin Chem 2001; 47:971-4.
Buhimschi IA, Buhimschi CS, Weiner CP. Am J Obstet Gynecol 2003; 188:203-8.
Chang EY, Barbosa E, Paintlia MK, et al. Am J Obstet Gynecol 2005; 193:952-6.
Horowitz RS, Dart RC, Jarvie DR, et al. J Toxicol Clin Toxicol 1997; 35:447-51.
McElhatton PR, Sullivan FM, Volans GN. Reprod Toxicol 1997; 11:85-94.

■ **Summary**

Pregnancy Category: B
Lactation Category: S (likely)

- ***N*-acetylcysteine** is indicated for the treatment of either cystic fibrosis or **acetaminophen** overdose during pregnancy.
- Future investigation may demonstrate a role for ***N*-acetylcysteine** in the treatment of the fetus for a myriad of pathologic conditions that share excess free radical generation.

Acyclovir—(Acivir Cream; Acivir Eye; Avirax; Avorax; Clovicin; Clovix; Entir; Supra-Vir; Zovirax)

International Brand Name—ACERPES (Germany); Acevir (Philippines); Acic Creme (Germany); Acicloftal (Italy); Aciclor (Venezuela); Aciclosina (Peru); Aciclovir-BC IV (Australia); Acihexal (Australia); Acilax cream (Hong Kong); Acitop (South Africa); Acivir Cream (India, Israel); Acivir Eye (India); Aclova (Korea); Aclovir (Taiwan, Thailand); Aclovirax (Hong Kong); Activir (France); Acyclo-V (Bahrain); Acylene (Malaysia); Acyron (Korea); Acyrova (Korea); Acyvir (Ecuador, Hong Kong, Italy, Korea); Aias (Korea); Apicol (Colombia); Avirax (Canada); Avorax (Hong Kong, Malaysia, Singapore); Avorax Cream (Malaysia); Azovir (Indonesia); Bearax (Singapore); Cicloferon (Mexico); Cicloviral (Colombia); Clinovir (Indonesia, Thailand); Clovicin (Taiwan); Clovir (Brazil); Cloviran (Chile); Colsor (Thailand); Cusiviral (Hong Kong, Malaysia, Singapore, Spain); Cyclivex (South Africa); Cyclo (Korea); Cyclomed (Israel); Cyclorax (Hong Kong); Cyclostad (Philippines); Cyclovir (India, South Africa); Cyllanvir (Philippines); Danovir (Singapore); Deherp (Taiwan, Thailand); Dravyr (Singapore); Dumophar (Indonesia); Eduvir (Indonesia); Entir (Singapore, Thailand); Erlvirax (Singapore); Eurovir (Paraguay); Exavir (Brazil); Expit (Uruguay); Herpefug (Germany); Herpex (Bahrain, India, Philippines); Herpoviric (Germany); Herpoviric Rp Creme (Germany); Inmerax (Chile); Innovirax (Philippines); Isavir (Mexico); Juviral (Germany); Laciken (Mexico); Leramex (Thailand); Lermex (Thailand); Lesaclor (Mexico); Libravir (Ecuador); Lisovyr (Argentina, Chile); Lovir (Malaysia, Singapore); Lovire (South Africa); Maclov (Mexico); Marvir (Thailand); Matrovir (Indonesia); Maynor (Spain); Medovir (Bulgaria, Israel, Malaysia, Singapore, Taiwan); Norum (Thailand); Olvit (Mexico); Oppvir (Taiwan, Thailand); Opthavir (Mexico); Poviral (Costa Rica, Dominican Republic, Ecuador, El Salvador, Guatemala, Honduras, Indonesia, Nicaragua, Panama); Proviral (Argentina); Qualiclovir (Hong Kong); Quavir (Indonesia); Ranvir (Thailand); Raxclo (Philippines); Supra-Vir (Israel); Supraviran (Germany); Supraviran Creme (Germany, Israel); Syntovir (Hong Kong); Vacrax (Malaysia); Vacrovir (Korea); Vermis (Thailand); Vicorax (Taiwan, Thailand); Viraban (New Zealand); Viralex (Philippines); Viralex-DS (Philippines); Virax (Korea); Vircella (Indonesia); Virest (Malaysia, Singapore); Virex (Colombia); Virless (China, Singapore, Taiwan); Viroclear (Hong Kong); Virogon (Thailand); Virolan (Taiwan); Viromed (Thailand); Vironida (Peru); Virucid (Hong Kong); Virules (Hong Kong); Virupos Eye Oint (Korea); Vivir (Korea); Warviron (Hong Kong); Zetavir (Mexico); Zeven Cream (Malaysia); Zevin (Hong Kong, Thailand); Zodiac (Korea); Zoral (Hong Kong, Singapore); Zoral Cream (Malaysia); Zorax (Singapore); Zorel (Indonesia); Zoter (Indonesia); Zovir (Denmark); Zoylex (Korea); Zumasid (Indonesia); Zyclir (Australia); Zyvir (Kenya)

■ **Drug Class** — Antivirals

■ **Indications** — Primary or secondary herpes infection/suppression; treatment or prevention of *Varicella* pneumonia

■ **Mechanism** — A synthetic, acyclic purine nucleoside that inhibits DNA polymerase by direct incorporation

■ **Dosage with Qualifiers**

Genital herpes, recurrent—200mg PO 5×/d ×10d

Genital herpes, suppressive—400mg PO bid for up to a year, or during pregnancy, from 36w onward; with HIV, 400-800mg PO 2-3×/d, or IV 5-10mg/kg q8h ×5-10d
Herpes zoster—800mg PO 5×/d ×7-10d
Ocular herpes—3% ointment 5×/d ×7-10d
Varicella, acute—800mg PO qid ×5d

- **Contraindications**—hypersensitivity to drug or class
- **Caution**—renal dysfunction or concurrent nephrotoxic drug

Maternal Considerations

Treatment is not curative, but rather intended to reduce the duration of symptoms and viral shedding. There is a long clinical experience free of obvious adverse effects. A recent meta-analysis concluded that prophylactic **acyclovir** beginning at 36w reduced the risks of clinical recurrence of genital herpes at delivery, cesarean section for recurrence, and herpes shedding at delivery. Suppression therapy is both effective and cost-effective whether or not the primary infection occurred during the current pregnancy. Because **acyclovir** is excreted via the kidneys, its t/2 may be reduced during pregnancy, but this has not been studied specifically. Its combination with **zidovudine** alters the clearance of both agents in pregnant rats.
Side effects include seizures, coma, leukopenia, thrombocytopenia, renal dysfunction, N/V, diarrhea, headache, dizziness, lethargy, rash, and confusion.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **acyclovir** crosses the human placenta. It is unclear whether maternal prophylaxis reduces the incidence of neonatal herpes. Post-marketing surveillance by Glaxo-Wellcome has not revealed any increase in or pattern of malformations after **acyclovir** exposure during the 1st trimester (756 pregnancies). A recent population-based study from Denmark that included 90 systemic and 995 topical exposures was likewise reassuring. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically.

Breastfeeding Safety

Acyclovir is passively secreted and achieves concentrations in breast milk higher than maternal serum, and is used to treat neonatal herpetic infection. It is generally considered compatible with breastfeeding. It has been estimated that the unsupplemented newborn would ingest 1-3mg/d.

Drug Interactions

Probenecid increases the mean **acyclovir** t/2 and AUC. Urinary excretion and renal clearance are correspondingly lower.

References

Academy of Pediatrics. Pediatrics 1994; 93:137-50.
Bork K, Kaiser T, Benes P. Arzneimittelforschung 2000; 50:656-8.
Braig S, Luton D, Sibony O, et al. Eur J Obstet Gynecol Reprod Biol 2001; 96:55-8.
Brown SD, Bartlett MG, White CA. Antimicrob Agents Chemother 2003; 47:991-6.
Eldridge RR, Ephross SA, Heffner CR, et al. Prim Care Update Obstet Gynecol 1998; 5:190-1.
Heuchan AM, Isaacs D. Med J Aust 2001; 174:288-92.
Hollier LM, Wendel GD. Cochrane Database Syst Rev 2008; (1):CD004946.
Leung DT, Sacks SL. Drugs 2000; 60:1329-52.
Little SE, Caughey AB. Am J Obstet Gynecol 2005; 193:1274-9.
Meyer LJ, de Miranda P, Sheth N, et al. Am J Obstet Gynecol 1988; 158:586-8.

Ratanajamit C, Vinther Skriver M, Jepsen P, et al. Scand J Infect Dis 2003; 35:255-9.
Scott LL, Alexander J. Am J Perinatol 1998; 15:57-62.
Scott LL, Hollier LM, McIntire D, et al. Infect Dis Obstet Gynecol 2001; 9:75-80.
Sheffield JS, Holier LM, Hill JB, et al. Obstet Gynecol 2003; 102:1396-403.
Taddio A, Klein J, Koren G. Ann Pharm 1994; 28:585-7.

Summary

Pregnancy Category: B
Lactation Category: S

- **Acyclovir** significantly reduces the duration of shedding and the number of recurrent HSV outbreaks during pregnancy.
- Prophylaxis to prevent recurrence should be initiated at 36w.

Adapalene—(Differin; Differine)

International Brand Name—Adaferin (India, Mexico); Adaferin Gel (Israel); Differine (France); Differin Gel (Austria, Germany, Ireland, Italy, Spain, Sweden, Switzerland)

Drug Class

Dermatologics; Retinoids

Indications

Acne vulgaris

Mechanism

Binds retinoid nuclear receptors to interfere with cellular differentiation, keratinization, and inflammatory processes

Dosage with Qualifiers

Acne vulgaris—apply (0.1%) cream or gel to the affected area once daily at night

- **Contraindications**—hypersensitivity to drug or class
- **Caution**—unknown

Maternal Considerations

Systemic absorption of **adapalene** across human skin is low, with none being detected in the plasma of 6 patients treated for acne in a standardized fashion for 5d with 2g. There are no adequate reports or well-controlled studies of **adapalene** in pregnant women. Women of child-bearing age should be fully informed of the risks and the importance of effective contraception. This also applies to patients with moderate forms of psoriasis, for which topical **tazaroten** is indicated.
Side effects include erythema, dryness, burning, scaling, and photosensitivity.

Fetal Considerations

There are no adequate studies of **adapalene** in human pregnancy. It is unknown whether **adapalene** crosses the human placenta. Though the pharmacology is encouraging, there are several reports in humans associating **adapalene** with fetal malformation after cutaneous exposure. The available information is insufficient to conclude cause and effect. Oral administration to rodents at 100-200× the MRHD increased the risk of malformation. No abnormalities were seen in pregnancies exposed to lower concentrations.

Breastfeeding Safety

There is no published experience in nursing women. It is unknown whether **adapalene** enters human breast milk. Considering the dose and route, it is unlikely to pose a significant risk to the breastfeeding neonate.

Drug Interactions

As **adapalene** may cause local irritation, simultaneous use of other topical agents such as medicated or abrasive soaps and

cleansers, soaps and cosmetics with a strong drying effect, and products with high concentrations of alcohol should be avoided if possible. Caution is also recommended in using preparations containing sulfur, resorcinol, or salicylic acid in combination with **adapalene**.

References

Autret E, Berjot M, Jonville-Bera AP, et al. Lancet 1997; 350:339.
[No authors]. Prescrire Int 1998; 7:148-9.
[No authors]. Prescrire Int 2005; 14:100-1.

Summary

Pregnancy Category: C
Lactation Category: U

- Best to avoid topical retinoids in early pregnancy as the disease process is rarely life threatening.
- Women of child-bearing age should be fully informed of the risks and the importance of effective contraception.
- There are alternative agents for which there is more experience during pregnancy and lactation.

Adenosine—(Adenic; Adenocar; Adenocard; Adeno-Jec; Adenoscan; Adenosine Phosphate; ATP)

International Brand Name—Adenocard (Brazil, Canada); Adenocor (Belgium, Bulgaria, China, Colombia, Denmark, Ecuador, Egypt, England, Ireland, Korea, Malaysia, Norway, Peru, South Africa, Spain, Taiwan, Thailand); Adenocur (Netherlands); Adenoject (India); Adenoscan (Hong Kong); Adenosina Biol (Argentina, Paraguay); Adrekar (Austria, Germany); Cardiovert (Philippines); Krenosin (France, Italy, Mexico); Krenosine (Switzerland)

Drug Class

Antiarrhythmics; Diagnostics

Indications

Paroxysmal SVT

Mechanism

Interrupts reentry pathways by slowing AV node conduction

Dosage with Qualifiers

Paroxysmal SVT conversion—3-6mg IV over 1-2sec; may double to 6mg and then 12mg if no response after 1-2min

- **Contraindications**—hypersensitivity to drug or class, 2nd or 3rd degree heart block or sick sinus syndrome
- **Caution**—asthma, chronic obstructive pulmonary disease

Maternal Considerations

An endogenous purine-based nucleoside, IV **adenosine** is the first choice for short-term management of paroxysmal supraventricular arrhythmia after a vagal maneuver fails. Co-administration of **midazolam** safely reduces recall of the unpleasant effects of **adenosine**. For long-term therapy, β-blocking agents with β_1 selectivity are first-line drugs; class Ic agents and the class III drug **sotalol** are effective therapeutic alternatives. **Adenosine** has been used on multiple occasions during pregnancy to treat paroxysmal SVT.
Side effects include arrhythmia (bradycardia, VF or ventricular tachycardia, asystole, complete heart block), bronchospasm, flushing, chest or groin pressure, dizziness, N/V, apprehension, palpitations, and headache.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. **Adenosine** crosses the human placenta, and though the kinetics remain to be detailed, it enhances placental perfusion. Rodent studies are reassuring, revealing no evidence of

teratogenicity. **Adenosine** has been administered successfully on a number of occasions directly into the umbilical vein to achieve control of a fetal SVT.

Breastfeeding Safety

There are no adequate reports or well-controlled studies in nursing women. **Adenosine** is a normal constituent of human breast milk, though the short t/2 suggests little, if any, of the exogenously administered **adenosine** will enter the milk.

Drug Interactions

Adenosine may be rarely associated with VF when combined with **digoxin** and **verapamil** use. Because of the potential for additive or synergistic depressant effects on the SA and AV nodes, however, **adenosine** should be used with caution in the presence of these agents.

The effects of **adenosine** are antagonized by methylxanthines such as **caffeine** and **theophylline**.

Adenosine effects are enhanced by **dipyridamole. Carbamazepine** may increase the degree of heart block produced by other agents.

References

Acevedo CG, Huambachano A, Perez E, et al. Placenta 1997; 18:387-92.

Chow T, Galvin J, McGovern B. Am J Cardiol 1998; 82:581-621.

Hourigan C, Safih S, Rogers I, et al. Emerg Med (Fremantle) 2001; 13:51-6.

Robins K, Lyons G. Br J Anaesth 2004; 92:140-3.

Tan HL, Lie KI. Eur Heart J 2001; 22:458-64.

Trappe HJ, Pfitzner P. Z Kardiol 2001; 90:36-44.

Summary

Pregnancy Category: B

Lactation Category: U

- Useful for the short-term treatment of either maternal or fetal tachycardia.

Albuterol—(Airet; Albuterol Sulfate; Asmalin; Asmanil; Asmavent; Butamol; Buventol; Proventil; Salbusian; Salbutamol; Theosal; Ventolin; Ventolin Rotacaps; Volmax)

International Brand Name—Aerolin (Brazil, Chile, Greece); Airhexal (Philippines); Airomir (Australia, Canada, France, Hong Kong, Malaysia, Singapore, Taiwan, Thailand); Almotex (Philippines); Asmacaire (Philippines); Asmadil (South Africa); Asmalin Pulmoneb (Philippines); Asmasal (Thailand); Asmatol (Argentina); Asmaven (England); Asmavent (Canada); Asmidon (Japan); Asmol CFC-Free (Australia); Asmol Uni-Dose (New Zealand); Asmovent (Malaysia); Assal (Mexico); Asthalin (India); Azmasol (Singapore); Broncho-Spray (Germany); Broncovaleas (Italy); Bronter (Colombia); Brytolin (Philippines); Butahale (Singapore); Buto-Asma (Singapore, Spain, Thailand); Butomix (Peru); Butotal (Chile); Buventol (Singapore, Taiwan); Buventol Easyhaler (France, Indonesia, Thailand); Cletal (Philippines); Cobutolin (England); Cybutol (Hong Kong); Dilatamol (Indonesia); Emplusal (Philippines); Epaq Inhaler (Australia); Exafil (Mexico); Glisend (Indonesia); Grafalin (Indonesia); Hivent DS (Philippines); Krosalburol (Ecuador); Libretin (Philippines); Medolin (Singapore); Mozal (Taiwan); Novosalmol (Canada); Parasma (Colombia); Provexel NS (Philippines); Prox-S (Philippines); Pulmol-S (Peru); Respax (New Zealand); Respreve (Hong Kong); Sabutol (Singapore); Salbetol (India); Salbron (Indonesia); Salbulin (Costa Rica, Dominican Republic, El Salvador, England, Guatemala, Honduras, Panama); Salbutalan (Mexico); Salbutan (Venezuela); Salbutin (Israel); Salbutol (Korea, Peru); Salbutron SR (Korea); Salbuven (Indonesia); Salbuvent (Norway); Salda (Thailand); Salden (Costa Rica, Ecuador, El Salvador, Guatemala, Honduras, Nicaragua, Panama); Salmaplon (India); Salmol (China); Salmundin Retard (Germany); Salomol (Taiwan); Sedalin (Philippines); Sultanol (Austria, Germany, Japan); Suprasma (Indonesia); Teoden (Brazil); Tobybron (Indonesia); Venalax (Philippines); Vencronyl (Philippines); Venetlin (Japan); Ventilan (Colombia, Portugal); Ventilastin Novolizer (Germany); Ventimax (South Africa); Ventodisks (China); Ventol (Israel); Ventolin (Argentina, Belgium, Bulgaria, Canada, China, Costa Rica, Czech Republic, Ecuador, El Salvador, Guatemala, Honduras, Hong Kong, Hungary, Indonesia, Ireland, Italy, Malaysia, Mexico, Netherlands, Nicaragua, Panama, Paraguay, Peru, Philippines, Spain, Switzerland, Taiwan, Thailand, Uruguay, Venezuela); Ventolin CFC-Free (Australia); Ventoline (Denmark, Finland, France, Norway, Sweden); Volmax (China, Ecuador, Hong Kong, New Zealand); Zebu (Thailand); Zenmolin (Hong Kong); Zibil (Mexico)

Drug Class	Adrenergic agonists; Bronchodilators
Indications	Bronchospasm; exercise-induced asthma
Mechanism	A selective β_2-agonist
Dosage with Qualifiers	Bronchospasm—1-2 puffs MDI q4-6h, max 12 puffs/d; or 2-4mg PO tid or qid Exercise-induced asthma—2 puffs MDI ×1 given 15-30min before exercise *NOTE: Numerous drug interactions are known. The reader should consult a detailed text if the patient is or has recently been on an MAOI or TCA, a β-adrenoceptor antagonist, a diuretic, or* ***digoxin****.* • **Contraindications**—hypersensitivity to drug or class • **Caution**—hyperthyroidism, CV disease, diabetes mellitus, seizure disorder
Maternal Considerations	In some countries, **albuterol** has been used as a tocolytic agent given IV, SC, or PO (also see **terbutaline** or **ritodrine,** whose efficacy it compares to). There is no evidence it will stop preterm or term labor. The maximum delay (compared to placebo), though, of 48h should permit maternal administration of corticosteroids. β-Mimetic tocolysis is associated with pulmonary edema, especially with multiple gestation, or in women concurrently receiving glucocorticoid therapy to hasten fetal lung maturation, or in association with infection. The mechanism is unclear. Treatment consists of oxygen supplementation and diuresis. Maternal serum glucose and plasma insulin levels peak soon after cessation of therapy and return to preinfusion levels within 2-3h. The decline in potassium is gradual and plateaus after 2h. Once the **albuterol**

infusion is stopped, the potassium returns to normal by 2h. Total WBC counts increase within an hour of initiating therapy. There is no need to administer insulin for hyperglycemia and/or potassium for hypokalemia unless the patient is a known diabetic or is severely affected and requires immediate surgery.
Side effects include bronchospasm with inhaler form, arrhythmia, tremor, nervousness, tachycardia, dizziness, headache, hypertension, nausea, hyperactivity, hypokalemia, and hyperglycemia.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. **Albuterol** appears to cross the human placenta, though the kinetics remain to be elucidated. Less than 10% is absorbed when administered by inhalation. There is no convincing evidence of teratogenicity after 1st trimester exposure. In general, long-term follow-up studies of infants exposed to β-mimetic tocolysis are reassuring. **Albuterol,** like other β-adrenoceptor agonists, is associated with a reduction in the incidence of RDS. A single abstract suggests an increased risk of newborn retinopathy. **Albuterol** is teratogenic in mice at doses lower than those used in humans.

Breastfeeding Safety

There is no published experience in nursing women. It is unknown whether **albuterol** enters human breast milk. Other β-adrenoceptor agonists such as **ritodrine** and **terbutaline** are considered safe for breastfeeding. Systemic absorption after inhalation is 10% or less.

Drug Interactions

Use with other sympathomimetic agents may lead to deleterious CV effects. This does not preclude the judicious use of an adrenergic agonist aerosol bronchodilator.
Albuterol should be administered with extreme caution to women using either MAOIs or TCAs (or within 2w of discontinuation).
β-Blockers may trigger severe bronchospasm in asthmatic women. However, under certain circumstances (e.g., as prophylaxis after MI), there may be no acceptable alternative to the use of a β-blocker in women with asthma.
The ECG changes and/or hypokalemia secondary to non–potassium-sparing diuretics may be acutely worsened by β-agonists.
Serum **digoxin** levels decrease about 20% after a single dose of either IV or oral **albuterol** to normal volunteers who ingested **digoxin** for 10 days.

References

Ashworth MF, Spooner SF, Verkuyl DA, et al. Br J Obstet Gynaecol 1990; 97:878-82.
Chua S, Razvi K, Wong MT, et al. J Obstet Gynaecol Res 1997; 23:381-7.
Michie CA, Braithwaite S, Schulenberg E, Harvey D. Arch Dis Child 1994; 71:F149.
Milliez JM, Flouvat B, Delhotal B, Jannet D. Obstet Gynecol 1992; 80:182-5.
[No authors]. Ann Allergy Asthma Immunol 2000; 84:475-80.
The Worldwide Atosiban versus Beta-agonists Study Group. BJOG 2001; 108:133-42.

Summary

Pregnancy Category: C
Lactation Category: S

- **Albuterol** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

- As a tocolytic, **albuterol** has no advantage over any other β-adrenoceptor agonist, prolonging pregnancy on average 48h over placebo.
- It is ineffective, like all β-adrenoceptor agonists, when used for preterm labor prophylaxis.
- β-Adrenoceptor agonists should be avoided in diabetic women. If unavoidable, the patient should be aggressively covered with a short-acting insulin.

Alendronate—(Fosamax)

International Brand Name—Aldrox (Chile); Alenato (Argentina); Alend (Korea); Alnax (Paraguay); Alovell (Indonesia); Arendal (Peru); Armol (Colombia); Bifemelan (Colombia); Bifosa (India); Bonapex (Egypt); Defixal (Costa Rica, Dominican Republic, El Salvador, Guatemala, Nicaragua, Panama); Endronax (Brazil); Eucalen (Colombia); Fixopan (Ecuador); Fosalan (Israel); Fosamax (Argentina, Austria, Belgium, Brazil, Bulgaria, Canada, Chile, Costa Rica, Czech Republic, Denmark, Ecuador, Egypt, El Salvador, England, France, Germany, Guatemala, Honduras, Hong Kong, Hungary, Indonesia, Ireland, Italy, Korea, Malaysia, Mexico, Netherlands, Nicaragua, Norway, Panama, Peru, Philippines, Poland, Singapore, South Africa, Spain, Sweden, Switzerland, Taiwan, Thailand, Venezuela); Fosmin (Peru); Fosval (Paraguay); Marvil (Peru, Uruguay); MaxiBone (Israel); MaxiBone 70 (Israel); Neobon (Colombia); Osdron (Brazil); Osdronat (Colombia); Oseotenk (Argentina); Osficar (Colombia); Oslene (Indonesia); Osteofar (Indonesia); Osteofos (Hong Kong); Osteopor (Uruguay); Osteosan (Chile); Osteovan (Costa Rica); Osticalcin (Colombia); Porosal (Venezuela); Tibolene (Colombia); Voroste (Indonesia)

Drug Class	Bisphosphonates; Calcium metabolism
Indications	Osteoporosis
Mechanism	Inhibits osteoclast resorption
Dosage with Qualifiers	Osteoporosis, postmenopausal treatment—10mg PO qd, or 70mg PO once a week taken with meals Osteoporosis, postmenopausal prevention—5mg PO qd, or 35mg PO once per week taken with meals Osteoporosis, steroid-induced—5mg PO qd taken with meals *NOTE: avoid supine position.* • **Contraindications**—hypersensitivity to drug or class, hypocalcemia, severe renal dysfunction • **Caution**—upper GI disease
Maternal Considerations	There are no adequate reports or well-controlled studies of **alendronate** in pregnant women. There appears only one case report of its use during pregnancy; the woman did respond. **Alendronate** is superior to **conjugated estrogens** (with or without **medroxyprogesterone**) for the prevention of bone loss in elderly women, though the combination is superior. ***Side effects*** include esophagitis, gastritis, dysphagia, esophageal ulcer, N/V, abdominal pain, arthralgia, myalgias, back pain, constipation, diarrhea, headache, chest pain, flu-like syndrome, and peripheral edema.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. Adult plasma levels are usually below the level of detection. There was no evidence of teratogenicity in two case series. **Alendronate** crosses the rodent placenta, decreasing bone density and delaying delivery. Both the total and ionized calcium are reduced in the rodent mother and fetus. The toxic effects are reversed by calcium administration.

Breastfeeding Safety

There is no published experience in nursing women. It is unknown whether **alendronate** enters human breast milk. However, the risk to the breastfed neonate is likely low considering the low maternal systemic levels.

Drug Interactions

Combined use of HRT and **alendronate** in postmenopausal osteoporotic women revealed the suppression of bone turnover was greater with the combination.
Calcium supplements, antacids, and some oral medications interfere with absorption of **alendronate**. Women should wait at least ½h after taking **alendronate** before taking any other oral medications.
The incidence of upper GI adverse events is increased in women receiving daily doses of **alendronate** greater than 10 mg and **aspirin**-containing products.

References

Greenspan SL, Resnick NM, Parker RA. JAMA 2003; 289:2525-33.
Minsker DH, Manson JM, Peter CP. Toxicol Appl Pharmacol 1993; 121:217-23.
Ornoy A, Wajnberg R, Diav-Citrin O. Reprod Toxicol 2006; 22:578-9.
Patlas N, Golomb G, Yaffe P, et al. Teratology 1999; 60:68-73.
Rutgers-Verhage AR, deVries TW, Torringa MJ. Clin Mol Teratol 2003; 67:203-4.
Samdani A, Lachmann E, Nagler W. Am J Phys Med Rehabil 1998; 77:153-6.

Summary

Pregnancy Category: C
Lactation Category: U
- **Alendronate** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Alfentanil—(Alfenta; Alfentanyl; Rapifen)

International Brand Name—Alfenil (Korea); Alfenta (Brazil, Canada); Brevafen (Argentina); Fanaxal (Spain); Fentalim (Italy); Rapifen (Bulgaria, Brazil, Chile, Costa Rica, Dominican Republic, El Salvador, Guatemala, Honduras, Hong Kong, Ireland, Israel, Mexico, Nicaragua, Panama, Paraguay, Poland, Slovenia, South Africa, Spain, Taiwan, Turkey, Uruguay, Venezuela)

Drug Class

Analgesics, narcotic

Indications

Analgesia either alone or in combination for labor or gynecologic pain

Mechanism

A short-acting lipophilic opioid

Dosage with Qualifiers

Anesthesia, induction—130-245mcg/kg IV (primarily with underlying cardiac disease undergoing a prolonged surgical procedure); more commonly 8-50mcg/kg at induction to blunt the pressor response to tracheal intubation
Anesthesia, maintenance—3-15mcg/kg IV prn, or 0.5-1mcg/kg/min continuous infusion

NOTE: chest wall rigidity is common, and neuromuscular blockers are usually given to enable mask ventilation before tracheal intubation.
Conscious sedation—3-8mcg/kg IV ×1

- **Contraindications**—hypersensitivity to drug or class
- **Caution**—chest wall rigidity; N/V; bradycardia; hepatic, renal, or pulmonary dysfunction; head injury; bowel obstruction

Maternal Considerations

Alfentanil is a short-acting narcotic with rapid onset. As with other lipophilic opioids, **alfentanil** reduces the total dose of local anesthetic analgesic needed to provide comfort when combined with **bupivacaine** for epidural analgesia while diminishing the likelihood of an undesired motor blockade. IV **alfentanil** given just prior to intubation reduces the associated pressor response in women with preeclampsia.
Side effects include respiratory arrest or depression, arrhythmia, seizure, coma, abuse or dependency, muscle rigidity, N/V, dizziness, hypertension, hypotension, tachycardia, bradycardia, confusion, sweating, dry mouth, constipation, and urinary retention.

Fetal Considerations

Alfentanil crosses the placenta when given IV, though its transfer rate is lower than **fentanyl** (which approximates **antipyrine**). Neither human embryo toxicity nor teratogenicity is reported, though 1st trimester human data are limited. **Alfentanil** is embryotoxic in rodents when given for 10-30d at doses 2-3× the MRHD. One limited monkey study concluded offspring had impaired ability to do simple cognitive tasks at 2-3mo of age after exposure at 14w gestation. Lipophilic and hydrophilic characteristics of the drug influence placental transfer, as do fluctuations in maternal flow. Neonatal depression characterized by reduced active and passive tone is reported when **alfentanil** is given shortly before delivery. Occasionally, a narcotic antagonist is necessary. There are no reported fetal or neonatal effects after its use for conduction anesthesia.

Breastfeeding Safety

Alfentanil is excreted into human the breast milk, though the amount excreted is too small to have any significant effect on the newborn.

Drug Interactions

The magnitude and duration of CNS and CV system effects may be enhanced when administered with other CNS depressants such as barbiturates, tranquilizers, opioids, or inhalation general anesthetics. Postoperative respiratory depression may be enhanced or prolonged.
Erythromycin may inhibit **alfentanil** clearance and increase the risk of prolonged or delayed respiratory depression. **Cimetidine** reduces the **alfentanil** clearance.
Perioperative administration of drugs affecting hepatic blood flow or enzyme function may reduce plasma **alfentanil** clearance and prolong recovery.

References

Ashton WB, James MF, Janicki P, Uys PC. Br J Anaesth 1991; 67:741-7.
Cooper RA, Devlin E, Boyd TH, Bali IM. Eur J Anaesthesiol 1993; 10:183-7.
Giesecke AH, Rice LJ, Lipton JM. Anesthesiology 1985; 63:A284.
Giroux M, Teixera MG, Dumas JC, et al. Biol Neonate 1997; 72:133-41.
Golub MS, Eisele JH Jr, Donald JM. Am J Obstet Gynecol 1988; 159:1280-6.
Rout CC, Rocke DA. Br J Anaesth 1990; 65:468-74.
Scherer R, Holzgreve W. Eur J Obstet Gynecol Reprod Biol 1995; 59:S17-29.
Zakowski MI, Ham AA, Grant GJ. Anesth Analg 1994; 79:1089-93.

Summary

Pregnancy Category: C
Lactation Category: S

- **Alfentanil** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Allopurinol—(Aipico; Alloremed; Alloscan; Alonol; Aloral; Aluline; Aluprin; Apurol; Isanol; Lopurin; Lysuron; Unizuric; Uricemil; Uriconorm-E; Zyloprim; Zyroric)

International Brand Name—Aceprax (Paraguay, Uruguay); Adenock (Japan); Alinol (Thailand); Allnol (Hong Kong); Allo 300 (Germany); Allo-Basan (Switzerland); Allohexal (Australia); Allopin (Thailand); Allopur (Norway, Switzerland); Allo-Puren (Germany); Alloril (Israel); Allorin (New Zealand); Allosig (Australia); Allozym (Japan); Allurase (Philippines); Allurit (Italy); Alopron (Puerto Rico); Alositol (Japan); Alpurase (Philippines); Alpurin (Philippines); Alunlan (Philippines, Taiwan); Alurin (Guatemala); Aluron (Venezuela); Anoprolin (Japan); Anzief (Japan); Apo-Allopurinol (Canada); Aprinol (Japan); Apurin (Denmark, Finland, Greece, Netherlands); Atisuril (Mexico); Bleminal (Germany); Caplenal (England, Ireland); Capurate (Australia, Taiwan); Cellidrin (Germany); Clint (South Africa); Erloric (Singapore); Etindrax (Mexico); Foligan (Germany, Switzerland); Gichtex (Austria); Hamarin (England); Isoric (Indonesia); Kemorinol (Indonesia); Ketanrift (Japan); Ketobun-A (Japan); Litinol (Venezuela); Llanol (Indonesia, Philippines); Lopurine (Philippines); Lo-Uric (South Africa); Lysuron 300 (Switzerland); Masaton (Japan); Medoric (Thailand); Mefanol (Ecuador); Mephanol (Hong Kong, Israel, Malaysia, South Africa, Switzerland); Milurit (Bulgaria, Hong Kong, Hungary); Miniplanor (Japan); Neufan (Japan); Nipurol (Venezuela); No-Uric (Israel); Progout (China, Hong Kong, Singapore); Proxuric (Indonesia); Puricemia (Indonesia); Puricos (South Africa); Purinase (Philippines); Purinol (Ireland, Malaysia); Purinox (Costa Rica, Dominican Republic, El Salvador, Guatemala, Honduras, Nicaragua, Panama); Puristen (Philippines); Ranpuric (South Africa); Remid (Germany); Riball (Japan); Rinolic (Indonesia); Salterprim (South Africa); Takanarumin (Japan); Tonsaric (Taiwan); Trianol (Philippines); Unizuric 300 (Mexico); Uric (Japan); Uricad (Thailand); Uriconorm (Switzerland); Urinol (Malaysia); Uripurinol (Germany); Urogquad (Argentina); Uroquad (Indonesia, Puerto Rico, South Africa); Urosin (Austria, Ecuador, Germany); Valeric (Singapore); Vitralgin (Peru); Xanturic (France); Xylonol (Taiwan); Zylapour (Greece); Zylol (Israel); Zyloprim (Canada, Paraguay, Philippines, South Africa); Zyloric (Argentina, Austria, Brazil, Chile, China, Greece, Hong Kong, India, Indonesia, Korea, Malaysia, Mexico, Peru, Poland, Slovenia, South Africa, Taiwan, Thailand, Turkey, Uruguay, Venezuela); Zyroric (Korea)

Drug Class	Antigouts; Antioxidants; Purine analogs
Indications	Gout, nephrolithiasis secondary to urate or calcium oxalate stones
Mechanism	A xanthine oxidase inhibitor that interferes with the conversion of xanthine and hypoxanthine to uric acid
Dosage with Qualifiers	Gout prophylaxis—100-800mg PO qd; titrate dose until uric acid <6mg/dl Urate nephrolithiasis prophylaxis—100-800mg PO qd Calcium oxalate calculi—200-300mg PO qd *NOTE: renal dosing.* • **Contraindications**—hypersensitivity to drug or class • **Caution**—renal dysfunction
Maternal Considerations	There are no adequate reports or well-controlled studies of **allopurinol** in pregnant women. It is rarely indicated for its traditional indications in pregnant or lactating women. There is a single report of a woman treated during pregnancy for primary gout with **allopurinol**. She delivered a healthy child at 35w. More often, **allopurinol** has been used during pregnancy for women undergoing treatment of acute leukemia. Of future interest is its potential as an antioxidant. **Allopurinol** was used unsuccessfully in one trial for the treatment of established preeclampsia. ***Side effects*** include agranulocytosis, aplastic anemia, thrombocytopenia, hepatic dysfunction, urticaria, Stevens-Johnson syndrome, toxic epidermal necrolysis, rash, diarrhea, pruritus, nausea, and gout flare.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. **Allopurinol** readily crosses the ovine placenta, where it reaches equilibrium within 30min. It reduces superoxide

generation in the brains of fetuses subject to intermittent umbilical cord occlusion. There is no evidence that **allopurinol** is teratogenic in humans. Cleft palate and skeletal defects are reported in some rodents.

Breastfeeding Safety

Allopurinol and its metabolite oxypurinol are excreted into breast milk to a limited degree and are considered compatible with breastfeeding. The average daily dose of **allopurinol** consumed by a 3kg neonate would be 0.6mg and of oxypurinol would be 24mg.

Drug Interactions

Allopurinol inhibits xanthine oxidase–catalyzed oxidation of **mercaptopurine** and **azathioprine** to 6-thiouric acid. Women taking **allopurinol** require ¼ to ⅓ reduction in their dose of **mercaptopurine/azathioprine**.
Allopurinol prolongs the t/2 of **dicumarol**. The PT should be reassessed periodically in women receiving both drugs.
Chlorpropamide's t/2 may be prolonged by **allopurinol,** since **allopurinol** and **chlorpropamide** compete for excretion by the renal tubule. The risk of hypoglycemia secondary to this mechanism may be increased in women with renal insufficiency.

References

Coddington CC, Albrecht RC, Cefalo RC. Am J Obstet Gynecol 1979; 133:107-8.
Committee on Drugs. Pediatrics 1994; 93:137-50.
Fujii T, Nishimura H. Jpn J Pharmacol 1972; 22:201-6.
Gulmezoglu AM, Hofmeyr GJ, Oosthuisen MM. Br J Obstet Gynaecol 1997; 104:689-96.
Kamilli I, Gresser U. Clin Investig 1993; 71:161-4.
Masaoka N, Nakajima Y, Hayakawa Y, et al. J Matern Fetal Neonatal Med 2005; 18:1-7.

Summary

Pregnancy Category: C
Lactation Category: S
- **Allopurinol** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Almotriptan—(Axert)

International Brand Name—Almogran (Belgium, Denmark, England, France, Germany, Ireland); Axert (Canada)

Drug Class

Serotonin receptor agonists

Indications

Migraine headache, acute

Mechanism

Binds with high affinity to 5-HT_{1D}, 5-HT_{1B}, and 5-HT_{1F} receptors, causing cranial vessel constriction.

Dosage with Qualifiers

Migraine headache, acute—6.25-12.5mg PO ×1; may repeat ×1 q2h; max 25mg/24h

NOTE: renal and hepatic dosing.

- **Contraindications—**hypersensitivity to drug or class, uncontrolled hypertension, ischemic heart disease, coronary spasm, basilar or hemiplegic migraines, 5-HT1 agonist or ergot use <24h
- **Caution—**cerebrovascular disease, PVD, ischemic bowel, cardiac risk factors, hepatic or renal dysfunction

Maternal Considerations	Migraine is a paroxysmal disorder with attacks of headache, N/V, photo- and phonophobia, and malaise. There is no published experience with **almotriptan** during pregnancy. Clinically, it is similar to **sumatriptan,** for which there is experience with during pregnancy. ***Side effects*** include hypertensive crisis, MI, coronary spasm, ventricular arrhythmias, CVA, peripheral vascular ischemia, bowel ischemia, N/V, somnolence, headache, paresthesias, and chest or jaw or neck pain or pressure.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **almotriptan** crosses the human placenta. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically, though embryo lethality was observed at 1000× the MRHD, and prolongation of pregnancy at 160× the MRHD.
Breastfeeding Safety	There is no published experience in nursing women. It is unknown whether **almotriptan** enters human breast milk.
Drug Interactions	SSRIs (e.g., **fluoxetine, fluvoxamine, paroxetine, sertraline**) are rarely reported to cause weakness, hyperreflexia, and incoordination when given with 5-HT_1 agonists. **Ketoconazole** and other potent CYP3A4 inhibitors increased the AUC for **almotriptan** by 60%. Although the interaction between **almotriptan** and other potent CYP3A4 inhibitors (e.g., **itraconazole, ritonavir, erythromycin**) has not been studied, increased exposures to **almotriptan** may be expected when used with these medications.
References	There is no published experience in pregnancy or during lactation.
Summary	**Pregnancy Category: C** **Lactation Category: U** • **Almotriptan** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk. • There are alternative agents for which there is more experience during pregnancy and lactation.

Aloe Vera—(Aloe Vera; Cape; Zanzibar; Socotrine)

International Brand Name—None identified.

Drug Class	Dermatologics
Indications	Wound healing
Mechanism	May neutralize or bind to the fibroblast growth factor-2 receptor
Dosage with Qualifiers	Wound healing—applied topically using a variety of formulations • **Contraindications—**hypersensitivity to drug or class • **Caution**—unknown
Maternal Considerations	**Aloe vera** gel comes from the inner tissue of the leaf and contains a myriad of compounds. Two FDA advisory panels concluded there was insufficient evidence that **aloe vera** is useful for the treatment of minor burns, cuts, or vaginal irritation. However, a recent study suggests **aloe vera** may accelerate wound healing by

	promoting gap junctional intercellular communication and proliferation of human skin fibroblasts. There are no adequate reports or well-controlled studies in pregnant women. It should never be ingested during pregnancy. ***Side effects*** include severe gastric cramping and diarrhea if taken internally.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses.
Breastfeeding Safety	There is no published experience in pregnancy. However, considering the topical route, it is unlikely the breastfed neonate would ingest clinically relevant amounts.
Drug Interactions	No drug-drug interaction studies in human subjects have been conducted.
References	There is no published experience in pregnancy or during lactation.
Summary	**Pregnancy Category: C** **Lactation Category: S** (likely) • **Aloe vera** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Alosetron hydrochloride—(Lotronex)

International Brand Name—Liminos (Mexico)

Drug Class	Antidiarrheals; Gastrointestinals; Serotonin receptor antagonist
Indications	Diarrhea-predominant irritable bowel syndrome
Mechanism	A selective and potent antagonist of the serotonin 5-HT_3 receptor
Dosage with Qualifiers	Diarrhea associated with irritable bowel syndrome—1mg PO bid • **Contraindications**—hypersensitivity to drug or class, constipation • **Caution**—unknown
Maternal Considerations	There are no published reports of **alosetron** use during pregnancy. ***Side effects*** include ischemic colitis, constipation, hypertension, allergic rhinitis, dyspepsia, and depressive disorders.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **alosetron** crosses the human placenta. Rodent studies are generally reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically, with the exception of the mouse, where cleft palate and skeletal defects were reported.
Breastfeeding Safety	There is no published experience in nursing women. It is unknown whether **alosetron** enters human breast milk. **Alosetron** is excreted into the milk of lactating rats.
Drug Interactions	Co-administration of **alosetron** and **fluvoxamine** is contraindicated. **Alosetron** is metabolized by a variety of hepatic CYP drug-metabolizing enzymes. **Fluvoxamine** inhibits CYP1A2, CYP3A4, CYP2C9, and CYP2C19. **Fluvoxamine** increases mean

alosetron plasma AUC some 6-fold and prolongs the t/2 by 3-fold. Other moderate CYP1A2 inhibitors, including quinolone antibiotics and **cimetidine**, should also be avoided unless necessary.
Ketoconazole is a strong inhibitor of CYP3A4 and increases **alosetron** plasma AUC by close to ⅓. Other strong CYP3A4 inhibitors, such as **clarithromycin, telithromycin,** protease inhibitors, **voriconazole,** and **itraconazole,** have not been evaluated but should be used with caution with **alosetron**.
Based on several *in vitro* and *in vivo* studies, it is unlikely **alosetron** will inhibit the hepatic metabolic clearance of drugs metabolized by the major CYP enzyme 3A4, as well as the CYP enzymes 2D6, 2C9, 2C19, 2E1, or 1A2.

References ..... There is no published experience in pregnancy or during lactation.

Summary ..... **Pregnancy Category: B**
Lactation Category: U
- **Alosetron** is rarely indicated during pregnancy and should be used only when the benefits outweigh any theoretic risks.

Alprazolam—(Alpralid; Alprazolam Intensol; Altraxic; Apo-Alpraz; Xanax; Xanax TS; Xanolam; Zoldac; Zolam; Zopax)

International Brand Name—Aceprax (Paraguay, Uruguay); Alcelam (Thailand); Alganax (Indonesia); Alnax (Thailand); Alpaz (Peru); Alplax (Argentina); Alpralid (Israel); Alpram (Korea); Alpranax (Israel); Alprax (Australia, India, Thailand); Alprocontin (India); Alprox (Israel, Taiwan); Altraxic (Philippines); Alviz (Indonesia); Alzam (South Africa); Alzax (Korea); Alzolam (India); Anax (Thailand); Anpress (Thailand); Ansiopax (Chile); Anxirid (South Africa); Anzion (Thailand); Apo-Alpraz (Canada, Singapore); Apraz (Brazil); Azor (South Africa); Calmlet (Indonesia); Cassadan (Germany); Constan (Japan); Daclor (Dominican Republic); Dixin (Colombia); Dizolam (Singapore); Drimpam (South Africa); Feprax (Indonesia); Frixitas (Indonesia); Frontal (Brazil); Kalma (Taiwan); Kinax (Taiwan); Marzolam (Thailand); Nalion (Hong Kong); Neupax (Mexico); Nirvan (Colombia); Pacyl (India); Panix (South Africa); Pharnax (Thailand); Prinox (Argentina); Renax (Hong Kong); Restyl (Israel); Sapram (Korea); Solanax (Japan); Tafil (Costa Rica, Denmark, El Salvador, Germany, Guatemala, Honduras, Mexico, Nicaragua, Panama, Venezuela); Tafil D (Mauritius); Tensivan (Colombia); Trankimazin (Spain); Tranquinal (Brazil, Ecuador, Paraguay, Peru, Uruguay); Tricalma (Chile, Peru); Valeans (Italy); Xanacine (Thailand); Xanagis (Israel); Xanax (Argentina, Belgium, Bulgaria, Canada, Colombia, Czech Republic, Ecuador, England, France, Germany, Greece, Hong Kong, Hungary, Ireland, Italy, Malaysia, Netherlands, Peru, Poland, Portugal, Switzerland, Taiwan, Thailand); Xanax SR (Singapore); Xanax TS (Canada); Xanax XR (Taiwan); Xanolam (South Africa); Xanor (Austria, Finland, Norway, Philippines, South Africa, Sweden); Xanor XR (Philippines); Zacetin (Korea); Zanapam (Korea); Zolam (India); Zopax (South Africa); Zotran (Chile); Zypraz (Indonesia)

Drug Class ..... Anxiolytics; Benzodiazepines; Sedatives

Indications ..... Acute anxiety

Mechanism ..... A short-acting benzodiazepine that reduces anxiety by enhancing GABA effects

Dosage with Qualifiers ..... Antianxietal—0.25-0.5mg PO tid, max 4mg/d
Panic disorder—0.5mg PO tid, up to 1mg after 3-4d
- **Contraindications**—hypersensitivity to drug or class, glaucoma, pregnancy, CNS depression
- **Caution**—hepatic or renal dysfunction

Maternal Considerations ..... **Alprazolam** is rarely indicated during pregnancy. There are few published reports of **alprazolam** use during pregnancy. Abrupt cessation of therapy is associated with a discontinuation-emergent

syndrome that includes neuropsychiatric, GI, dermatologic, CV, and visual symptoms.
Side effects include physical dependence, syncope, tachycardia, seizures, respiratory depression, coma, drowsiness, lightheadedness, dry mouth, depression, headache, constipation, diarrhea, N/V, insomnia, blurred vision, hypotension, increased salivation, and dermatitis.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. While there is no evidence that **alprazolam** is a human teratogen by either case reports or post-marketing surveillance, **diazepam** has been associated with fetal malformations. There is also concern based on studies with other benzodiazepines that postnatal behavior might be altered by antenatal exposure. Neonatal withdrawal has been reported. Treatment with **phenobarbital** is beneficial. In rodents, mice exposed to **alprazolam** demonstrate more individual than group activities and avoid open areas, and the males are more aggressive.

Breastfeeding Safety

Alprazolam enters breast milk by passive diffusion, achieving an M:P ratio of 0.36 ingesting 0.3-5mcg/kg/d. This is approximately 3% of the weight-adjusted maternal dose. Though the risk is reasonably small, **alprazolam** should be avoided during lactation because of the potential that it might alter neurodevelopment and because of the documented risks of withdrawal.

Drug Interactions

Benzodiazepines such as **alprazolam** can produce additive CNS depressant effects when given with other psychotropic medications, anticonvulsants, antihistaminics, ethanol, and other drugs that themselves produce CNS depression.
Drugs or diseases that cause dry mouth or raise stomach pH may slow disintegration or dissolution, resulting in slowed or decreased absorption.
Alprazolam begins its metabolism by CYP3A hydroxylation. Drugs that inhibit this pathway may have a profound effect on the clearance of **alprazolam**. Known drugs of concern include **fluoxetine, propoxyphene,** and oral contraceptives.
Clinical studies of other benzodiazepines suggest a possible drug interaction between **alprazolam** and **diltiazem, isoniazid,** macrolide antibiotics such as **erythromycin** and **clarithromycin,** and grapefruit juice. *In vitro* studies of other benzodiazepines suggest possible interactions with **ergotamine, cyclosporine, amiodarone, nicardipine,** and **nifedipine**.
Carbamazepine can increase **alprazolam** metabolism and thus decrease plasma levels.

References

Anderson PO, McGuire GG. DICP Ann Pharmacother 1989; 23:614.
Christensen HD, Gonzalez CL, Rayburn WF. Am J Obstet Gynecol 2003; 189:1452-7.
Gidal J, Acs N, Banhidy F, Czeizel A. Toxicol lnd Health 2008; 24:53-60.
Oo CY, Kuhn RJ, Desai N, et al. Br J Clin Pharmacol 1995; 40:231-6.
St. Clair SM, Schirmer RG. Obstet Gynecol 1992; 80:843-6.

Summary

Pregnancy Category: D
Lactation Category: NS (likely)

- **Alprazolam** should be avoided during pregnancy and lactation unless there are no other safer options.
- There are alternative agents for which there is more experience during pregnancy and lactation.

Alteplase—(Actilyse; Activacin; Activase; TPA)

International Brand Name—Actilyse (Austria, Bangladesh, Belgium, Brazil, Bulgaria, Colombia, Czech Republic, Denmark, England, Finland, France, Germany, Greece, Hungary, Italy, Japan, Mexico, Netherlands, Norway, Pakistan, Poland, Portugal, South Africa, Spain, Sweden, Switzerland); Activacin (Japan)

Drug Class	Thrombolytics
Indications	Acute MI, pulmonary embolus, acute ischemic stroke
Mechanism	Human recombinant tissue plasminogen activator is a serine protease that converts plasminogen to plasmin in the presence of fibrin.
Dosage with Qualifiers	Acute MI—within 4h of symptom onset and based on weight: <67kg, 15mg bolus IV, followed by 0.75mg/kg IV over the next 30min (not to exceed 50mg), then 0.50mg/kg over the next 60min (not to exceed 35mg); >66kg, 15mg bolus IV, followed by 50mg IV over 30min, then 35mg over the next 60min Pulmonary embolus—100mg IV over 120min; initiate **heparin** therapy near the end or immediately following the **alteplase** when either the PTT or TT returns to <2× normal Acute ischemic stroke—given within 4h of symptom onset: 0.9mg/kg IV over 60min; begin with 10% of dose as an IV bolus over 1min (max total dose 90mg) • **Contraindications**—hypersensitivity to drug or class, intracranial hemorrhage, seizure at onset of stroke, internal bleeding, intracranial neoplasm, aneurysm, hypertension (>185/110mmHg S/D) • **Caution**—unknown
Maternal Considerations	There are no adequate reports or well-controlled studies of **alteplase** in pregnant women. There are case reports of its use during pregnancy for the treatment of PE, MI, and peripheral thrombosis without an apparent increase in risk for hemorrhage, abruption, and PROM or preterm labor. ***Side effects*** include cerebral hemorrhage, arrhythmias, severe bleeding, anaphylaxis, hypotension, N/V, and fever.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **alteplase** crosses the human placenta. It could theoretically interfere with implantation. In light of its high molecular weight, **alteplase** is unlikely to cross the placenta. Rodent teratogenicity studies have not been conducted.
Breastfeeding Safety	There is no published experience in nursing women. While tissue plasminogen activator is a normal constituent of human breast milk, it is unknown whether **alteplase** increases that level.
Drug Interactions	Drugs that alter platelet function (e.g., **aspirin, dipyridamole, abciximab**), in addition to **heparin** and vitamin K antagonists, may increase the risk of bleeding if administered prior to, during, or after **alteplase**. There are post-marketing reports of orolingual angioedema associated with **alteplase**.
References	Baudo F, Caimi TM, Redaelli R, et al. Am J Obstet Gynecol 1990; 163:1274-5. Grand A, Ghadban W, Perret SP, et al. Ann Cardiol Angeiol 1996; 45:517-22.

Huang WH, Kirz DS, Gallee RC, Gordey K. Obstet Gynecol 2000; 96:838.
Nassar AH, Abdallah ME, Moukarbel GV, et al. J Perinat Med 2003; 31:257-60.
Schumacher B, Belfort MA, Card RJ. Am J Obstet Gynecol 1997; 176:716-9.

Summary

Pregnancy Category: C
Lactation Category: U

- **Alteplase** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.
- It is effective for acute thrombotic events that place the patient's survival in question.

Amantadine—(Contenton; Endantadine; Infectoflu; Mantandan; Shikitan; Symmetrel; Topharmin)

International Brand Name—Aldinam (Chile); Amanda (Taiwan); Amandin (Taiwan); Amandine (Uruguay); Amantan (Belgium); Amantix (Colombia); Amantrel (India); Amazolon (Japan); a.m.t. (Germany); Atarin (Finland); Boidan (Japan); Endantadine (Canada); Enzil (Taiwan); Hofcomant (Austria, Finland); Infectoflu (Germany); Mantadan (Italy); Mantadix (Belgium); Mantidan (Brazil); Padiken (Mexico); Paritrel (Israel); Parkintrel (Korea); PK-Merz (Austria, Chile, Costa Rica, Czech Republic, Dominican Republic, Germany, Guatemala, Hong Kong, Hungary, Israel, Korea, Malaysia, Panama, Paraguay, Portugal, South Africa, Switzerland, Taiwan); Prayanol (Chile); Protexin (Spain); Symmetrel (Austria, Canada, England, Germany, Greece, Ireland, Netherlands, Norway, Philippines, South Africa, Switzerland, Venezuela); Tregor (Germany); Virofral (Sweden); Virosol (Argentina)

Drug Class

Antivirals; Dopaminergics; Extrapyramidal disorders

Indications

Treatment or prevention of influenza A, treatment of extrapyramidal reactions or parkinsonism

Mechanism

Unknown; appears to interfere with release of viral nucleic material into the host cell

Dosage with Qualifiers

Influenza A treatment—200mg PO qd until 24-48h after symptoms resolve
Influenxa A prophylaxis—200mg PO qd beginning immediately after exposure and continuing at least 10d
Extrapyramidal reactions—100mg PO qd to tid (max 300mg/d)
Parkinsonism—begin 100mg PO qd, increase to bid after 1w, max 400 mg/d; reduce to 100mg/d if taking other antiparkinsonism drugs

NOTE: renal dosing.

- **Contraindications**—hypersensitivity to drug or class
- **Caution**—seizure disorder, heart failure, liver disease, CV disease, geriatric population

Maternal Considerations

The published experience with **amantadine** during pregnancy consists of isolated case reports. **Amantadine** has also been used to treat the fatigue associated with MS. There has been a progressive increase in **amantadine** resistant influenza A.
Side effects include CHF, nausea, dizziness, insomnia, anxiety, depression, hallucinations, constipation, ataxia, somnolence, and agitation.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **amantadine** crosses the human placenta. The human experience is of concern.

There are several case reports of CV abnormalities in exposed fetuses. Rats exposed to 7× the MRHD show embryotoxicity and a variety of malformations, while there is no effect at doses 5-6× the MRHD.

Breastfeeding Safety

Amantadine is excreted in trace amounts into human milk. Though the kinetics and safety are unknown, the unsupplemented term infant would ingest <1mg/d assuming an M:P ratio of 1.

Drug Interactions

Administration with **triamterene/hydrochlorothiazide** may increase the plasma **amantadine** concentration.
Administration with **trimethoprim-sulfamethoxazole** may impair **amantadine** renal clearance, causing higher plasma concentrations.
Administration with **quinine** or **quinidine** may reduce **amantadine** renal clearance.

References

Hagell P, Odin P, Vinge E. Mov Disord 1998; 13:34-8.
Levy M, Pastuszak A, Koren G. Reprod Toxicol 1991; 5:79-81.
Pandit PB, Chitayat D, Jefferies AL, et al. Reprod Toxicol 1994; 8:89-92.
Rosa F. Reprod Toxicol 1994; 8:89-92.

Summary

Pregnancy Category: C
Lactation Category: U

- **Amantadine** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.
- There are alternative agents for which there is more experience during pregnancy and lactation.

Ambenonium chloride—(Mytelase)

International Brand Name—Mytelase (Belgium, Czech Republic, Finland, France, Hungary, Japan, Sweden); Mytelase Chloride (Czech Republic, Finland, France, Hungary, Japan, Poland, Sweden)

Drug Class

Cholinesterase inhibitors; Musculoskeletal agents; Stimulants, muscle

Indications

Myasthenia gravis

Mechanism

Cholinesterase inhibitor with all the pharmacologic actions of acetylcholine

Dosage with Qualifiers

Myasthenia gravis—begin 5-25mg PO tid; max 200mg/d

NOTE: individualization is the norm; there is a narrow therapeutic margin.

- **Contraindications**—hypersensitivity to drug or class, atropine use
- **Caution**—asthma, bradycardia, epilepsy, hyperthyroidism, mechanical GI or urinary obstruction

Maternal Considerations

There are no adequate reports or well-controlled studies of **ambenonium** in pregnant women. The published experience consists of small series and case reports. **Ambenonium** is similar in action to **neostigmine,** but longer acting and with a lower incidence of GI side effects.
Side effects include cardiac arrest, bronchospasm, cholinergic crisis, salivation, fasciculation, headache, drowsiness, and GI abnormalities such as diarrhea and abdominal pain.

Fetal Considerations ····· There are no adequate reports or well-controlled studies in human fetuses. **Ambenonium** is not likely to cross the placenta because it is ionized at physiologic pH. However, other cholinesterase inhibitors have been associated with transient muscular weakness in the neonate.

Breastfeeding Safety ····· There is no published experience in nursing women. **Ambenonium** is not likely to be excreted into breast milk because it is ionized at physiologic pH.

Drug Interactions ····· No drug-drug interaction studies in human subjects have been conducted.

References ····· Chambers DC, Hall JE, Boyce J. Obstet Gynecol 1967; 29:597-603.

Summary ····· **Pregnancy Category: C**
Lactation Category: U
- **Ambenonium** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Amikacin—(Amikin)

International Brand Name—Akacin (Thailand); Akicin (Korea, Thailand); Akim (Ecuador); Alostil (Indonesia); Amicacina (Spain); Amicasil (Italy); Amicin (India); Amikacina (Chile); Amikafur (Mexico); Amikan (Italy); Amikayect (Mexico); Amikin (Brazil, Bulgaria, Canada, Colombia, Costa Rica, Czech Republic, Ecuador, El Salvador, England, Guatemala, Honduras, Hong Kong, Hungary, Indonesia, Ireland, Korea, Malaysia, Mexico, Nicaragua, Panama, Peru, Philippines, Poland, Singapore, Switzerland, Taiwan); Amiklin (France); Amikozit (Israel); Amiktam (Korea); Amukin (Belgium, Netherlands); Apalin (Hong Kong); Biklin (Argentina, Austria, Denmark, Finland, Germany, Philippines, Sweden, Venezuela); Biokacin (Paraguay); Briclin (Uruguay); Briklin (Greece); Chemacin (Italy); Cinmik (Philippines); Gamikal (Mexico); Glukamin (Ecuador); Kacinth-A (South Africa); Kanbine (Spain); Kormakin (Philippines); Lanomycin (Greece); Likacin (Taiwan, Thailand); Lukadin (Italy); Miacin (Israel); Nica (Philippines); Novamin (Brazil); Onikin (Philippines); Orlobin (Greece); Pediakin (Philippines); Pierami (Taiwan); Riklinak (Argentina); Savox (Taiwan); Selaxa (Greece); Selemycin (Hong Kong, Israel, Malaysia); Tybikin (Thailand); Yectamid (Mexico)

Drug Class ····· Aminoglycosides; Antibiotics

Indications ····· Short-term treatment of serious bacterial infections

Mechanism ····· A semisynthetic **kanamycin** derivative that inhibits protein synthesis by binding to the 30S ribosomal subunit

Dosage with Qualifiers ····· Bacterial infection—15mg/kg/d IM/IV divided q8-24h; max 1.5g/d
UTI—250mg IM bid

NOTE: renal dosing.

- **Contraindications**—hypersensitivity to drug or class
- **Caution**—renal dysfunction

Maternal Considerations ····· There are no adequate reports or well-controlled studies of **amikacin** in pregnant women. Pregnancy increases the maternal clearance of aminoglycosides in general. Women with normal renal function should receive a dose of **amikacin** that reflects the increased clearance.
Side effects include neuromuscular blockade, renal toxicity, auditory toxicity, rash, fever, headache, paresthesias, vomiting, eosinophilia, anemia, hypotension, and arthralgia.

Fetal Considerations ····· There are no adequate reports or well-controlled studies in human fetuses. Placental transfer of **amikacin** may be slightly higher than the β-lactams but is lower than maternal levels.

Aminoglycosides can damage the fetal kidney presumably because of delayed clearance, and irreversible failure has been reported after some aminoglycosides, but not **amikacin. Amikacin** may have less fetal renal toxicity than **gentamicin**. There is no evidence of teratogenicity or interference with fertility. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically.

Breastfeeding Safety

Amikacin is excreted into breast milk, but at low concentrations. Oral absorption is poor, suggesting little systemic risk to the neonate.

Drug Interactions

Neuromuscular blockade and respiratory paralysis are reported after parenteral injection or topical instillation, and after aminoglycosides. The possibility of these events should be considered in patients receiving anesthetics or neuromuscular blocking agents such as **tubocurarine, succinylcholine,** or **decamethonium,** or in patients receiving massive transfusions of citrate-anticoagulated blood. Calcium salts may reverse the blockade.
Systemic, oral, or topical neurotoxic or nephrotoxic agents, particularly **bacitracin, cisplatin, amphotericin B, cephaloridine, paromomycin, viomycin, polymyxin B, colistin, vancomycin,** or other aminoglycosides, should be avoided.
Potent diuretics (**ethacrynic acid** or **furosemide**) should be avoided as these by themselves may cause ototoxicity. Diuretics can also enhance aminoglycoside toxicity by altering antibiotic concentrations.

References

Bernard B, Abate M, Thielen PF, et al. J Infect Dis 1977; 135:925-32.
Mallie JP, Coulon G, Billerey C, et al. Kidney Int 1988; 33:36-44.
Zhang Y, Zhang Q, Xu Z. Zhonghua Fu Chan Ke Za Zhi 1997; 32:288-92.

Summary

Pregnancy Category: D
Lactation Category: S

- Aminoglycosides are indicated during pregnancy when the benefit outweighs the risk.

Amiloride—(Amilospare; Arumil; Midamor; Moduretic 5-50)

International Brand Name—Adco-Retic (South Africa); Add-Acten (Israel, South Africa); Ameride (Spain); Amilco (Denmark); Amil-Co (England); Amilco Mite (Denmark); Amilocomp beta (Germany); Amiloretic (South Africa); Amithiazide (Hong Kong); Amitrid (Taiwan); Amizide (Australia, Malaysia, South Africa, Taiwan); Amuretic (Israel); Apo-Amilzide (Canada, Malaysia); Betaretic (South Africa); Bildiuretic (Thailand); Hyperetic (Thailand); Kaluril (Israel); Lorinid (Indonesia); Lorinid Mite (Indonesia); Miduret (Thailand); Moduret (Canada); Moduretic (Australia, Belgium, Brazil, Czech Republic, Denmark, Ecuador, England, Finland, Germany, Greece, Hong Kong, Ireland, Italy, Mexico, Netherlands, Poland, Portugal, Sweden, Switzerland, Taiwan, Thailand); Moduretic Mite (Norway); Moure-M (Thailand); Novamilor (Canada); Rhefluin (Mexico); Sefaretic (Hong Kong); Tiaden (Taiwan); Uniretic (Israel); Yostiretic (Israel)

Drug Class

Antihypertensives; Diuretics, potassium sparing

Indications

Adjunct treatment of hypertension or CHF

Mechanism

Inhibits sodium resorption at the distal convoluted tubule, cortical collecting tubule, and collecting duct

Dosage with Qualifiers

Hypertension—5-10mg PO qd; max 20mg
CHF—5-10mg PO qd; max 20mg

Lithium-induced polyuria—5-10mg PO bid

NOTE: may be combined with ***hydrochlorothiazide****.*

- **Contraindications**—hypersensitivity to drug or class, hyperkalemia, renal insufficiency, anuria, potassium-sparing diuretic use
- **Caution**—diabetes mellitus (increases risk of hyperkalemia)

Maternal Considerations

There are no adequate reports or well-controlled studies of **amiloride** in pregnant women. The published experience is limited to the occasional case report.
Side effects include aplastic anemia, hyperkalemia, neutropenia, headache, N/V, diarrhea, muscle cramps, weakness, and cough.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. **Amiloride** crosses the placenta in modest amounts. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses 20-25× higher than the MRHD.

Breastfeeding Safety

Amiloride is concentrated in breast milk and should probably be avoided while breastfeeding.

Drug Interactions

Risk of hyperkalemia is increased when given with an ACE inhibitor, **cyclosporine,** or **tacrolimus**.
Alcohol, barbiturates, and narcotics may cause orthostatic hypotension.
May decrease the hypoglycemic effect of oral hypoglycemic agents and insulin.
May potentiate other antihypertensive drugs.
Corticosteroids, ACTH use may enhance electrolyte depletion.
May increase responsiveness to skeletal muscle relaxants and nondepolarizing agents (e.g., **tubocurarine**).
Diuretics reduce the renal clearance of **lithium** and increase the risk of **lithium** toxicity.

References

Deruelle P, Dufour P, Magnenant E, et al. Eur J Obstet Gynecol Reprod Biol 2004; 115:106-7.
Hall DR, Odendaal HJ. Int J Gynaecol Obstet 1998; 60:63-4.

Summary

Pregnancy Category: B
Lactation Category: U

- **Amiloride** is rarely required in pregnancy.
- There are alternative agents for which there is more experience during pregnancy and lactation.

Aminocaproic acid—(Amicar; Capracid; Epsikapron)

International Brand Name—Amicar (Canada, Mexico, South Africa); Capramol (France); Caproamin (Spain, Venezuela); Caprolisin (Italy); Epsicaprom (Portugal); Epsilonaminocapronsav (Hungary); Hemocaprol (Spain); Ipsilon (Argentina, Brazil, Japan, Paraguay, Uruguay); Resplamin (Japan)

Drug Class

Hemostatics

Indications

Hemorrhage associated with excess fibrinolysis (protamine test negative, euglobulin lysis test positive, and platelet count normal): e.g., placental abruption, missed abortion, cardiac surgery or cirrhosis, treatment of a megakaryocytosis, ITP, agranulocytosis, and hereditary hemorrhagic telangiectasia

Mechanism	Inhibition of plasminogen activator
Dosage with Qualifiers	Hemorrhage—typically 4-5g IV or PO over 1st hour, followed by 1g/h IV; max 30g/d • **Contraindications**—hypersensitivity to drug or class, DIC unassociated with primary fibrinolysis, hemorrhage of unknown etiology • **Caution**—renal or hepatic dysfunction, CAD
Maternal Considerations	There are no adequate reports or well-controlled studies of **aminocaproic acid** in pregnant women. It has been used in a variety of hemorrhagic circumstances. The literature consists predominantly of case reports. ***Side effects*** include seizures, acute renal failure, cardiac arrhythmias, dizziness, myopathy, myositis, rhabdomyolysis, confusion, and clotting disorders.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **aminocaproic acid** crosses the human placenta. **Aminocaproic acid** decreases implantation in a variety of animal models. Rodent teratogenicity studies have not been reported.
Breastfeeding Safety	There are no adequate reports or well-controlled studies in nursing women. It is unknown whether **aminocaproic acid** enters human breast milk.
Drug Interactions	No drug-drug interaction studies in human subjects have been conducted.
References	Landers DF, Newland M, Penney LL. J Reprod Med 1989; 34:988-93. Neubert AG, Golden MA, Rose NC. Obstet Gynecol 1995; 85:831-3. Peng TC, Kickler TS, Bell WR, Haller E. Am J Obstet Gynecol 1991; 165:425-6.
Summary	**Pregnancy Category: C** **Lactation Category: U** • **Aminocaproic acid** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk. • Consideration should be given to the availability of alternative therapies when possible.

Aminoglutethimide—(Cytadren)

International Brand Name—Cytadren (Australia); Orimeten (Argentina, Austria, Belgium, Brazil, Bulgaria, Chile, China, Czech Republic, Egypt, England, Finland, Germany, Hungary, Ireland, Italy, Netherlands, Norway, Poland, Portugal, Spain, Sweden, Switzerland); Orimetene (France, Greece, Hong Kong, Malaysia, Taiwan)

Drug Class	Adrenal corticosteroid inhibitors
Indications	Suppression of adrenal function in women with Cushing's disease until definitive treatment can be undertaken
Mechanism	Inhibits multiple steps in steroid synthesis, including the C-11-, C-18-, and C-21-hydroxylases, thus diminishing the conversion of cholesterol to δ^5-pregnenolone

Dosage with Qualifiers

Cushing's disease—begin 250mg PO qid under hospitalized supervision; adjust until the desired cortisol level is reached (>2g/d not recommended)

- **Contraindications**—hypersensitivity to drug or class
- **Caution**—may suppress aldosterone, leading to hypotension (orthostatic or persistent)

Maternal Considerations

There are no adequate reports or well-controlled studies of **aminoglutethimide** in pregnant women. **Aminoglutethimide** may cause adrenocortical hypofunction, especially under stressful conditions. Patients should be treated with **hydrocortisone** (not **dexamethasone**) and a mineralocorticoid. **Aminoglutethimide** is also used to treat women with estrogen-sensitive breast cancer.
Side effects include all manifestations of adrenal insufficiency, neutropenia, agranulocytosis, headache, vomiting, and rash.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. Pseudohermaphroditism is observed in about 2/5000 pregnancies treated with **aminoglutethimide**. Rodent studies revealed embryotoxicity and teratogenicity at doses smaller than those usually recommended for humans.

Breastfeeding Safety

There is no published experience in nursing women. It is unknown whether **aminoglutethimide** enters human breast milk.

Drug Interactions

Aminoglutethimide accelerates **dexamethasone** metabolism. **Aminoglutethimide** diminishes the effect of **coumarin** and **warfarin**.

References

No current relevant references.

Summary

Pregnancy Category: D
Lactation Category: U

- **Aminoglutethimide** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Aminophylline—(Aminophylline; Drafilyn ''Z''; Inophyline; Norphyl; Novphyllin; Somophylin; Synthophyllin; Theourin; Truphylline)

International Brand Name—Aminofilina (Ecuador, Guatemala); Aminomal (Czech Republic, Italy); Anephyllin (Japan); Asiphylline (Taiwan); Asthcontin (Korea); Cardiomin (Chile); Drafilyn ''Z'' (Mexico); Eufilin (Brazil); Eufilina (Spain); Eufilina Mite (Portugal); Euphyllin (Austria, Belgium, Bulgaria, Czech Republic, Finland, Germany, Netherlands, Norway); Kyophyllin (Japan); Neophyllin (Malaysia, Singapore); Pediatric Asthcontin for Children SR (Korea); Peterphyllin (South Africa); Phyllocontin (Canada, England, Ireland, Taiwan); Phyllotemp (Germany, Greece); Tefamin (Italy); Teofylamin (Denmark); Unifilin (Brazil)

Drug Class

Antiasthmatics; Bronchodilators; Xanthine derivatives

Indications

Relief and prevention of symptoms of asthma and/or reversible bronchospasm

Mechanism

Unknown; phosphodiesterase inhibitor that increases cAMP

Dosage with Qualifiers

Bronchospasm—0.3-0.8mg/kg/h IV preceded by a variety of recommended loading doses (0.3-6mg/kg over 12h IV); alternatively 10-16mg/kg/d PO

NOTE: see a pharmacologic reference for specific guidance. Serum levels should be periodically monitored and maintained between 10 and 20mcg/ml.

- **Contraindications**—hypersensitivity, seizure disorder, peptic ulcer disease, cardiac arrhythmia
- **Caution**—renal or hepatic dysfunction, CHF

Maternal Considerations

Aminophylline is a mixture of theophylline and theophylline base. Approximately ⅓ of pregnant women with asthma get worse, ⅓ get better, and ⅓ remain clinically unchanged. Well-controlled asthma does not affect pregnancy outcome; uncontrolled asthma may increase the risk of IUGR and preterm delivery. There are no adequate reports or well-controlled studies of **aminophylline** in pregnant women, but there is a long clinical experience. Clearance and the volume of distribution appear increased by pregnancy. IV **aminophylline** is not recommended unless the patient requires hospitalization. Even then, randomized trials suggest it provides no benefit over inhaled steroids. Uterine blood flow, as reflected by Doppler flow, is unaffected. Drug interactions are common and should be sought before prescribing.
Side effects include seizures, respiratory arrest, arrhythmias, N/V, insomnia, headache, fever, agitation, tremor, and tachycardia.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. **Aminophylline** crosses the human placenta rapidly, reaching an F:M ratio approaching unity. While there is no substantive evidence in humans, teratogenicity and embryotoxicity are reported in rats and rabbits at doses that exceed the MRHD by 20-50×. This effect is dose dependent. The proconvulsant effect of **aminophylline** on cortical epileptic after-discharges varies during ontogeny. Recently, it was suggested that the combination of maternal magnesium sulfate and **aminophylline** reduced the incidence of neonatal intracranial hemorrhage in preterm neonates. This observation remains to be confirmed.

Breastfeeding Safety

Aminophylline is excreted into breast milk and may cause irritability or other signs of toxicity in nursing neonates. However, it is generally considered compatible with breastfeeding.

Drug Interactions

High-dose **allopurinol, cimetidine, ciprofloxacin, erythromycin, trolandomycin,** oral contraceptives, and **propranolol** all increase **theophylline** levels.
The combination of **theophylline** and **phenytoin** decreases serum levels of both.
Rifampin decreases serum **theophylline** levels.
Lithium increases serum **theophylline** levels.

References

Bernaskova K, Mares P. Epilepsy Res 2000; 39:183-90.
Cosmi EV, Luzi G, Fusaro P, et al. Eur J Obstet Gynecol Reprod Biol 1992; 46:7-11.
Di Renzo GC, Mignosa M, Gerli S, et al. Am J Obstet Gynecol 2005; 192:433-8.
Schatz M. Drug Saf 1997; 16:342-50.
Schatz M, Harden K, Forsythe A, et al. J Allergy Clin Immunol 1988; 81:509-17.
Shibata M, Wachi M, Kawaguchi M, et al. Methods Find Exp Clin Pharmacol 2000; 22:101-7.

Wendel PJ, Ramin SM, Barnett-Hamm C, et al. Am J Obstet Gynecol 1996; 175:150-4.

Summary

Pregnancy Category: C
Lactation Category: S

- **Aminophylline** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.
- Mild asthma is best managed during pregnancy with inhaled β2 agonists; multistep therapy for moderate asthma includes inhaled **cromolyn sodium,** inhaled **beclomethasone dipropionate,** and oral **theophylline**.

Amiodarone—(Amiodarex; Amiohexal; Amiorone; Cardarone; Cordarone; Cordarone I.V.; Rythmarone)

International Brand Name—Aldarin (South Africa); Aldarone (India); Amidodacore (Israel); Amiobeta (Germany); Amiocar (Argentina); Amiodacore (Israel); Amiodarex (Germany); Amiodarona (Chile); Amiogamma (Germany); Amiohexal (Germany); Amiorit (Colombia); Ancaron (Japan); Angiodarona (Brazil); Angoron (Greece); Aratac (Australia, Malaysia, Singapore, Taiwan, Thailand); Arycor (Colombia); Atlansil (Argentina, Brazil, Chile, Ecuador, Peru, Uruguay); Braxan (Costa Rica, El Salvador, Guatemala, Honduras, Mexico, Nicaragua, Panama); Cardinorm (Australia); Cardiorona (Mexico); Corbionax (France); Cordarex (Germany); Cordaron (Bulgaria); Cordarone (Barbados, Belgium, Bulgaria, Canada, China, Colombia, Costa Rica, Curacao, Czech Republic, Dominican Republic, Ecuador, El Salvador, Finland, France, Guatemala, Honduras, Hong Kong, Hungary, Indonesia, Italy, Korea, Malaysia, Mexico, Netherlands, Netherlands Antilles, Nicaragua, Norway, Panama, Paraguay, Peru, Philippines, Poland, Portugal, Sweden, Switzerland, Taiwan, Thailand); Cordarone X (England, India, Ireland, South Africa); Cornaron (Germany); Coronovo (Argentina); Daronal (Colombia); Diarona (Uruguay); Eurythmic (India); Forken (Mexico); Hexarone (South Africa); Kendaron (Indonesia); Miodar (Dominican Republic); Procor (Israel); Sedacoron (Austria, Hong Kong, Taiwan); Tachydaron (Germany); Tiaryt (Indonesia); Trangorex (Spain, Venezuela)

Drug Class

Antiarrhythmics, class III

Indications

Prevention and suppression of malignant ventricular and supraventricular arrhythmias, atrial fibrillation, and hypertrophic cardiomyopathy

Mechanism

Prolongs phase 3 of the action potential and noncompetitively inhibits α- and β-adrenoceptors

Dosage with Qualifiers

Ventricular arrhythmia, malignant—load 800-1600mg PO qd ×1-3w until response, then 200-600mg PO qd; alternatively, 150mg IV bolus over 10min, then 1mg/min IV ×6h, then 0.5mg/min IV for 18h
Supraventricular arrhythmia—load 800-1600mg PO qd ×1-3w until response, then 200-600mg PO qd
Atrial fibrillation—load 800-1600mg PO qd ×1-3w until response, then 200-600mg PO qd; alternatively, 300mg IV over 1h, then 20mg/kg over 24h, then 600mg PO qd ×1w, then 400 mg/d
Hypertrophic cardiomyopathy—load 800-1600mg PO qd ×1-3w until response, then 200-600mg PO qd

- **Contraindications**—hypersensitivity to drug or class, 2nd or 3rd degree heart block, severe SA node disease, bradycardia
- **Caution**—hepatic dysfunction, pulmonary disease, thyroid disease

Maternal Considerations

There are no adequate reports or well-controlled studies of **amiodarone** in pregnant women. The published experience is limited to fewer than 100 pregnancies. There are many alternatives to **amiodarone** during pregnancy.

Side effects include arrhythmias, heart failure, AV block, hepatic failure, pulmonary toxicity, N/V, fatigue, abdominal pain, anorexia, constipation, vision abnormalities, edema, peripheral neuropathy, tremor, ataxia, and dizziness.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. Placental transport occurs, but studies suggest low transfer especially when the umbilical venous pressure is elevated. **Amiodarone** has been used in isolated instances to treat a fetal arrhythmia. Among 64 pregnancies exposed to **amiodarone,** 17% of neonates had hypothyroidism (10 detected at birth, 1 *in utero*), 18% of whom had a goiter. Hypothyroidism was transient in all, though 5 were treated short-term. Neurodevelopmental assessment of the hypothyroid infants, when carried out, revealed in some instances mild abnormalities often similar to the nonverbal learning disability syndrome. These features were also reported in some **amiodarone**-exposed euthyroid infants, suggesting a direct neurotoxic effect of **amiodarone** during fetal life. Fetal hypothyroidism has been reported in **amiodarone**-resistant fetal arrhythmia.

Breastfeeding Safety

Amiodarone is excreted in breast milk at concentrations high enough to have a pharmacologic effect. The reported M:P ratio ranges from 4.6 to 13, with concentrations in women ingesting 400mg/d ranging from 2.8 to 16.4mg/L. Neonatal hypothyroidism is reported.

Drug Interactions

Amiodarone may affect the metabolism of numerous drugs, and the potential for clinical impact is real. **Amiodarone** is metabolized by CYP3A4 and CYP2C8. Protease inhibitors are known to inhibit CYP3A4 to some degree. **Cimetidine** inhibits CYP3A4 and can increase serum **amiodarone** levels. Grapefruit juice inhibits CYP3A4 metabolism of **amiodarone** by the intestinal mucosa, causing an increased plasma level. **Amiodarone** suppresses CYP1A2, CYP2C9, CYP2D6, and CYP3A4, causing unexpected high plasma levels of drugs metabolized by these CYP enzymes. Affected drugs include **cyclosporine, simvastatin, digoxin, quinidine, procainamide, phenytoin, flecainide,** β-blockers, calcium channel antagonists, and **warfarin**. Chronic (>2w) oral **amiodarone** impairs the metabolism of **phenytoin, dextromethorphan,** and **methotrexate**.
Rifampin and **St. John's wort** accelerate **amiodarone** metabolism by inducing CYP3A4.

References

Bartalena L, Bogazzi F, Braverman LE, Martino E. J Endocrinol Invest 2001; 24:116-30.
Joglar JA, Page RL. Curr Opin Cardiol 2001; 16:40-5.
Magee LA, Nulman I, Rovet JF, Koren G. Neurotoxicol Teratol 1999; 21:261-5.
McKenna WJ, Harris L, Rowland E, et al. Am J Cardiol 1983; 51:1231-3.
Plomp TA, Vulsma T, de Vijlder JJ. Eur J Obstet Gynecol Reprod Biol 1992; 43:201-7.
Pradhan M, Manisha M, Singh R, Kapoor A. Fetal Diagn Ther 2006; 21:72-6.
Schmolling J, Renke K, Richter O, et al. Ther Drug Monit 2000; 22:582-8.
Vanbesien J, Casteels A, Bougatef A, et al. J. Am J Perinatol 2001; 18:113-6.

Summary

Pregnancy Category: D
Lactation Category: NS

- **Amiodarone** should be avoided during pregnancy and lactation unless no other medical option exists.
- There are alternative agents for which there is more experience during pregnancy and lactation.

Amitriptyline—(Amicen; Amilent; Amyzol; Elavil; Larozyl; Pinsanu; Vanatrip)

International Brand Name—Adepril (Italy); Amilit (Italy); Amineurin (Germany); Amiplin (Taiwan); Amiprin (Japan); Amitrip (New Zealand); Amyline (Ireland); Amytril (Brazil); Anapsique (Mexico); Antalin (Chile); Apo-Amitriptyline (Canada); Domical (England); Elatrol (Israel); Elatrolet (Israel); Elavil (France); Enafon (Korea); Lantron (Japan); Laroxyl (France, Germany, Italy); Miketorin (Japan); Neurotol (Paraguay); Novoprotect (Germany); Pinsaun (Taiwan); Protanol (Brazil); Qualitriptine (Hong Kong); Redomex (Belgium); Sarotard (Korea); Saroten (Cyprus, Denmark, Finland, Germany, Greece, Iran, Portugal, South Africa, Sweden, Switzerland); Sarotena (India); Saroten Retard (Malaysia); Sarotex (Netherlands, Norway, Uruguay); Syneudon (Germany); Teperin (Hungary, Iraq, Jordan); Trepiline (South Africa); Tridep (India); Tripta (Malaysia, Thailand); Triptizol (Italy); Trynol (Taiwan); Tryptal (Israel); Tryptanol (Argentina, Brazil, Ecuador, Hong Kong, Japan, Malaysia, Mexico, New Zealand, Peru, South Africa, Thailand); Tryptizol (Austria, Belgium, Denmark, Egypt, England, Netherlands, Norway, Portugal, Spain, Sweden, Switzerland); Trytomer (India); Uxen (Argentina)

Drug Class

Antidepressants; Tricyclics

Indications

Depression, chronic pain, rarely headache

Mechanism

Unknown; inhibits NE and serotonin reuptake

Dosage with Qualifiers

Depression—begin 50-75mg (or 75-100mg if observed in the hospital) PO qhs, max 300mg PO qhs; alternatively, 20-30mg IM q6h
Chronic pain—begin 0.1mg/kg/d, titrate slowly over 2-3w; max 150mg

NOTE: may be combined with chlordiazepoxide or perphenazine.

- **Contraindications**—hypersensitivity to drug or class, use of an MAOI within 14d
- **Caution**—urinary retention, seizure history, glaucoma, thyroid disease, hepatic dysfunction, suicide risk

Maternal Considerations

Depression is common during and after pregnancy, but typically goes unrecognized. Pregnancy is not a reason *a priori* to discontinue psychotropic drugs. Despite the fact that pregnant women are often exposed to tricyclic agents, there are no well-controlled studies of **amitriptyline** during pregnancy. The drug is metabolized by CYP2D6, which is reduced in some Caucasians (about 7-10% of Caucasians are so-called poor metabolizers); the prevalences of poor metabolizers among Asian, black, and other populations are unclear. Poor metabolizers have higher than expected plasma concentrations when given usual doses. Thus, serum levels should be monitored during pregnancy. Although **amitriptyline** has no effect on placental blood flow in gravid sheep, the pressor response to NE, but not **phenylephrine,** is enhanced. Off-label uses include bulimia, nocturnal enuresis, panic migraine, panic disorder, and postherpetic neuralgia.
Side effects include MI, seizures, stroke, agranulocytosis, thrombocytopenia, dry mouth, drowsiness, constipation, urinary retention, blurred vision, increased appetite, and confusion.

Fetal Considerations

Both **amitriptyline** and its sib, **nortriptyline,** cross the human placenta. Though there is no causal evidence, case reports suggest CNS/limb abnormalities and developmental delay. While rodent studies are generally reassuring at doses below 10× the MRHD, studies at 10-33× the MRHD reveal CNS and facial abnormalities. Long-term effects on serotonergic receptors are postulated but not confirmed.

Breastfeeding Safety

Multiple studies reveal that, while **amitriptyline** is excreted into the breast milk, the neonatal concentrations are extremely low.

Drug Interactions

Drugs that inhibit CYP2D6 convert a normal metabolizer to a poor one. These drugs include **quinidine, cimetidine,** many other antidepressants, phenothiazines, and the type 1C antiarrhythmics such as **propafenone** and **flecainide**. SSRIs also inhibit CYP2D6 to varying degrees.

References

Heikkinen T, Ekblad U, Laine K. Psychopharmacology (Berl) 2001; 153:450-4.
Kornstein SG. J Clin Psychiatry 2001; 62(Suppl)24:11-7.
Mason BD, Van Petten GR. Am J Obstet Gynecol 1978; 131:868-71.
Wen SW, Walker M. J Obstet Gynaecol Can 2004; 26:887-92.
Wisner KL, Perel JM, Findling RL. Am J Psychiatry 1996; 153:1132-7.

Summary

Pregnancy Category: D
Lactation Category: S (likely)

- **Amitriptyline** should be used during pregnancy only if the benefit justifies the potential perinatal risk.
- As for most psychotropic drugs, using monotherapy and the lowest effective quantity given in divided doses to minimize the peaks may minimize the risks to the perinate.
- **Amitriptyline** is probably a drug of choice for breastfeeding women.

Amlodipine—(Norvasc)

International Brand Name—Amcard (India); Amdepin (South Africa); Amdipin (Colombia); Amilo (Taiwan); Amloc (Argentina, Chile); Amlocar (Peru); Amlodin (Japan); Amlodine (Taiwan); Amlopin (Korea, Poland); Amlopine (Thailand); Amlor (Belgium, France, Israel); Amlosyn (Colombia); Amlovas (Costa Rica, Dominican Republic, El Salvador, Guatemala, Honduras, Nicaragua, Panama); Amlow (Israel); Amodipin (Korea); Ampliron (Paraguay); Amze (Argentina); Anydipine (Korea); Calchek (India); Cardinor (Colombia); Duactin 5 (Israel); Eucoran (Colombia); Istin (England, Ireland); Lama (India); Lovas (Thailand); Mydopine (Israel); Normodipine (Singapore); Norvas (Colombia, Mexico, Spain); Norvasc (Austria, Canada, Chile, China, Denmark, Ecuador, Finland, Germany, Greece, Hong Kong, Hungary, Israel, Italy, Japan, Korea, Malaysia, Netherlands, Norway, Peru, Philippines, Portugal, Singapore, Sweden, Switzerland, Taiwan, Thailand, Uruguay, Venezuela); Norvask (Bulgaria, Indonesia); Novalopine (Korea); Presilam (Chile); Sinop (Argentina); Tensivask (Indonesia); Vasocal (Ecuador); Vasten (Colombia)

Drug Class

Calcium channel blockers; Dihydropyridines

Indications

Chronic hypertension, angina (chronic stable and variant)

Mechanism

Inhibits calcium ion influx into smooth muscle and myocardium

Dosage with Qualifiers

Chronic hypertension—5-10mg PO qd
Angina (chronic stable and variant)—5-10mg PO qd

*NOTE: may be combined with **benazepril,** an ACEI, or **atorvastatin,** a lipid-lowering agent.*

- **Contraindications**—hypersensitivity to drug or class
- **Caution**—unknown

Maternal Considerations	There are no well-controlled studies in women of **amlodipine** during pregnancy. Other calcium channel antagonists are used as inhibitors of myometrial contraction, and **amlodipine** has similar properties. There are no reports of its use as a tocolytic agent. ***Side effects*** include arrhythmias, headache, dizziness, fatigue, nausea, palpitations, abdominal pain, muscle cramps, and syncope.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **amlodipine** crosses the human placenta. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses 8-23× the MRHD.
Breastfeeding Safety	There is no published experience in nursing women. It is unknown whether **amlodipine** enters human breast milk.
Drug Interactions	No drug-drug interaction studies in human subjects have been conducted.
References	Lechner W, Bergant A, Solder E, Kolle D. Wien Med Wochenschr 1996; 146:466-8.
Summary	**Pregnancy Category: C** **Lactation Category: U** • **Amlodipine** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk. • There are alternative agents for which there is more experience during pregnancy and lactation.

Amobarbital—(Amybal; Amycal; Amytal Sodium; Isobec; Placidel; Sumital)

International Brand Name—None identified.

Drug Class	Anxiolytics; Barbiturates; Sedative-hypnotics
Indications	Anxiety, sedative, hypnotic
Mechanism	Barbiturate
Dosage with Qualifiers	Anxiety—1 tab PO qhs (see Note) Sedative—30-50mg PO/IM/IV bid or tid Hypnotic—65-200mg PO/IM/IV qhs (IV rate <50mg/min) *NOTE: renal and hepatic dosing; often combined with* ***secobarbital*** *(50mg/50mg or 100mg/100mg tabs).* • **Contraindications**—hypersensitivity to drug or class, hepatic dysfunction, porphyria • **Caution**—renal dysfunction, respiratory disease
Maternal Considerations	There are no adequate reports or well-controlled studies of **amobarbital** in pregnant women. ***Side effects*** include respiratory depression, apnea, dyspnea, hepatotoxicity, N/V, somnolence, agitation, confusion, ataxia, nervousness, hallucinations, nightmares, constipation, CNS depression, and insomnia.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. **Amobarbital** crosses the human placenta, achieving an F:M ratio near unity. Though there was some suggestion of a nonspecific risk of malformation in exposed offspring, subsequent studies were reassuring.

Breastfeeding Safety

There is no published experience in nursing women. It is unknown whether **amobarbital** enters human breast milk, though similar agents do.

Drug Interactions

Barbiturates decrease the anticoagulant response to most oral anticoagulants. Women stabilized on anticoagulants may require adjustment if barbiturates are added or withdrawn.
Barbiturates can enhance the metabolism of corticosteroids. Women stabilized on corticosteroids may require adjustments if barbiturates are added or withdrawn.
Barbiturates may interfere with oral absorption of **griseofulvin,** though the impact on clinical efficacy is not established. Best to avoid concomitant use.
Barbiturates shorten the doxycycline t/2 for up to 2w after their discontinuation.
The impact of barbiturates on **phenytoin** metabolism is variable. Thus, **phenytoin** and barbiturate blood levels should be monitored more frequently if given concurrently.
Valproate and **valproic acid** increase the **amobarbital** serum levels.
Other CNS depressants, including sedatives or hypnotics, antihistamines, tranquilizers, or alcohol, may produce additive depressant effects.
MAOIs prolong the effects of barbiturates.
Pretreatment with or concurrent use of **phenobarbital** may decrease the effect of **estradiol**. There are reports of women treated with **phenobarbital** who become pregnant while taking oral contraceptives. Alternate contraceptive methods should be suggested.

References

Draffan GH, Dollery CT, Davies DS, et al. Clin Pharmacol Ther 1976; 19:271-5.

Summary

Pregnancy Category: D
Lactation Category: U

- While the evidence of **amobarbital** safety during pregnancy is conflicting, alternative agents are available for all indications.

Amoxapine—(Asendin)

International Brand Name—Adisen (Korea); Amoxan (Japan); Asendin (Indonesia); Asendis (England, Ireland); Defanyl (France); Demolox (Denmark, India, Portugal, Spain)

Drug Class

Antidepressants, type 4; Tricyclics

Indications

Depression

Mechanism

Unknown; inhibits NE and serotonin reuptake

Dosage with Qualifiers

Depression—begin 50mg PO bid; max 600mg qd

- **Contraindications**—hypersensitivity to drug or class, MAOI use within 14d, acute MI
- **Caution**—unknown

Maternal Considerations

Depression is common during and after pregnancy, but typically goes unrecognized. Pregnancy is not a reason *a priori* to discontinue psychotropic drugs. There are no adequate reports or well-controlled studies of **amoxapine** use in pregnant women. There are only scattered case reports to draw upon. **Amoxapine** is similar in efficacy to **imipramine**.
Side effects include seizures, neuroleptic malignant syndrome, tardive dyskinesia, drowsiness, blurred vision, constipation, dry mouth, anxiety, palpitations, insomnia, nightmares, headache, fatigue, profuse sweating, rash, edema, galactorrhea, increased prolactin, and excessive appetite.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. Rodent studies are generally reassuring, revealing no evidence of teratogenicity. Embryotoxicity was seen at human dose levels, and fetotoxicity at multiples of the MRHD.

Breastfeeding Safety

Amoxapine is excreted in the breast milk, though the levels were <180mcg/L (<20mcg/kg/d) in one study after 250mg/kg/d, representing <20% of the maternal plasma level.

Drug Interactions

The biochemical activity of CYP2D6 (debrisoquin hydroxylase) is reduced in 7-10% of Caucasians (“poor metabolizers”). There are no reliable estimates of the poor metabolizer prevalence among Asian, African, and other populations. Poor metabolizers have higher than expected plasma concentrations of TCAs. The increase in plasma concentration varies (up to 8×) depending on the percentage of drug metabolized by CYP2D6.
The drugs that inhibit CYP2D6 include those metabolized by the enzyme (many antidepressants, phenothiazines, and the type 1C antiarrhythmics **propafenone** and **flecainide**) and those that are not (**quinidine, cimetidine**). SSRIs (e.g., **fluoxetine, sertraline, paroxetine**) inhibit CYP2D6 to a varying degree. Co-administration requires prudence.
Concomitant use of TCAs with drugs that inhibit CYP2D6 may necessitate lower doses than usually prescribed, or an increase if one of the drugs is withdrawn. Monitor tricyclic plasma levels when given with a known CYP2D6 inhibitor.

References

Gelenberg AJ. J Nerv Ment Dis 1979; 167:635-6.
Gelenberg AJ, Wojcik JD, Lydiard RB, et al. J Clin Psychiatry 1984; 45:54-9.

Summary

Pregnancy Category: C
Lactation Category: U

- There are other agents of equal efficacy, such as **imipramine,** for the treatment of depression for which there is more experience during pregnancy.

Amoxicillin—(Amoflux; Amoxiden; Amoxil; Amoxin; Amoxipenil; Amoxycillin; Anemol; Apitart; Aspenil; Audumic; Biomox; Bridopen; Excillin; Gemox; Imoxil; Jerramcil; Larotid; Limox; Pensyn; Polymox; Protexillin; Reloxyl; Ronemox; Samosillin; Samthongcillin; Senox; Sigmopen; Suprapen; Trilaxin; Trimox; Twicyl; Unicillin; Virgoxillin; Wymox; Yisulon; Zamocillin)

International Brand Name—Abdimox (Indonesia); Acilina (Paraguay); Acimox (Mexico); Acticillin (Thailand); Actimoxi (Spain); Adbiotin (Colombia); Agerpen (Spain); A-Gram (France); Alfamox (Italy); Almodan (England); Almorsan (Argentina); Amagesen Solutab (Germany); Ameclina (Mexico); Amoclen (Czech Republic); Amodex (France); Amo-flamisan (Spain); Amo-flamsian (Spain); Amoflux (Brazil); Amohexal (Australia); Amolin (Hong Kong, Japan, Taiwan); Amonex (Korea); Amophar GE (France); Amosine (Indonesia); Amoval (Peru); Amox (Italy); Amoxa (Hong Kong, Singapore); Amoxal (Colombia, Venezuela); Amoxapen (Hong Kong, Korea, Singapore); Amoxaren (Spain); Amoxcil (China); Amoxcillin (Thailand); Amoxcin (Taiwan); Amoxi (Israel); Amoxi-basan (Germany); Amoxicilina (Colombia, Ecuador); Amoxiclin (Peru); Amoxidal (Argentina, Uruguay); Amoxihexal (Germany); Amoxil (Australia, Brazil, Ecuador, England, Greece, Indonesia, Ireland, Mexico, Peru); Amoxil Duo (Australia); Amoxillin (Israel, Italy, Norway); Amoxipen (Italy, Peru); Amoxipenil (Chile); Amoxisol (Mexico); Amoxivan (India); Amoxivet (Mexico); Amoxy (Thailand); Amoxy-diolan (Germany); Amoxypen (Germany, Peru); Apo-Amoxi (Malaysia); Ardine (Mexico, Spain); Aroxin (Singapore); Azillin (Switzerland); Bacihexal (Philippines); Bactamox (Costa Rica, Dominican Republic, El Salvador, Guatemala, Honduras, Nicaragua, Panama, Venezuela); Bactox Ge (France); Beamoxy (Malaysia); Bimox (Colombia); Bintamox (Indonesia); Biotamoxal (Argentina); Bioxidona (Spain); Bioxyllin (Indonesia); Bristamox (Ecuador, France, Peru, Sweden); Broadmetz (Philippines); Cilamox (Philippines); Clamox (Finland); Clamoxyl (Austria, Belgium, France, Germany, Japan, Netherlands, Peru, Portugal, Spain, Switzerland); Clonamox (China); Coamoxin (Spain); Doxamil (Mexico); Draximox (Denmark); Edamox (Hong Kong); Efpinex (Japan); Erphamoxy (Indonesia); Eupen (Dominican Republic, El Salvador, Guatemala, Honduras, Nicaragua, Panama, Spain); Flemoxin (China); Flemoxine Ge (France); Foxolin (Korea); Fullcilina (Argentina); Gexcil (Philippines); Gimalxina (Mexico); Gomcillin (Korea); Grinsul (Argentina); Grunamox (Ecuador); Hamoxillin (Hong Kong); Hiconcil (Belgium, Bulgaria, France, Indonesia, Israel, Netherlands); Hidramox (Mexico); Hosboral (Spain); Ibiamox (Australia, Israel, Taiwan, Thailand); Ikamoxil (Indonesia); Imacillin (Denmark, Norway, Sweden); Imaxilin (Colombia); Inamox (Indonesia); Intermox (Philippines); Isimoxin (Italy); Julphamox (Peru); Jutamox (Germany); Kamoxin (Thailand); Ladoxillin (Philippines); Lamoxy (India); Larocilin (Argentina); Macromox (Philippines); Magnimox (Peru); Maxamox (New Zealand); Maxcil (South Africa); Medimox (Indonesia); Meixil (Thailand); Mopen (Italy); Morgenxil (Spain); Mox (India); Moxacin (New Zealand); Moxaline (Belgium); Moxilen (Hong Kong, Malaysia, Singapore, Taiwan); Moximar (Philippines); Moxitab (Thailand); Moxtid (Indonesia); Moxylin (Ecuador); Moxypen (Israel, South Africa); Moxyvit (Israel); Neogram (Colombia); Novabritine (Belgium); Novamox (Philippines); Novamoxin (Canada); Novenzymin (Argentina); Novoxil (Brazil); Optium (Argentina); Ospamox (Austria, Bulgaria, Costa Rica, Dominican Republic, El Salvador, Germany, Guatemala, Honduras, Hong Kong, Indonesia, Malaysia, New Zealand, Nicaragua, Panama, Peru, Portugal, Uruguay); Pamocil (Italy); Pamoxicillin (Taiwan); Pamoxin (Korea); Panvilon (Philippines); Pasetocin (Japan); Penamox (Argentina, China, Mexico, Peru); Penbiosyn (Philippines); Pondnoxcill (Thailand); Rancil (Thailand); Ranmoxy (South Africa); Ranoxil (Thailand); Ranoxyl (Malaysia); Robamox (Indonesia); Rocillin (South Africa); Romoxil (Philippines); Ronemox (India); Saltermox (South Africa); Sawacillin (Japan); Sawamezin (Japan); Servamox (Taiwan); Shamoxil (Israel); Sia-mox (Thailand); Sil-A-mox (Thailand); Simoxil (Italy); Solpenox (Indonesia); Superpeni (Spain); Teramoxyl (Philippines); Tolodina (Spain); Tormoxin (Republic of Yemen); Triafamox (Argentina); Triamoxil (Argentina); Trifamox (Argentina, Paraguay); Trimox (Thailand); Vastamox (Philippines); Velamox (Peru); Vistrep (Philippines); Widecillin (Indonesia); Winpen (South Africa); Xiltrop (Indonesia); Zamox (Colombia); Zamoxil (Malaysia); Zerrsox (Philippines); Zimox (Italy)

Drug Class	Antibiotics; Penicillins
Indications	Gram-positive and -negative infection (systemic, venereal, endocarditis)
Mechanism	Bactericidal; inhibits biosynthesis of cell wall mucopeptide
Dosage with Qualifiers	Bacterial infection—250-500mg PO tid, or 500-750mg PO bid Gonorrhea, uncomplicated—3g PO ×1 *Chlamydia trachomatis*—500mg PO tid ×7d Endocarditis prophylaxis—2g PO ×1, 0.5-1h prior to the procedure

H. pylori infection—1g PO bid ×10-14d (combined with **clarithromycin** and **lansoprazole** or **omeprazole**).

NOTE: adjust for CrCl: if 10-30ml/min, administer q12h; if <10ml/min, administer q24h.

- **Contraindications**—hypersensitivity to drug or class
- **Caution**—CMV or EBV infection, renal dysfunction, cephalosporin allergy, PKU

Maternal Considerations

Similar to **ampicillin, amoxicillin** is generally considered safe during pregnancy. It provides a >90% cure rate for *Chlamydia*, and is the most cost-effective treatment followed by a single 1g dose of **azithromycin** for nonresponders.
Side effects include thrombocytopenia, agranulocytosis, anaphylaxis, leukopenia, anemia, Stevens-Johnson syndrome, seizures, hepatotoxicity, N/V, diarrhea, rash, urticaria, and eosinophilia.

Fetal Considerations

Amoxicillin crosses the placenta and may reach therapeutic levels in the fetus and AF after maternal administration. It is generally considered safe for the fetus. There are no reports of associated defects, and rodent studies are reassuring.

Breastfeeding Safety

Amoxicillin is excreted into the breast milk in low concentrations, but is generally considered safe during lactation.

Drug Interactions

Probenecid decreases the renal tubular secretion of **amoxicillin**. **Chloramphenicol,** macrolides, sulfonamides, and tetracyclines may interfere with the bactericidal effects of penicillin *in vitro.*

References

Edwards RK, Locksmith GJ, Duff P. Obstet Gynecol 2000; 96:60-4.
Hueston WJ, Lenhart JG. Arch Fam Med 1997; 6:551-5.
Jacobson GF, Autry AM, Kirby RS, et al. Am J Obstet Gynecol 2001; 184:1352-4.
Miller JM, Martin DH. Drugs 2000; 60:597-605.

Summary

Pregnancy Category: B
Lactation Category: S

- There are no current concerns with **amoxicillin** use in appropriately selected pregnant women.

Amoxicillin-clavulanate potassium—(Amoclan; Amoclav; Augmentin)

International Brand Name—Aclam (Indonesia); Ambilan (Peru); Amocla (Korea); Amocla Duo (Korea); Amoclan (Israel, Korea); Amoclav (Germany); Amolanic (Korea); Amolanic Duo (Korea); Amometin (Korea); Amoxiclav (Mexico); Amoxiclav-BID (Mexico); Amoxiclav-Teva (Israel); Amoxi Plus (Paraguay); Amoxsiklav (Thailand); Amoxsiklav 3X (Thailand); Amoxsiklav Forte (Thailand); Amoxxlin (Korea); Ancla (Indonesia); Auclatin Duo Dry Syrup (Korea); AugMaxcil (South Africa); Augmentan (Germany); Augmentin (China, Costa Rica, Dominican Republic, Ecuador, El Salvador, Guatemala, Honduras, Hong Kong, India, Japan, Korea, Malaysia, Nicaragua, Panama, Peru, Thailand, Uruguay, Venezuela); Augmentine (Spain); Augmex (Singapore); Augpen (Thailand); Augucillin Duo (Korea); Augurcin (Philippines); Ausclav (Australia); Ausclav Duo 400 (Australia); Ausclav Duo Forte (Australia); Auspilic (Indonesia); Bactiv (Philippines); Bactoclav (Philippines); Bioclavid (Germany, Philippines); Bioclavid Forte (Philippines); Cavumox (Thailand); Clacillin Duo Dry Syrup (Korea); Clamax (Korea); Clamentin (South Africa); Clamobit (Indonesia); Clamonex (Korea, Singapore); Clamovid (Hong Kong, Malaysia, Singapore); Clamoxin (Mexico); Clamoxyl (Australia); Clamoxyl Duo 400 (Australia); Clamoxyl DuoForte (Australia); Clarin-Duo (Korea); Clavamox (Israel); Clavinex (Chile, Ecuador, Peru); Clavoxil (Brazil); Clavoxilin Plus (Peru); Clavulin (Canada, Colombia, Costa Rica, Dominican Republic, El Salvador, Guatemala, Honduras, Nicaragua, Panama, South Africa); Clavulin Duo Forte (Australia); Clavulox Duo (Argentina, Paraguay); Clavumox (Germany, Peru, South Africa); Cramon Duo (Korea); Croanan Duo Dry Syrup (Korea); Curam (Australia, Colombia, Costa Rica, Dominican Republic, El Salvador, Guatemala, Malaysia, Nicaragua, Panama, Peru, Singapore, Taiwan, Thailand); Danoclav (Indonesia); Darzitil Plus (Argentina); E-Moxclav (Israel); Enhancin (Philippines, Singapore); Fleming (Hong Kong); Fugentin (Singapore); Fulgram (Dominican Republic, El Salvador, Guatemala, Honduras, Nicaragua, Panama); Fullicilina Plus (Argentina); Gumentin (Korea); Hibiotic (Israel); Inciclav (Indonesia); Klamonex (Korea); Kmoxilin (Korea); Lactamox (Korea); Lansiclav (Indonesia); Moxiclav (Israel, Singapore); Moxicle (Korea); Moxyclav (South Africa); Natravox (Philippines); Novamox (Brazil); Nufaclav (Indonesia); Palentin (Indonesia); Quali-Mentin (Hong Kong); Ranclav (South Africa, Thailand); Suplentin (Philippines); Synermox (New Zealand); Velamox CL (Peru); Vestaclav (Malaysia); Viaclav (Indonesia); Vulamox (Colombia); Xiclav (Indonesia)

Drug Class ····· Antibiotics; β-Lactamase inhibitors; Penicillins

Indications ····· Gram-positive and -negative infection (systemic, venereal, endocarditis) with sensitive bacteria; preterm PROM

Mechanism ····· Bactericidal; inhibits biosynthesis of cell wall mucopeptide. **Clavulanate** extends the antibiotic spectrum to include bacteria normally resistant to **amoxicillin**.

Dosage with Qualifiers ····· Bacterial infection—250-500mg PO tid, or 500-875mg PO bid
Preterm PROM—250mg/125mg (**amoxicillin/clavulanate**) PO qid ×10d or delivery
Gonorrhea, uncomplicated—3g PO ×1
Chlamydia trachomatis—500mg PO tid ×7d
Endocarditis prophylaxis—2g PO ×1, 0.5-1h prior to the procedure
H. pylori infection—1g PO bid ×10-14d (combined with **clarithromycin** and **lansoprazole** or **omeprazole**)

NOTE: adjust for CrCl: if 10-30ml/min, administer q12h; if <10ml/min, administer q24h.

- **Contraindications**—hypersensitivity to drug or class, Augmentin-associated hepatic dysfunction
- **Caution**—CMV or EBV infection, hepatic or renal dysfunction, cephalosporin allergy, PKU

Maternal Considerations ····· Oral **amoxicillin** is poorly absorbed during labor. **Amoxicillin-clavulanate** does not improve treatment of preterm labor and intact membranes. While **amoxicillin-clavulanate** is associated with prolongation of the latency interval after PPROM, there is a greater risk of necrotizing enterocolitis compared to either placebo or **erythromycin**. Thus, **erythromycin** is preferred for this indication. The incidence of maternal infectious complications is reduced by most antibiotic regimens. More recently, **amoxicillin-clavulanate** has been used as part of a

multidrug regimen to treat drug-resistant tuberculosis during pregnancy. (See **amoxicillin**.)
Side effects include thrombocytopenia, agranulocystosis, anaphylaxis, leukopenia, anemia, Stevens-Johnson syndrome, seizures, hepatotoxicity, N/V, diarrhea, rash, urticaria, and eosinophilia.

Fetal Considerations

Amoxicillin-clavulanate is unassociated with malformation in animal and human studies. However, the numbers of human studies are limited. **Amoxicillin-clavulanate** use may increase the risk of necrotizing enterocolitis when used for prophylaxis in women with PPROM. (See **amoxicillin**.)

Breastfeeding Safety

This class of drug is excreted in milk, but no adverse effects are reported.

Drug Interactions

Probenecid decreases the renal tubular secretion of **amoxicillin**. **Chloramphenicol,** macrolides, sulfonamides, and tetracyclines may interfere with the bactericidal effects of penicillin *in vitro*. All broad-spectrum antibiotics may reduce the efficacy of oral contraceptives.

References

Czeizel AE, Rockenbauer M, Sorensen HT, Olsen J. Eur J Obstet Gynecol Reprod Biol 2001; 97:188-92.
Kenyon SL, Taylor DJ, Tarnow-Mordi W, ORACLE Collaborative Group. Lancet 2001; 357:979-94.
Takashima T, Danno K, Tamura Y, et al. Kekkaku 2006; 81:413-8.

Summary

Pregnancy Category: B
Lactation Category: S

- **Amoxicillin-clavulanate** does not increase the rate of successful tocolysis in women with preterm labor and intact membranes.
- While **amoxicillin-clavulanate** prolongs the latency interval after PPROM, it may be associated with an increased risk of necrotizing enterocolitis. **Erythromycin** is preferred for this indication.

Amphetamine-dextroamphetamine—(Adderall)

International Brand Name—None identified.

Drug Class

Adrenergic agonists; Amphetamines; Anorexiants; CNS stimulants

Indications

ADD, narcolepsy

Mechanism

Unknown

Dosage with Qualifiers

ADD—2.5mg PO qam; increase by 2.5mg qw until satisfactory effect; alternatively, 10mg time-release PO qam, or 5mg PO immediate-release qam up to bid
Narcolepsy—5-60mg PO qam
Obesity—5mg PO qam

- **Contraindications**—hypersensitivity to drug or class, moderate to severe hypertension, hyperthyroidism, substance abuse, glaucoma, MAO inhibitor use <14d, symptomatic CV disease
- **Caution**—psychosis, mild hypertension, tics

Maternal Considerations

Amphetamines are noncatecholamine sympathomimetic amines with both peripheral and CNS activities. There are no adequate reports or well-controlled studies of **amphetamine-dextroamphetamine** in pregnant women. **Methamphetamine** is metabolized to **amphetamine. Amphetamine** dependency is associated with preterm delivery. With perhaps the exception of narcolepsy, **amphetamines** should rarely be used during pregnancy.

Side effects include cardiomyopathy, tachycardia, tremor, psychosis, dependency, headache, hypertension, dizziness, dry mouth, dyspepsia, constipation, abdominal pain, anorexia, weight loss, mood lability, asthenia, diarrhea, and urticaria.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. Infants born to **amphetamine**-dependent women show signs of withdrawal, suggesting placental transfer. **Amphetamine** is associated with an increased prevalence of IUGR. It is embryotoxic and teratogenic in some rodents when given at high doses. Case-control studies do not reveal a pattern of teratogenicity, though scattered case reports list various defects associated with 1st trimester usage. Antenatal **amphetamine** exposure is associated with aggressive behavior and delayed development in children under 14y of age.

Breastfeeding Safety

Amphetamine is concentrated in human breast milk and generally considered incompatible with breastfeeding.

Drug Interactions

GI acidifying agents such as **guanethidine, reserpine, ascorbic acid,** and fruit juices lower absorption.

Urinary acidifiers such as **ammonium chloride** increase urinary excretion, while urinary alkalinizers such as **acetazolamide** and some thiazides decrease urinary excretion. Co-administration should be avoided.

Adrenergic receptor antagonists are inhibited by **amphetamines**.

GI alkalinizing agents such as **sodium bicarbonate** increase the absorption of **amphetamines**. Co-administration should be avoided.

May enhance the effects of tricyclics or sympathomimetics. Co-administration with **desipramine** or **protriptyline** and possibly other tricyclics causes sustained increases in the brain concentration of **amphetamine** and potentiates the CV effects.

MAOIs slow **amphetamine** metabolism, increasing its effect on the neuronal release of NE and other monoamines, causing headaches and other signs of hypertensive crisis.

Chlorpromazine blocks dopamine and NE receptors, inhibiting the central stimulant effects of **amphetamine**. It is used to treat **amphetamine** poisoning.

Haloperidol blocks dopamine receptors, inhibiting the central stimulant effects of **amphetamine**.

Potentiates the analgesic effect of **meperidine**.

Enhances the adrenergic effect of **norepinephrine**.

May delay intestinal absorption of **phenobarbital** and **phenytoin;** co-administration may generate a synergistic anticonvulsant action.

References

Eriksson M, Jonsson B, Steneroth G, Zetterstrom R. Scand J Publ Health 2000; 28:154-7.

Smith LM, LaGasse LL, Derauf C, et al. Pediatrics 2006; 118:1149-56.

Steiner E, Villen T, Hallberg M, Rane A. Eur J Clin Pharmacol 1984; 27:123-4.

Summary	**Pregnancy Category: C** **Lactation Category: NS** • This schedule II drug is rarely indicated in reproductive-age women and should be avoided. • Dependent women should be counseled and enrolled in detoxification programs.

Amphotericin B—(Abelcet; AmBisome; Amphocin; Amphotec; Fungilin; Fungizone IV; Fungizone Topical)

International Brand Name—Amfostat (Argentina); Ampho-Moronal (Germany); Amphotec (Argentina); Fungizon (Brazil, Chile); Fungizone (Canada, China, France, India, Kenya, Nigeria, Peru, South Africa, Tanzania)

Drug Class	Antifungals
Indications	Systemic fungal infection
Mechanism	Binds to cell wall sterols, changing membrane permeability
Dosage with Qualifiers	Systemic fungal infection—aspergillosis, 3-4mg/kg/d IV, max 7.5mg/kg/d; systemic candidiasis, 3.9-6mg/kg/d IV *NOTE: also available coupled to liposomes (AmBisome) or cholesteryl (Amphotec).* • **Contraindications**—hypersensitivity to drug or class • **Caution**—renal dysfunction
Maternal Considerations	There are no adequate reports or well-controlled studies of **amphotericin** in pregnant women. It remains the drug of choice for systemic, invasive mycotic infections, whether life-threatening or less severe. **Amphotericin** has been used extensively during pregnancy without increased risk of complications. Unfortunately little if any information is available regarding the safety of the newer lipid formulations. It has also been used for the treatment of meningoencephalitis. ***Side effects*** include seizures, ventricular arrhythmias, asystole, hemorrhagic gastroenteritis, renal failure, thrombocytopenia, agranulocytopenia, hepatic dysfunction, chills, fever, hypertension, N/V, headache, anorexia, diarrhea, and rash.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. **Amphotericin** crosses the human placenta and is deposited in the fetal tissues. Therapeutic levels are found in fetal tissues weeks after cessation. There are no reports of teratogenicity. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically.
Breastfeeding Safety	There is no published experience in nursing women. It is unknown whether **amphotericin** enters human breast milk.
Drug Interactions	Antineoplastic agents may enhance renal toxicity, bronchospasm, and hypotension. Corticosteroids and ACTH may potentiate **amphotericin B**–induced hypokalemia and predispose to cardiac dysfunction. Avoid concomitant use.

Amphotericin B–induced hypokalemia may potentiate **digoxin** toxicity. Serum potassium levels and cardiac function should be monitored closely.
Imidazoles (e.g., **ketoconazole, miconazole, clotrimazole, fluconazole**) may induce fungal resistance to **amphotericin B** when used concurrently. Administer with caution, especially in immunocompromised patients.
Amphotericin B–induced hypokalemia may enhance the curariform effect of skeletal muscle relaxants (e.g., **tubocurarine**). Serum potassium levels should be monitored.

References

Dean JL, Wolf JE, Ranzini AC, Laughlin MA. Clin Infect Dis 1994; 18:364-8.
Ellinoy BR. Am J Obstet Gynecol 1973; 115:285-6.
Sobel JD. Drug Saf 2000; 23:77-85.

Summary

Pregnancy Category: B
Lactation Category: U

- A body of case reports indicates that **amphotericin B** remains the drug of choice for systemic, invasive mycotic infections, whether life-threatening or less severe.

Ampicillin—(Adumic; Amblosin; Ampen; Ampesid; Ampibel; Ampicillin; Ampiclox; Ampikel; Ampil; Ampisol; Austrapen; Bionacillin; Cinpillin; Copharcilin; Cryocil; Doktacillin; Fortapen; Herpen; Ingacillin; Isocillin; Marcillin; Nelpicil; Pentrex; Pfizerpen; Principen; Protexillin; Resan; Statcillin; Tampicillin; Tokiocillin; Totacillin; Trilaxan; Ukapen; Vialicina)

International Brand Name—Aldribid (Philippines); Aletmicina (Argentina); Ambiopi (Indonesia); Amcillin (Indonesia, Thailand); Amfipen (England, Ireland); Amipenix (Japan); Ampecu (Ecuador); Ampen (Venezuela); Ampenolet (Greece); Ampex (Indonesia); Ampexin (Malaysia); Ampibex (Colombia); Ampiblan (Colombia); Ampicher (Ecuador); Ampicil (Brazil); Ampicilina (Ecuador); Ampicin (Canada, Philippines); Ampiclox (Singapore); Ampicyn (Taiwan); Ampifen (Netherlands); Ampiflex (Peru); Ampiger (Brazil); Ampilin (India); Ampillin (Malaysia); Ampimedin (Paraguay); Ampipen (India, South Africa); Ampitenk (Argentina); Ampivral (Colombia); Amplibin (Peru); Ampliblan (Colombia); Amplivacil (Philippines); Ampolin (Taiwan); Amsapen (Mexico); Anglopen (Mexico); Apo-Ampi (Canada); Binotal (Austria, Brazil, Colombia, Ecuador, Germany, Mexico, Peru, Uruguay); Biocil (Malaysia); Bremcillin (Indonesia); Bridopen (Philippines); Britapen (Spain); Cimexillin (Switzerland); Citicil (Italy); Clovillin (Philippines); Deripen (Ecuador); Dhacillin (Hong Kong, Malaysia); Diferin (Mexico); Doltirol (Argentina); Dotirol (Peru); Duacillin (Malaysia); Eracillin (Thailand); Eurocin (Philippines); Excillin (Philippines); Gramcil (Philippines); H-Ambiotico (Colombia); Hostes (Argentina); Ibimycin (Australia); Ikacillin (Indonesia); Intramed (South Africa); Iwacillin (Japan); Jenampin (Germany); Julphapen (Peru); Magnapen (Peru); Marticil (Philippines); Maxipen (Colombia); Mecil-N (Philippines); Novo-Ampicillin (Canada); Nuvapen (Spain); Omnipen (Ecuador, Mexico, Peru); Pamecil (Hong Kong, Malaysia, Singapore); Panacta (Philippines, Singapore); Penbritin (Belgium, Ecuador, England, Hong Kong, Indonesia, Ireland, Malaysia, Mexico, Peru, Philippines, South Africa); Penodil (Hong Kong); Penstabil (Germany); Pentrexyl (Belgium, Denmark, Ecuador, England, Greece, Hong Kong, Israel, Mexico, Peru, Taiwan, Thailand); Petercillin (South Africa); Picylin (Colombia); Polypen (Philippines); Pricillin (Singapore); Primapen (Indonesia); Roscillin (India); Semicillin (Hungary); Servicillin (Ecuador); Shacillin (Israel); Sintelin (Peru); Standcillin (Malaysia); Synthocilin (India); Tolimal (Argentina); Totapen (France); Tricil (South Africa); Trifalicina (Argentina); Trihypen (Thailand); Trilaxin (Philippines); Usampi (Bulgaria); Vacillin (Thailand); Viccillin (Indonesia); Vidopen (England, Ireland); Virucil (Colombia); Vitapen (Israel)

Drug Class

Antibiotics; Penicillins

Indications

GBS and endocarditis prophylaxis, treatment of susceptible gram-positive and -negative organisms

Mechanism

Bactericidal by the inhibition of cell wall mucopeptide synthesis

Dosage with Qualifiers

GBS prophylaxis—2g IV load, then 1-2g IV q4h at least 4h prior to delivery
Endocarditis prophylaxis—2g IV/IM ×1 (give 30min prior to procedure)
Endocarditis treatment—12g IV qd
Bacterial infection—250-500mg PO q6h (max 14g/d), or 0.5-2g IV/IM q6h
Bacterial meningitis—2g IV loading dose, then 1-2g IV q4-6h
Cesarean section prophylaxis—2g IV after umbilical cord clamping
Gonorrhea—3.5g PO with 1g probenecid

- **Contraindications**—hypersensitivity to drug or drug class, pseudomembranous colitis
- **Caution**—EBV and CMV infection, penicillin or cephalosporin allergy, renal dysfunction

Maternal Considerations

Well absorbed orally except during labor, **ampicillin** is one of the most commonly used antibiotics during pregnancy. In addition to the noted indications, **ampicillin** was used without success in combination with tocolytic agents to delay or avoid preterm delivery. In comparison to nonpregnant women, pregnancy significantly increases the **ampicillin** elimination rate constant and total body clearance and decreases the serum t/2 and AUC. As a result, the dose during pregnancy should be increased and the interval decreased. **Ampicillin** clearance is reduced by pyelonephritis and rises with successful treatment. This suggests the dosing interval should be reduced from 6h to 4h after the first 24h of therapy. When combined with **sulbactam, ampicillin** significantly prolongs the latency interval between rupture and delivery. **Ampicillin** alone is less effective.
Side effects include seizures, thrombocytopenia, agranulocytosis, Stevens-Johnson syndrome, interstitial nephritis, hemolytic anemia, N/V, diarrhea, headache, confusion, eosinophilia, and rash.

Fetal Considerations

There is a wide body of clinical experience with **ampicillin** during pregnancy. There is no evidence of teratogenicity in either humans or rodents. Throughout pregnancy, fetal drug levels reach maternal equilibrium 1-3h after administration; thereafter, fetal drug levels exceed maternal values. AF levels are low during early pregnancy, but rise with advancing gestation and may exceed maternal values 6-8h after drug administration.

Breastfeeding Safety

Minimal amounts of **ampicillin** are excreted in breast milk. It is generally considered compatible with breastfeeding.

Drug Interactions

Probenecid decreases the renal tubular secretion of **ampicillin,** increasing the plasma concentration.
Chloramphenicol, macrolides, sulfonamides, and tetracyclines may interfere with the bactericidal effects of penicillin *in vitro.*

References

Akhtamova ZM, Kholodov LE, Dorokhov VV, et al. Antibiot Med Biotekhnol 1985; 30:228-32.
Chamberlain A, White S, Bawdon R, et al. Am J Obstet Gynecol 1993; 168:667-73.
Czeizel AE, Rockenbauer M, Sorensen HT, Olsen J. Am J Obstet Gynecol 2001; 185:140-7.
Kenyon SL, Taylor DJ, Tarnow-Mordi W, ORACLE Collaborative Group. Lancet 2001; 357:979-94.

Lewis DF, Fontenot MT, Brooks GG, et al. Obstet Gynecol 1995; 86:392-5.
Nau H. Dev Pharmacol Ther 1987; 10:174-98.
Spinnato JA, Youkilis B, Cook VD, et al. J Matern Fetal Med 2000; 9:348-50.
Zhang Y, Zhang Q, Xu Z. Zhonghua Fu Chan Ke Za Zhi 1997; 32:288-92.

Summary

Pregnancy Category: B
Lactation Category: S

- **Ampicillin** appears safe and effective for use during pregnancy and lactation when indicated.
- **Ampicillin** is as effective for post-cesarean prophylaxis as other, broader spectrum agents.

Ampicillin-sulbactam sodium—(Ubacillin; Unasyn)

International Brand Name—Ampibactam (Korea); Ampibactan (Venezuela); Ansulina (Taiwan); Bactacin (Korea); Cinam (Indonesia); Combicid (Thailand); Dibacin (Korea); Picyn (Indonesia); Prixin (Paraguay); Rukasyn (Korea); Sulam (Thailand); Sulbacin (India, Korea); Sultamicilina (Argentina); Ubacillin (Korea); Ubactam (Korea); Unacid (Germany, Switzerland); Unacim (France); Unasyn (Austria, Brazil, Chile, China, Colombia, Costa Rica, Czech Republic, Ecuador, El Salvador, Guatemala, Honduras, Hong Kong, Hungary, Indonesia, Italy, Korea, Malaysia, Nicaragua, Panama, Peru, Philippines, Spain, Taiwan, Thailand); Unasyna (Argentina, Mexico, Uruguay)

Drug Class

Antibiotics; Penicillins

Indications

Bacterial infection secondary to susceptible gram-positive and -negative organisms

Mechanism

Bactericidal by the inhibition of cell wall mucopeptide synthesis. Coupling to the β-lactamase inhibitor sulbactam enhances the spectrum of coverage.

Dosage with Qualifiers

Bacterial infection—1.5-3g IV/IM q6h; max 8g/d

NOTE: renal dosing.

- **Contraindications**—hypersensitivity to drug or drug class
- **Caution**—EBV and CMV infection, penicillin or cephalosporin allergy, renal dysfunction

Maternal Considerations

Ampicillin-sulbactam is a reasonable selection for prophylaxis in women undergoing cesarean section. **Ampicillin** does not prolong the latency interval after PPROM unless paired with **sulbactam**. In comparison to nonpregnant women, pregnancy significantly increases the **ampicillin** elimination rate constant and total body clearance and decreases the serum t/2 and AUC. As a result, the dose during pregnancy should be increased and the interval decreased. **Ampicillin** clearance is reduced by pyelonephritis and rises with successful treatment. This suggests the dosing interval should be reduced from 6h to 4h after the first 24h of therapy. ***Side effects*** include vaginitis, seizures, thrombocytopenia, agranulocytosis, leukopenia, anemia, Stevens-Johnson syndrome, interstitial nephritis, toxic epidermal necrosis, hemolytic anemia, N/V, diarrhea, headache, confusion, eosinophilia, and rash.

Fetal Considerations

Ampicillin-sulbactam reduces neonatal infectious morbidity after PPROM, but to no greater extent than **erythromycin,** which also prolongs the latency interval. There is no substantive evidence of teratogenicity. Rodent studies are reassuring, revealing no

evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically.

Breastfeeding Safety ..... Minimal amounts of **ampicillin-sulbactam** are excreted in breast milk. It is generally considered compatible with breastfeeding.

Drug Interactions ..... **Probenecid** decreases the renal tubular secretion of **amoxicillin,** increasing the plasma concentration.
Chloramphenicol, macrolides, sulfonamides, and tetracyclines may interfere with the bactericidal effects of penicillin *in vitro.*

References .....

Akhtamova ZM, Kholodov LE, Dorokhov VV, et al. Antibiot Med Biotekhnol 1985; 30:228-32.
Chamberlain A, White S, Bawdon R, et al. Am J Obstet Gynecol 1993; 168:667-73.
Lewis DF, Brody K, Edwards MS, et al. Obstet Gynecol 1996; 88:801-5.
Lewis DF, Fontenot MT, Brooks GG, et al. Obstet Gynecol 1995; 86:392-5.
Lovett SM, Weiss JD, Diogo MJ, et al. Am J Obstet Gynecol 1997; 176:1030-8.
Noyes N, Berkeley AS, Freedman K, Ledger W. Infect Dis Obstet Gynecol 1998; 6:220-3.

Summary .....
Pregnancy Category: B
Lactation Category: S
- **Ampicillin-sulbactam** appears safe and effective for use during pregnancy and lactation when indicated.

Amprenavir—(Agenerase)

International Brand Name—Agenerase (Argentina, Australia, Brazil, Canada, Chile, Colombia, Israel, Mexico, Uruguay, Venezuela)

Drug Class ..... Antivirals; Protease inhibitors

Indications ..... HIV

Mechanism ..... HIV-1 protease inhibitor; potent CYP inhibitor

Dosage with Qualifiers ..... HIV—1200mg PO bid or tid (take with food); increase dose to 1200mg PO tid if given with **efavirenz**

- **Contraindications**—hypersensitivity to drug or class, and **cisapride, astemizole,** or **midazolam** use
- **Caution**—hypersensitivity to sulfonamides, hepatic or renal dysfunction

Maternal Considerations ..... There are limited published case reports of **amprenavir** use during pregnancy.
Side effects include Stevens-Johnson syndrome, N/V, diarrhea, rash, hyperglycemia, hypertriglyceridemia, headache, fatigue, taste change, perioral tingling, and depression.

Fetal Considerations ..... **Amprenavir** crosses the human placenta. In one study, umbilical cord blood concentrations were below detection in 10/40 samples for **nelfinavir** and 25/40 samples for its metabolite M8, 9/11 samples for **ritonavir,** 4/6 samples for **indinavir,** and 5/6 samples for **saquinavir,** but concentrations were detectable in 3/3 samples

for **amprenavir**. In various rodents, doses of **amprenavir** well below the MRHD were associated with an increased abortion rate and deficient long bone ossification.

Breastfeeding Safety

It is unknown whether **amprenavir** is excreted in human breast milk. Breastfeeding is contraindicated in HIV-infected nursing women where formula is available to reduce the risk of neonatal transmission.

Drug Interactions

Amprenavir inhibits CYP3A4 metabolism and should not be administered with medications that are also CYP3A4 substrates.
Co-administration with **rifampin** may blunt the virologic response and may lead to possible resistance to **amprenavir** or to the class of protease inhibitors.
Efavirenz, nevirapine, saquinavir, and **didanosine** each decrease the concentration of **amprenavir**.
Indinavir, lopinavir/ritonavir, and **nelfinavir** each increase the concentration of **amprenavir**.
Delavirdine may blunt the virologic response and may lead to possible resistance to **amprenavir**.
Co-administration with **St. John's wort** (*Hypericum perforatum*) may lead to loss of virologic response and possible resistance to **amprenavir** or to the class of protease inhibitors.
Co-administration with **dihydroergotamine, ergonovine, ergotamine,** or **methylergonovine** is contraindicated due to the potential for life-threatening reactions such as acute ergot toxicity characterized by peripheral vasospasm and ischemia.
Cisapride and **pimozide** are contraindicated due to the potential of a life-threatening cardiac arrhythmia.
Co-administration with HMG-CoA reductase inhibitors such as **lovastatin** or **simvastatin** is contraindicated due to the risk of myopathy, including rhabdomyolysis.
Oral contraceptives may blunt the virologic response and may lead to possible resistance to **amprenavir**. Non-hormonal contraception is recommended.

References

Chappuy H, Treluyer JM, Rey E, et al. Am J Obstet Gynecol 2004; 191:558-62.
Bawdon RE. Infect Dis Obstet Gynecol 1998; 6:244-6.

Summary

Pregnancy Category: C
Lactation Category: NS

- **Amprenavir** should be used during pregnancy only when the potential benefit justifies the risk to the fetus.
- **Amprenavir** appears to more readily cross the human placenta compared to similar antiretroviral agents.
- Physicians are encouraged to register pregnant women with the Antiretroviral Pregnancy Registry (1-800-258-4263) for a better follow-up of the outcome while under treatment with **amprenavir**.

Anagrelide hydrochloride—(Agrylin)

International Brand Name—None identified.

Drug Class — Platelet inhibitors

Indications — Essential thrombocythemia

Mechanism — Unknown

Dosage with Qualifiers

Essential thrombocythemia—begin 0.5mg PO qid; increase as necessary to max 10mg/d

- **Contraindications**—hypersensitivity to drug or class
- **Caution**—CV disease, hepatic or renal dysfunction

Maternal Considerations

Pregnant women with essential thrombocythemia have an increased risk of 1st trimester loss that is not predictable by the prepregnancy platelet count or reducible by **aspirin** therapy. There are no adequate reports or well-controlled studies of **anagrelide** in pregnant women. There are only scattered case reports of its use during pregnancy.
Side effects include CHF, stroke, MI, chest pain, hemorrhage, thrombocytopenia, tachycardia, headache, diarrhea, asthenia, abdominal pain, rash, dyspepsia, anorexia, malaise, and paresthesias.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. Rodent studies are reassuring, revealing no evidence of teratogenicity. However, very high doses were associated with delayed delivery and its sequelae.

Breastfeeding Safety

There is no published experience in nursing women. It is unknown whether **anagrelide** enters human breast milk.

Drug Interactions

There is a report suggesting **sucralfate** can interfere with **anagrelide** absorption.

References

Petrides PE. Semin Thromb Hemost 2006; 32:399-408.
Wright CA, Tefferi A. Eur J Haematol 2001; 66:152-9.

Summary

Pregnancy Category: C
Lactation Category: U

- **Anagrelide** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Anakinra—(Kineret)

International Brand Name—Kineret (Denmark, England, Ireland)

Drug Class

Antirheumatics; Interleukin receptor antagonists

Indications

Essential thrombocythemia

Mechanism

Inhibits the IL-1 type 1 receptor

Dosage with Qualifiers

Rheumatoid arthritis, moderate to severe—100mg SC q24h; check ANC at baseline and q3mo

- **Contraindications**—hypersensitivity to drug or class, serious infection, concurrent live vaccine
- **Caution**—renal dysfunction, asthma

Maternal Considerations

There are no published reports of **anakinra** use during pregnancy. Native IL-1 type 1 receptor antagonist has variably been associated with recurrent pregnancy loss, and is increased in AF and umbilical venous blood obtained from pregnancies complicated by PPROM.
Side effects include thrombocytopenia, neutropenia, infection, injection site reaction, sinusitis, URI symptoms, nausea, diarrhea, and abdominal pain.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **anakinra** crosses the human placenta. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically.

Breastfeeding Safety

There is no published experience in nursing women. It is unknown whether **anakinra** enters human breast milk. Native IL-1 type 1 receptor antagonist is present in breast milk, and the concentration is increased by mastitis.

Drug Interactions

No drug-drug interaction studies in human subjects have been conducted.

References

Buescher ES, Hair PS. Cell Immunol 2001; 210:87-95.
Fukuda H, Masuzaki H, Ishimaru T. Int J Gynaecol Obstet 2002; 77:123-9.
Levrant S, Coulam CB, Jeyendran RS. Am J Reprod Immunol 2008; 60:224-8.
Unfried G, Tempfer C, Schneeberger C, et al. Fertil Steril 2001; 75:683-7.

Summary

Pregnancy Category: B
Lactation Category: U

- **Anakinra** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Anthralin—(A-Fil; Amitase; Anthraderm; Anthra-Derm; Anthraforte; Anthra-Tex; Dithranol; Drithocreme; Dritho-Scalp; Lasan; Micanol; Psoriatec)

International Brand Name—Anthraforte 1 (Canada); Anthramed (Indonesia); Anthranol (Belgium, England, Israel, Philippines, Spain); Anthranol 0.1 (Canada); Anthranol 0.2 (Canada); Anthranol 0.4 (Canada); Anthrascalp (Canada); Desmoline (Portugal); Dithranol-Hermal (Germany); Dithrocream (Australia, England, Israel); Ditrastick (Finland, Hungary); Filorose (Greece); Micanol (Belgium, Canada, Israel); Psoradexan (Bulgaria); Psoralon (Germany, Norway); Psorinol (India)

Drug Class

Dermatologics; Psoriasis

Indications

Psoriasis, pustular

Mechanism

Unknown; inhibits T lymphocytes

Dosage with Qualifiers

Psoriasis—begin at 0.1% topically and cover for 8-24h; may accelerate to 1-3% topically and cover for 5-60min and apply bid

- **Contraindications**—hypersensitivity to drug or class, lesions on the face or genitals
- **Caution**—renal dysfunction, salicylate allergy

Maternal Considerations

Psoriasis is a chronically recurring inflammatory disease that affects the skin, scalp, and joints. Pregnancy may precipitate pustular psoriasis. There are no adequate reports or well-controlled studies of **anthralin** in pregnant women. Though it is generally considered safe for use during pregnancy, there are few data to support a conclusion either way.

	Side effects include irritation, contact dermatitis, discoloration of hair and nails, and erythema.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. Rodent teratogenicity studies have apparently not been conducted.
Breastfeeding Safety	There is no published experience in nursing women. It is unknown whether **anthralin** enters human breast milk. The route and dosing frequency suggest it is unlikely the breastfeeding neonate would ingest a clinically relevant amount.
Drug Interactions	No drug-drug interaction studies in human subjects have been conducted.
References	Arnold WP, Boelen RE, van de Kerkof PC. Ned Tijdschr Geneeskd 1995; 139:1170-3. Tauscher AE, Fleischer AB, Phelps KC, Feldman SR. J Cutan Med Surg 2002; 6:561-70.
Summary	**Pregnancy Category: C** **Lactation Category: U** • **Anthralin** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Antihemophilic factor—(Alphanate; Bioclate; Factor VIII; Green Eight; Haemoctin SDH; Helixate; Hemofil-M; Humate-P; Hyate:C; Koate; Koate-Hp; Kogenate; Melate; Nybcen; Omrixate; Profilate)

International Brand Name—Advate (England, Ireland); AHF (New Zealand); Alphanate (Hong Kong, Malaysia); Bayer Koate-HP (Philippines); Beriate (Sweden); Beriate hs (Hungary); Beriate HS (Germany); Beriate-p (Spain, Taiwan); Biostate (Australia); Cutter Koate-HP (Taiwan); Emoclot DI (India); Fandhi (Israel); Green Eight (Korea); Haemate (Denmark, Sweden); Haemate HS (Germany, Switzerland); Haemate P (Israel, Taiwan); Haemate-P (Italy, Netherlands, Spain); Haemoctin SDH (Singapore); Haemosolvate Factor VIII (South Africa); Helixate NexGen (England, Ireland); Hemofil M (France, Germany, Hong Kong, Israel, Italy, Malaysia, Philippines, Spain, Sweden, Taiwan); Hyate C (Taiwan); Koate (Sweden); Koate DVI (Argentina, Chile, Colombia, Costa Rica, Dominican Republic, El Salvador, Guatemala, Honduras, Malaysia, Mexico); Koate-DVI (Hong Kong, Philippines, Uruguay); Koate HP (Canada, Malaysia); Koate-hp (Greece); Koate hs (Italy); Kogenate (Canada, France, Ireland, Israel, New Zealand, Taiwan); Kogenate FS (Australia, Canada, New Zealand); Kryobulin S-TIM3 Immuno (Switzerland); Kryobulin TIM 3 (Czech Republic, Hungary, South Africa); Monarc M (Israel); Monarc-M (Israel); Monoclate-p (Denmark, Greece, Spain, Sweden); Monoclate-P (Austria, England, France, Ireland, Israel, Taiwan); Nordiocto (Denmark); Octonativ-M (Sweden); OmRixate (Israel); Profilate (Germany, Sweden); Profilate OSD (Israel, Taiwan); Profilate SD (Hong Kong, Indonesia, Malaysia, Philippines, Thailand); Recombinate (Canada, Denmark, England, France, Germany, Ireland); Refacto (England, Ireland); Ristofact (Germany)

Drug Class	Antihemophilics; Blood clotting factors
Indications	Congenital factor VIII deficiency
Mechanism	Replacement
Dosage with Qualifiers	Congenital factor VIII deficiency—dose highly variable, reflecting weight and severity of deficiency and the presence of inhibitors *NOTE: in general, 1 IU/kg will increase circulating factor VIII by 2%.*

- **Contraindications**—hypersensitivity to drug or class
- **Caution**—hepatic dysfunction

Maternal Considerations

Not surprisingly, there are no adequate reports or well-controlled studies of **antihemophilic factor** in pregnant women since the factor VIII deficiency is X-linked. Unbalanced lyonization or crossover during meiosis would account for the rare reports in women if accurate. Replacement is of little clinical use in women with an acquired inhibitor of factor VIII.
Side effects include anaphylaxis, HIV, hepatitis, urticaria, wheezing, nausea, fever, chills, and chest tightness.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. Animal studies have not been performed, explaining the FDA classification as C.

Breastfeeding Safety

There are no adequate reports or well-controlled studies in nursing women.

Drug Interactions

No drug-drug interaction studies in human subjects are reported.

References

There are no current relevant references.

Summary

Pregnancy Category: C
Lactation Category: S (likely)
- **Antihemophilic factor** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Antithrombin III concentrate—(ATnativ; Thrombate III)

International Brand Name—Anthrobin P (Japan); Antithrombin III (Hong Kong); Antithrombin III Immuno (South Africa); Atenativ (Germany, Spain); Atenativ 500 (Austria, Hungary, Switzerland); Atend (Mexico); Athimbin HS 500 (Austria); Kybernin P (Argentina, Brazil); Neuart (Japan); Thrombate III (Canada)

Drug Class

Anticoagulants; Blood clotting factors

Indications

ATIII deficiency, congenital or acquired

Mechanism

Replacement

Dosage with Qualifiers

ATIII deficiency (congenital or acquired)—treatment of thromboembolism: 50-100U/min IV, titrate to ATIII activity levels; prophylaxis: 50-100U/min IV, titrate to ATIII activity levels

NOTE: in general, 1 IU/kg increases ATIII levels by 1-2.1%; goal 80-120%.

- **Contraindications**—hypersensitivity to drug or class
- **Caution**—unknown

Maternal Considerations

There are no adequate studies of **antithrombin III concentrate** in pregnant women. ATIII consumption during normal pregnancy is increased to the level associated with sepsis in the nonpregnant patient. Women with congenital ATIII deficiency have dramatically increased risk of thromboembolic disease during pregnancy. **Heparin** may be ineffective, depending upon the ATIII level. Replacement is effective prophylaxis and treatment of acute thrombosis and must be performed on an ongoing basis. Preeclampsia is a cause of acquired ATIII deficiency secondary to

	increased consumption. Several studies suggest ATIII replacement may improve maternal outcome in women with preeclampsia. ***Side effects*** include dizziness, nausea, bitter taste, cramps, and chest tightness.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. There are no reports of adverse fetal effects, and the size of the molecule indicates placental transfer is unlikely. Rodent teratogenicity studies apparently have not been conducted. As an endogenous substance, **antithrombin III concentrate** is unlikely to have any adverse fetal effects.
Breastfeeding Safety	There are no adequate reports or well-controlled studies in nursing women. It is unknown whether **antithrombin III concentrate** enters human breast milk.
Drug Interactions	No drug-drug interactions in human subjects are reported.
References	Brandt P. Thromb Res Suppl 1981; 22:15-24. Kobayashi T, Terao T, Ikenoue T, et al; BI 51 017 Study Group. Semin Thromb Hemost 2003; 29:645-52. Paternoster DM, De Fusco D, Tambuscio B. Int J Gynaecol Obstet 2000; 71:175-6. Weiner CP, Herrig JE, Pelzer GD, Heilskov J. Throm Res Suppl 1990; 58:395-401. Yamada T, Yamada H, Morikawa M, et al. J Obstet Gynaecol Res 2001; 27:189-97.
Summary	**Pregnancy Category: C** **Lactation Category: U** • **Antithrombin III concentrate** may be used safely during pregnancy and lactation for the treatment of ATIII deficiency.

Arbutamine—(GenESA)

International Brand Name—None identified.

Drug Class	Adrenergic agonists; Chronotropes; Diagnostics, nonradioactive; Inotropes
Indications	Provokes cardiac stress in lieu of exercise testing
Mechanism	Sympathomimetic with β-adrenoceptor selectivity; may limit regional subendocardial perfusion
Dosage with Qualifiers	Cardiac imaging under stress—administered by a computerized system; use only with continuous cardiac monitoring. Max dose 0.8mcg/kg/min, max total dose 10mcg/kg. • **Contraindications**—hypersensitivity to drug or class, IHSS, history of recurrent ventricular tachycardia, implanted pacemaker • **Caution**—unknown
Maternal Considerations	There are no reports of **arbutamine** use during pregnancy. ***Side effects*** include tremor, angina, arrhythmia, headache, dizziness, anxiety, and palpitations.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. Rodent studies are reassuring, revealing no evidence of teratogenicity.

Breastfeeding Safety	There are no adequate reports or well-controlled studies in nursing women. It is unknown whether **arbutamine** enters human breast milk. However, considering the indication, it is unlikely the breastfed neonate would ingest clinically relevant amounts after one-time use.
Drug Interactions	β-Adrenergic antagonists may blunt the response to **arbutamine** and should be withdrawn at least 48h before conducting an **arbutamine** system test.
References	There is no published experience in pregnancy or during lactation.
Summary	**Pregnancy Category: B** **Lactation Category: U** • Indicated when the medical risks to the mother outweigh any theoretic risk to the fetus.

Ardeparin sodium—(Normiflo)

International Brand Name—None identified.

Drug Class	Anticoagulants; Low-molecular-weight heparins
Indications	DVT prophylaxis for joint replacement
Mechanism	Binds to and accelerates ATIII activity; also binds **heparin** cofactor II
Dosage with Qualifiers	DVT prophylaxis—begin 50 anti-Xa U/kg SC q12h evening before surgery ×14d • **Contraindications**—hypersensitivity to drug or class or pork products, bleeding, thrombocytopenia, **heparin**-induced thrombocytopenia • **Caution**—IM or IV use, neuraxial anesthesia may be contraindicated depending on dosing regimen desired. Anesthesiologist must know of intended dosing regimen before surgery.
Maternal Considerations	There is no published experience with **ardeparin** during pregnancy. This class of drugs is being used with increasing frequency during pregnancy for the treatment of thrombophilia. ***Side effects*** include hemorrhage, injection site hematoma, fever, N/V, bruising, arthralgia, and chest pain.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. Its molecular weight suggests **ardeparin** does not cross the placenta. Rodent studies at up to 3× the MRHD revealed no evidence of impaired fertility or fetal harm. However, when administered at 7× and 11× the MRHD, scoliosis and cardiac defects, respectively, were noted.
Breastfeeding Safety	There are no adequate reports or well-controlled studies in nursing women. It is unknown whether **ardeparin** enters human breast milk.
Drug Interactions	**Ardeparin** may accentuate other anticoagulant agents.

References	There is no published experience in pregnancy or during lactation.
Summary	**Pregnancy Category: C** **Lactation Category: U** • There are alternative agents for which there is more experience during pregnancy and lactation.

Argatroban—(Acova)

International Brand Name—Novastan (Japan, Korea)

Drug Class	Anticoagulants; Thrombin inhibitors
Indications	Either prophylaxis or treatment of thrombosis in women with **heparin**-induced thrombocytopenia
Mechanism	Unknown; directly inhibits thrombin
Dosage with Qualifiers	Heparin-induced thrombocytopenia—2mcg/kg/min IV; adjust dose based on aPTT; maximum 10mcg/kg/min DIC—0.7mcg/kg/min (response desired is a platelet count >120K/mm^3, decreased fibrin or FDP <20, or no decrease in ATIII levels); alternatively, 100mcg/kg IV over 1min, then 1-3mcg/kg/min for 6-72h *NOTE: hepatic dosing.* • **Contraindications**—hypersensitivity to drug or class, major bleeding • **Caution**—hepatic dysfunction, severe hypertension, conduction anesthesia, surgery, GI lesions
Maternal Considerations	There are no adequate reports or well-controlled studies of **argatroban** in pregnant women. The published experience is limited to case reports. ***Side effects*** include hemorrhage, GI bleeding, cardiac arrest, hypotension, fever, diarrhea, N/V, and cough.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **argatroban** crosses the human placenta. Rodent studies have not revealed evidence of either impaired fertility or teratogenicity, though the doses used were smaller than those employed clinically.
Breastfeeding Safety	There are no adequate reports or well-controlled studies in nursing women. It is unknown whether **argatroban** enters human breast milk. **Argatroban** is detected in rat breast milk.
Drug Interactions	**Argatroban** may accentuate other anticoagulant agents.
References	McCrae KR, Bussel JB, Mannucci PM, et al. Hematology (Am Soc Hematol Educ Program) 2001; 282-305. Taniguchi S, Fukuda I, Minakawa M, et al. Surg Today 2008; 38:59-61.
Summary	**Pregnancy Category: B** **Lactation Category: U** • **Argatroban** is a somewhat unique drug that should be used only when the risk to the mother outweighs the theoretic risk to the fetus.

Ascorbic acid—(Ascor L 500; Cee-500; Cenolate; Mega-C/A Plus; Vitamin C)

International Brand Name—Acidylina (Italy); Agrumina (Italy); Arkovital C (France); Asconvita (Philippines); Ascorbin (Malaysia); Ascorcee (Philippines); Askorbin (Indonesia); C500 (Israel); Cebion (Austria, Chile, Colombia, Czech Republic, Greece, Israel, Italy, Peru, Portugal, Spain); Cecap (Hong Kong); CeCe (Korea); Cecon (Philippines, Puerto Rico); Cecon Drops (Australia); Ceevifil (Philippines); Celin (India); Cenol (Belgium); Cetebe (Bulgaria); Cetrinets (Malaysia); Cevalin (Mexico); Ce-Vi-Sol (Mexico); Cewin (Brazil); Citravite (India, New Zealand); C-Vimin (Finland, Sweden); C-Will (Thailand); Dancimin C (Indonesia); Dayvital (Netherlands); Flavettes (Hong Kong); Ikacee (Indonesia); Leder C (Taiwan); Leder-C (Ecuador); Limcee (India); Pro-C (Australia); Redoxon (Argentina, Austria, Brazil, Colombia, Finland, Greece, Hong Kong, Ireland, Italy, Paraguay, Peru, Portugal, Spain, Switzerland, Uruguay, Venezuela); Redoxon C (Puerto Rico, South Africa); Redoxon Forte (India, Mexico); Scorbex (South Africa); Sweetcee (Thailand); Synum C (Germany); Take-C (Taiwan); Tanvimil-C (Argentina); Upsa C (Costa Rica, Dominican Republic, El Salvador, Guatemala, Honduras, Nicaragua, Panama); Veinobiase (Costa Rica, Dominican Republic, El Salvador, Guatemala, Honduras, Nicaragua, Panama); Vi-C 500 (Israel); Vicef (South Africa); Vitac (Chile); Vita-Cedol Orange (Puerto Rico); Vitacimin (Peru); Vitascorbol (France); Vorange (Malaysia); Xon-ce (Indonesia)

Drug Class ..... Vitamin, nutritional

Indications ..... Nutritional deficiency; nutritional supplementation: pregnancy, scurvy

Mechanism ..... Necessary cofactor for DNA synthesis and erythropoiesis

Dosage with Qualifiers .....

Nutritional deficiency—0.15-0.18 mg PO/SC/IM qd
Dietary supplementation, pregnancy—0.8-1mg PO qd
Dietary supplementation, scurvy—150-250mg PO qd or bid ×2w, then 50mg PO bid

- **Contraindications**—hypersensitivity to drug or class, undiagnosed anemia
- **Caution**—unknown

Maternal Considerations .....

Ascorbic acid is an essential vitamin that acts as a coenzyme for collagen formation, tissue repair, and the synthesis of lipids and proteins. It has both reducing and antioxidant properties and is necessary for many physiologic functions (e.g., metabolism of iron and folic acid, resistance to infection, and preservation of blood vessel integrity). Signs and symptoms of early **ascorbic acid** deficiency include malaise, irritability, arthralgia, hyperkeratosis, nosebleed, and petechial hemorrhages. Prolonged deficiency leads to clinical scurvy. There has been limited study of **ascorbic acid** during human pregnancy. Supplementation with **ascorbic acid** and vitamin E does not reduce the rate of preeclampsia in women at high risk. Women with established early-onset preeclampsia (<32w) likewise do not benefit from pharmacologic doses. **Ascorbic acid** is consumed during labor, perhaps because of oxygen free radical generation during the ischemia-reperfusion associated with uterine contractions. Women who consume low amounts of **ascorbic acid** appear to have an increased risk of developing gestational diabetes. However, maternal supplementation of replete women with 500mg daily does not seem to alter the serum level after 1mo. Supplementation does not reduce the prevalence of preterm delivery.
Side effects include anorexia, N/V, abdominal pain, flatus, altered sleep patterns, irritability, overactivity, erythema, rash, and itching.

Fetal Considerations .....

There are no adequate and well-controlled studies in human fetuses. It is unknown how **ascorbic acid** crosses the human placenta. In the pig, transfer increases with advancing gestational age. In the human, umbilical vein **ascorbic acid** levels are lower

in the preterm compared to the term fetus. **Ascorbic acid** concentrations in cesarean and vaginal delivery patients are higher in AF than fetal plasma. In one randomized trial initiated at 35w gestation, maternal intake of 500mg **ascorbic acid** failed to alter the fetal serum level from placebo. High doses of **ascorbic acid** taken during pregnancy are reported to cause scurvy in infants removed from this environment at birth. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically. In diabetic rats, **ascorbic acid** supplementation reduces the malformation rate.

Breastfeeding Safety

There are no adequate reports or well-controlled studies in nursing women. **Ascorbic acid** is excreted in breast milk; the RDA for breastfeeding women is 90-100mg. The milk concentration corresponds with maternal dietary intake, but excessive supplementation has little incremental effect on it. The level in refrigerated milk declines by a third within 24h.

Drug Interactions

No drug-drug interactions in human subjects are reported.

References

Buss IH, McGill F, Darlow BA, Winterbourn CC. Acta Paediatr 2001; 90:813-5.

Ching S, Mahan DC, Ottobre JS, Dabrowski K. J Nutr 2001; 131:1997-2001.

Gulmezoglu AM, Hofmeyr GJ, Oosthuisen MM. Br J Obstet Gynaecol 1997; 104:689-96.

Pressman EK, Cavanaugh JL, Mingione M, et al. Am J Obstet Gynecol 2003; 189:1720-5.

Rumbold AR, Crowther CA, Haslam RR, et al; ACTS Study Group. N Engl J Med 2006; 354:1796-806.

Siman CM, Eriksson UJ. Diabetologia 1997; 40:1416-24.

Steyn PS, Odendaal HJ, Schoeman J, et al. J Obstet Gynaecol 2003; 23:150-5.

Woods JR Jr, Cavanaugh JL, Norkus EP, et al. Am J Obstet Gynecol 2002; 187:1179-83.

Zhang C, Williams MA, Sorensen TK, et al. Epidemiology 2004; 15:597-604.

Summary

Pregnancy Category: A (**C** if exceeds RDA)
Lactation Category: S

- **Ascorbic acid** is an essential vitamin contained in most prenatal vitamins.

Aspirin—(Aspergum; Bufferin; Easprin; Ecotrin; Empirin; Fasprin; Genacote; Halfprin; Zorprin)

International Brand Name—AAS (Argentina, Brazil, Spain); Acesal (Italy); Acetard (Denmark, Finland, Sweden); Aceticil (Brazil); Acetosal (Israel); Actorin (Thailand); Adiro (Mexico, Venezuela); Albyl-E (Norway); Anacin (Israel); Anasprin (Brazil); Ansin (Taiwan); Anthrom (Philippines); Aptor (Indonesia); Asaphen E.C. (Canada); Asapor (Finland); Asatard (South Africa); Asawin (Colombia, Ecuador, Mexico, Peru); Aspa (Taiwan); Aspec (New Zealand); Aspec-EC (Philippines); Aspent (Thailand); Aspex (Israel); Aspilets (Indonesia); Aspirem (Puerto Rico); Aspirina (Chile, Colombia, Ecuador); Aspirin Bayer (Hong Kong); Aspirisucre (France); Aspro (Austria, Belgium, Czech Republic, England, Germany, Hungary, Ireland, Israel, Italy, Malaysia, Netherlands, Portugal, Spain, Switzerland); Asrina (Thailand); ASS (Germany); Asta (Paraguay); Astrix (Philippines); Bayaspirina (Argentina); Bayer Aspirin (Australia); Bayer Aspirin Cardio (South Africa); Bex (Australia); Bokey (Hong Kong); Bufferin (Italy, Uruguay); Bufferin Low Dose (Singapore); Caprin (England); Cardioaspirina (Colombia, Peru); Caspirin (Malaysia); Ceto (Indonesia); Claragine (France); Colfarit (Austria, Czech Republic, Germany, Hungary, Switzerland); Comoprin (Thailand); Cortal (Philippines); Dispril (Belgium, Israel, Sweden); Disprin (England, Hong Kong, India, Ireland, Malaysia, Puerto Rico); Dusil (Malaysia); Ecasil (Brazil); Ecotrin (Argentina, Chile, Costa Rica, Dominican Republic, El Salvador, Guatemala, Honduras, Mexico, New Zealand, Nicaragua, Panama, Taiwan); Ecotrin 650 (Hong Kong); Encine EM (Taiwan); Enteroprin (Philippines); Entrophen (Canada); Eskotrin (Venezuela); Globentyl (Denmark, Norway); Godamed (Israel); Idotyl (Denmark); Keypo (Taiwan); Melabon (Germany); NAspro (Indonesia); Novasen (Canada); Nu-Seals (Israel, South Africa); Plewin (Chile); Proprin (England); Rhonal (Argentina, Belgium, Bulgaria, Ecuador, Netherlands, Peru, Spain, Switzerland, Venezuela); Rhonal for Children (Korea); Ronal (Brazil); Solprin (Australia); Spren (Australia); Tevapirin (Israel); Thrombo-Aspilets (Indonesia); Tromalyt (Colombia); Tromcor (Philippines); V-AS (Thailand)

Drug Class ..... Analgesics, non-narcotic; Antipyretics; NSAIDs; Platelet inhibitors; Salicylates

Indications ..... Fever, mild pain, TIAs, MI, arthritis, rheumatic fever

Mechanism ..... Unknown; likely multiple as it inhibits the synthesis and release of prostaglandins by interfering with transcription factors and irreversibly inhibits cyclooxygenase, while its analgesia appears 2nd to peripheral and central effects

Dosage with Qualifiers .....

Fever—325-650mg PO/PR q4h prn
Analgesia—325-650mg PO/PR q4h prn
Preeclampsia prophylaxis—81mg PO qd
Antiphospholipid syndrome—81mg PO qd alone if unassociated with fetal demise, otherwise coupled with **heparin** (fractionated or unfractionated)
TIA—650mg PO bid
MI—325mg PO qd to prevent recurrence
Arthritis—3.6-5.4g PO qd in divided doses
Rheumatic fever—5-8g PO qd in divided doses; treat for 1-2w, then taper over 2-8w

*NOTE: typically enteric-coated to assure release in the upper small intestine, where absorption is optimal. May be combined with caffeine and **butalbital** (without or with **codeine** or **hydrocodone**) and sold as Fiorinal, or with **propoxyphene** and sold as Darvon, or with **dipyridamole**.*

- **Contraindications**—hypersensitivity to drug or class, G6PD deficiency, bleeding disorder
- **Caution**—GI lesions, renal or hepatic dysfunction, TTP, hypoprothrombinemia

Maternal Considerations ..... **Aspirin** is a potent drug with a complex and still incompletely understood mechanisms of action. It is ubiquitous in the pharmacopeia, being combined with a multitude of agents. **Aspirin** is recommended by the American Heart Association for women with a 10y risk of coronary heart disease of 10% or

higher, and by the U.S. Preventive Services Task Force for women whose 5y risk of coronary heart disease is 3% or higher.
Women ingesting large quantities of **aspirin** are at risk for myriad complications. Though one prospective case-control study suggested that the antenatal use of **ibuprofen, naproxen,** and possibly **aspirin** but not **acetaminophen** increased the risk of spontaneous abortion; the risk for **aspirin** was not confirmed in a more recent study. Chronically high salicylate levels are associated with prolonged pregnancy, increased puerperal bleeding, decreased birth weight, and stillbirth. It is generally recommended that high doses of **aspirin** be avoided during the last trimester.
Low-dose **aspirin** plus **heparin** appears effective treatment for antiphospholipid syndrome characterized by recurrent 1st trimester losses. It is not an effective treatment for idiopathic recurrent losses absent a thrombophilia. **Aspirin** and moderate-intensity **warfarin** appear equally effective for preventing recurrent stroke for women with a single positive antiphospholipid antibody test result and prior stroke.
Controversy continues regarding the benefit of low-dose **aspirin** for the prevention of preeclampsia, though no complications of treatment have been documented and several meta-analyses suggest a modest reduction in preeclampsia and IUGR. In one randomized controlled trial, almost 20,000 women underwent uterine artery Doppler screening at 22-24w; 560 women with abnormal Doppler flow profiles were randomized to low-dose **aspirin** (150mg/d) or placebo. There was no improvement in either maternal or perinatal outcome.
Side effects include GI bleeding, thrombocytopenia, anaphylaxis, angioedema, Reye's syndrome, hepatitis, dyspepsia, tinnitus, rash, abnormal LFTs, bruising, and bleeding.

Fetal Considerations

Aspirin does cross the placenta. Maternal **aspirin** ingestion has been linked to gastroschisis and small intestine atresia independent of fever or cold symptoms. Low-dose **aspirin** doses alter fetal cyclooxygenase activity, but no sequelae are known.

Breastfeeding Safety

The use of **aspirin** in single doses should not pose any risk to the breastfeeding newborn. In contrast, women on high doses of **aspirin** such as that for arthritis or rheumatic fever might best avoid breastfeeding, as the neonatal salicylate level may reach therapeutic levels.

Drug Interactions

Aspirin may decrease the effects of **probenecid, sulfinpyrazone,** and **phenylbutazone**.
Alcohol has a synergistic effect with **aspirin** in causing GI bleeding.
Administration of corticosteroids with **aspirin** may increase the risk of GI ulceration and may reduce serum salicylate levels.
Concomitant administration with pyrazolone derivatives (**phenylbutazone, oxyphenbutazone,** and possibly **dipyrone**) may increase the risk of GI ulceration.
Urinary alkalinizers decrease **aspirin** effectiveness by increasing the rate of salicylate excretion.
Phenobarbital decreases **aspirin** effectiveness by enzyme induction.
Serum **phenytoin** levels may be increased by **aspirin**.
Propranolol may decrease **aspirin's** anti-inflammatory action by competing for the same receptors.

References

Coomarasamy A, Papaioannou S, Gee H, Khan KS. Obstet Gynecol 2001; 98:861-6.

Duley L, Henderson-Smart D, Knight M, King J. BMJ 2001; 322:329-33.
Empson M, Lassere M, Craig J, Scott J. Cochrane Database Syst Rev 2005; (2):CD002859.
Empson M, Lassere M, Craig JC, Scott JR. Obstet Gynecol 2002; 99:135-44.
Farquharson R, Quenby S, Greaves M. Obstet Gynecol 2002; 100:408-15.
Li DK, Liu L, Odouli R. BMJ 2003; 327:368-73.
Lim W, Crowther MA, Eikelboom JW. JAMA 2006; 295:1050-7.
Keim SA, Klebanoff MA. Epidemiology 2006; 17:435-9.
Pearson TA, Blair SN, Daniels SR, et al. Circulation 2002; 106:388-91.
Spigset O, Hagg S. Paediatr Drugs 2000; 2:223-38.
Tegeder I, Pfeilschifter J, Geisslinger G. FASEB J 2001; 15:2057-72.
Unsworth J, d'Assis-Fonseca A, Beswick DT, Blake DR. Ann Rheum Dis 1987; 46:638-9.
U.S. Preventive Services Task Force. Ann Intern Med 2002; 136:157-160.
Werler MM, Sheehan JE, Mitchell AA. Am J Epidemiol 2002; 155:26-31.
Yu CK, Papageorghiou AT, Parra M, et al. Ultrasound Obstet Gynecol 2003; 22:233-9.

Summary

Pregnancy Category: D
Lactation Category: S (likely)

- **Aspirin** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.
- **Aspirin** may be associated with fetal abnormalities and spontaneous abortion when taken in the 1st trimester.
- The evidence that low-dose **aspirin** improves pregnancy outcome in at-risk women remains weak.

Atenolol—(Alinor; Atolmin; Blotex; B-Vasc; Seles; Tenolin; Tenormin; Tensig)

International Brand Name—Ablok (Brazil); Adoll (Hong Kong); Alonet (Singapore); Altol (India); Anolene (Korea); Anolpin (Korea); Anselol (New Zealand); Antipressan (England, Ireland); Apo-Atenolol (Israel); Arandin (Korea); Atarox (Paraguay); Atcardil (Philippines); Atecard (India); AteHexal (Australia, Germany); Atenblock (Finland); Atendol (Germany); Atenet (Denmark); Ateni (Israel); Atenil (Switzerland); Ateno (Israel); Atenogamma (Germany); Atenol (Italy); Atereal (Germany); Aterol (South Africa); Atestad (Philippines); Atinol (Taiwan); Atolmin (Korea); Betablok (Indonesia); Betacar (Chile); Betacard (Bahrain, India); Betarol (Korea); Betatop Ge (France); Beten (Malaysia); Bloket (Paraguay); Blokium (Chile, Costa Rica, Dominican Republic, El Salvador, Guatemala, Honduras, Nicaragua, Panama, Venezuela); Blotex (Mexico); B-Vasc (South Africa); Cardioten (Philippines); Coratol (Malaysia, Thailand); Durabeta (Philippines); Evitocor (Germany); Farnormin (Indonesia); Felo-Bits (Argentina); Hypernol (Singapore); Internolol (Indonesia); Loten (Malaysia); Lo-ten (Hong Kong, New Zealand, Taiwan); Lotenal (Korea); Martenol (Hong Kong); Mirobect (Taiwan); Myocord (Argentina); Neotenol (Brazil); Nolol (Dominican Republic, Thailand); Normalol (Israel); Normaten (Hong Kong); Normiten (Israel); Nortelol (Thailand); Noten (Australia, Malaysia, Singapore); Oraday (Malaysia, Thailand); Plenacor (Brazil, Colombia, Ecuador); Preloc (Thailand); Premorine (Argentina); Prenolol (Singapore, Thailand); Prenormine (Argentina); Ranlol (Malaysia); Rozamin (Korea); Serten (Philippines); Stermin (Taiwan); Temoret (Korea); Tenblok (Indonesia); Tenidon (Denmark); Tenoblock (Finland); Tenocor (Thailand); Tenol (Thailand); Tenolin (Canada); Tenolol (Singapore, Thailand); Tenopress (Israel); Tenoprin (Finland); Tenormin (Australia, Canada, Chile, Ecuador, Mexico, Peru, Uruguay, Venezuela); Tenormine (France); Tenostat (Philippines); Tensig (Australia); Ternolol (Hong Kong); Therabloc (Philippines); Urosin (Malaysia, Taiwan); Vascoten (Hong Kong, Malaysia, Singapore, Thailand); Velorin (Philippines); Vericordin (Argentina); Wesipin (Taiwan)

Drug Class ..... Antiadrenergics; β-blockers

Indications ..... Hypertension, MI, and angina pectoris

Mechanism

Selectively antagonizes the β_1 adrenoceptor

Dosage with Qualifiers

Hypertension—50mg PO qd; increase to 100mg qd after 7d
MI—begin 5mg IV over 5min ×2 (10min apart), then 50mg PO q12h ×7d, then 100mg qd
Angina—50mg PO qd, max 200mg qd

- **Contraindications**—hypersensitivity to drug or class, 2nd or 3rd degree heart block, sinus bradycardia, cardiac insufficiency
- **Caution**—renal dysfunction

Maternal Considerations

Hypertension complicates 5-10% of pregnancies and is a leading cause of maternal and perinatal death and morbidity. Severe hypertension (systolic BP = 170mmHg and/or diastolic BP = 110mmHg) should be treated immediately. Mild, chronic hypertension is associated with increased maternal and fetal risks, but there is no consensus as to whether mild to moderate hypertension should be treated during pregnancy. The incidence of transient severe hypertension, antenatal hospitalization, proteinuria, and neonatal RDS may be decreased by therapy, but fetal growth may be impaired. In one small trial, **atenolol** reduced the incidence of preeclampsia in women selected for increased cardiac output. Of all β-blockers, the evidence that **atenolol** is associated with IUGR is the strongest, but appears to reflects excess maternal β-blockade, causing a decrease in cardiac output.
Atenolol has also been used to treat congenital long QT syndrome during pregnancy.
Side effects include CHF, bronchospasm, bradycardia, cold extremities, fatigue, nausea, rash, and hypotension.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. **Atenolol** crosses the placenta. There is no substantive evidence of teratogenicity. As a group, β-blockers are associated with IUGR, though controversy continues as to whether this is drug or disease related. **Atenolol** reduces cardiac output, and failure to reduce the dose to prevent an excessive decline in output is associated with IUGR. Some rodent studies reveal a dose-dependent increase in embryo/fetal resorption.

Breastfeeding Safety

Atenolol is concentrated in breast milk, and significant bradycardia may occur in newborns nursed by women on **atenolol**. It should probably be avoided.

Drug Interactions

Catecholamine-depleting drugs (e.g., **reserpine**) may have an additive effect when given with β-blocking agents.
Calcium channel blockers may have an additive effect when given with **atenolol**.
β-Blockers may exacerbate the rebound hypertension that can follow the withdrawal of **clonidine**. If the two drugs are given together, the β-blocker should be withdrawn several days before the gradual withdrawal of **clonidine**. If replacing **clonidine** with a β-blocker, the β-blocker should be delayed for several days after the **clonidine** has been stopped.
Prostaglandin synthase–inhibiting drugs (e.g., **indomethacin**) may decrease the hypotensive effects of β-blockers.
Use of IV β-blockers and IV **verapamil** has resulted in serious adverse reactions, especially in patients with severe cardiomyopathy, CHF, or recent MI.
Patients with a history of anaphylactic reaction to a variety of allergens may have a more severe reaction on repeated challenge, either accidental, diagnostic, or therapeutic, while taking

β-blockers. Such patients may be unresponsive to the usual doses of **epinephrine** used to treat the allergic reaction.

References

Briggs GG, Nageotte MP. Ann Pharmacother 2001; 35:859-61.
Easterling TR, Brateng D, Schmucker B, et al. Obstet Gynecol 1999; 93:725-33.
Easterling TR, Carr DB, Brateng D, et al. Obstet Gynecol 2001; 98:427-33.
Hurst AK, Shotan A, Hoffman K, et al. Pharmacotherapy 1998; 18:840-6.
Lip GY, Beevers M, Churchill D, et al. Am J Cardiol 1997; 79:1436-8.
Magee LA. Best Pract Res Clin Obstet Gynaecol 2001; 15:827-45.

Summary

Pregnancy Category: D
Lactation Category: NS

- **Atenolol** is associated with IUGR unless maternal cardiac output is monitored.
- There are other alternatives with a greater margin of safety.

Atorvastatin—(Lipitor)

International Brand Name—Ator (Israel); Atorlip (Colombia); Atovarol (Colombia); Edy (Colombia); Glustar (Colombia); Lowlipen (Colombia); Sortis (Germany); Storvas (India); Tahor (France, Mauritius)

Drug Class

Antihyperlipidemics; HMG-CoA reductase inhibitors; Statin

Indications

Hypercholesterolemia, hypertriglyceridemia, dysbetalipoproteinemia, and familial hypercholesterolemia

Mechanism

Inhibits HMG-CoA reductase

Dosage with Qualifiers

Hypercholesterolemia, hypertriglyceridemia, dysbetalipoproteinemia, familial hypercholesterolemia—begin 10mg PO qd; monitor response every 8-12w, increasing to a max of 80mg qd

NOTE: monitor LFTs periodically beginning 12w after initiating therapy and with escalation.

- **Contraindications**—hypersensitivity to drug or class, active hepatic disease, unexplained elevated LFTs, pregnancy, lactation
- **Caution**—history of liver disease or alcohol abuse

Maternal Considerations

Compared to **fluvastatin, lovastatin, pravastatin,** or **simvastatin, atorvastatin** is associated with the lowest level of resource use and costs when used to treat patients with hypercholesterolemia. **Atorvastatin** is also associated with the highest percentage of patients achieving their desired clinical targets. There is a single case report of **atorvastatin** use during pregnancy after inadvertent exposure. Though the outcome was normal, the safety of **atorvastatin** during pregnancy remains to be established.
Side effects include rhabdomyolysis, hepatotoxicity, dyspepsia, constipation, diarrhea, rash, myalgias, and elevated LFTs or CPK.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. **Atorvastatin** is an inhibitor of P-glycoprotein. While it is unknown whether **atorvastatin** crosses the human placenta, it crosses the rodent placenta. One review of 214 pregnancy exposures and 70 informative cases noted 31 adverse outcomes in

22 neonates with structural defects, 4 with IUGR, and 5 fetal deaths. There were two principal groups of recurrent structural defects: **cerivastatin** and **lovastatin** were associated with 4 reports of severe, midline CNS defects; **simvastatin, lovastatin,** and **atorvastatin** were all associated with limb deficiencies, including 2 similar complex lower limb defects after **simvastatin** exposure. There were also 2 cases of VACTERL among the limb deficiency cases. All adverse outcomes were reported following exposure to **cerivastatin, simvastatin, lovastatin,** or **atorvastatin,** which are lipophilic and should equilibrate between maternal and fetal compartments. None were reported after exposure to **pravastatin,** which is poorly transported across the rodent placenta. These authors suggest that statins may have secondary effects on sterol-dependent morphogens such as Sonic Hedgehog. Further study is necessary. **Atorvastatin** reaches fetal hepatic concentrations similar to maternal plasma. While there is no evidence of teratogenicity in rodents even at high doses, there is a dose-dependent increase in IUGR, a decrease in survival, and behavioral abnormalities that were gender-dependent. Rare structural defects have occasionally been reported in association with other HMG-CoA reductase inhibitors.

Breastfeeding Safety

There are no adequate reports or well-controlled studies in nursing women. It is unknown whether **atorvastatin** enters human breast milk. However, its poor oral absorption and high degree of protein binding suggest it is unlikely clinically relevant amounts will be found. **Atorvastatin** is excreted into the breast milk of rats.

Drug Interactions

Plasma concentrations of **atorvastatin** decrease some 25% when **colestipol** and **atorvastatin** are given together. However, LDL-C reduction is greater with co-administration.
Plasma **digoxin** concentrations increase by some 20% when given with **atorvastatin**.
Plasma concentrations of **atorvastatin** increase some 40% when given with **erythromycin,** a CYP3A4 inhibitor.
Atorvastatin increases AUC values for **norethindrone** and **ethinyl estradiol** by 30% and 20%, respectively. These increases should be considered when selecting an oral contraceptive.

References

Dostal LA, Schardein JL, Anderson JA. Teratology 1994; 50:387-94.
Edison RJ, Muenke M. Am J Med Genet A 2004; 131:287-98.
Henck JW, Craft WR, Black A, et al. Toxicol Sci 1998; 41:88-99.
Holtzman CW, Wiggins BS, Spinler SA. Pharmacotherapy 2006; 26:1601-7.
Smith DG, McBurney CR. Pharmacoeconomics 2003; 21(Suppl 1): 13-23.
Yaris F, Yaris E, Kadioglu M, et al. Reprod Toxicol 2004; 18:619-21.

Summary

Pregnancy Category: X
Lactation Category: U

- Hyperlipidemia is a chronic problem. **Atorvastatin** appears the most cost-effective of the available statins.
- Cessation of statin therapy during pregnancy should not significantly impact the long-term course of hypercholesterolemia.
- **Atorvastatin** should be used during the first trimester and lactation only if the benefit justifies the potential perinatal risk.

Atovaquone—(Mepron)

International Brand Name—Mepron (Canada); Wellvone (Australia, Austria, Denmark, England, France, Germany, Ireland, Italy, Netherlands, South Africa, Sweden, Switzerland)

Drug Class	Antiprotozoals
Indications	PCP pneumonia in patients intolerant of trimethoprim-sulfamethoxazole
Mechanism	Unknown
Dosage with Qualifiers	PCP pneumonia for patients who cannot tolerate trimethoprim-sulfamethoxazole—750mg PO bid ×21d Malaria—1000mg PO (with 400mg proguanil ×3d) *NOTE: not for prophylaxis; may be combined with proguanil.* • **Contraindications**—hypersensitivity to drug or class • **Caution**—unknown
Maternal Considerations	There are no adequate reports or well-controlled studies of **atovaquone** during pregnancy. Several studies suggest the combination of **atovaquone** and proguanil is effective malaria prophylaxis. The pharmacokinetics of **atovaquone** were recently determined in women with multidrug-resistant falciparum malaria treated by **artesunate-atovaquone-proguanil** during their 2nd and 3rd trimesters. The triple combination was well-tolerated and highly effective. The outcomes of pregnancy were all normal. Population mean (±SEM) oral clearance (Cl/F) estimates were 313 ± 33ml/h/kg and 1109 ± 43ml/h/kg, total apparent volume of distribution (V_d/F) was 13.0 ± 1.3l/kg and 22.9 ± 1.4l/kg, and terminal elimination t/2 was 29.1h and 14.3h for **atovaquone** and **proguanil,** respectively. Using conventional and population analyses, Cl/F and V_d/F estimates for **atovaquone** and **proguanil** were 2× and plasma concentrations <½ those reported in healthy subjects and patients with acute malaria. This suggests the dose of **atovaquone** and proguanil should be increased for the treatment of malaria during pregnancy. ***Side effects*** include rash, fever, nausea, diarrhea, headache, insomnia, hyperglycemia, and elevated amylase.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. Published studies do not permit any conclusion on safety. It is unknown whether **atovaquone** crosses the human placenta. **Atovaquone** crosses the rodent placenta, reaching an F:M ratio approximating 0.3. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically. Though maternal and placental parasitemia is reduced by maternal pharmacotherapy, there is as yet no detectable reduction in perinatal mortality.
Breastfeeding Safety	There are no adequate reports or well-controlled studies in nursing women. It is unknown whether **atovaquone** enters human breast milk. In rats, the M:P ratio approximates 1:3.
Drug Interactions	**Atovaquone** is highly bound to plasma protein (>99.9%). Caution is recommended administering **atovaquone** with other plasma protein–bound drugs with narrow therapeutic indices, as competition for binding sites may occur.

Rifampin results in a significant decrease in average steady-state plasma **atovaquone** concentrations. Alternatives to **rifampin** should be considered during the course of PCP treatment with **atovaquone**.
Rifabutin, another rifamycin, is structurally similar to **rifampin** and may possibly have some of the same drug interactions as **rifampin**.

References

Garner P, Gulmezoglu AM. Cochrane Database Syst Rev 2006; (4):CD000169.
McGready R, Ashley EA, Moo E, et al. J Infect Dis 2005; 192:846-53.
McGready R, Stepniewska K, Edstein MD, et al. Eur J Clin Pharmacol 2003; 59:545-52.
Na-Bangchang K, Manyando C, Ruengweerayut R, et al. Eur J Clin Pharmacol 2005; 61:573-82.

Summary

Pregnancy Category: C
Lactation Category: U

- **Atovaquone** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Atovaquone-proguanil—(Malarone)

International Brand Name—Malarone (Belgium, Canada, Denmark, England, France, Ireland, Israel, Peru, Singapore)

Drug Class

Antimalarials; Antiprotozoals

Indications

Malaria prophylaxis, malaria treatment

Mechanism

Atovaquone inhibits mitochondrial electron transport in parasite. Proguanil inhibits dihydrofolate reductase.

Dosage with Qualifiers

Malaria prophylaxis—250/100mg PO qd (if >40kg); begin 1-2d before traveling to malarial area and continue for 7d after return; repeat dose if emesis <1h from administration.
Malaria treatment—1000/400mg PO qd ×3d; not for severe, complicated, or cerebral malaria; repeat dose if emesis <1h from administration.

NOTE: take with food or milk.

- **Contraindications—**hypersensitivity to drug or class, CrCl <30ml/min if prophylaxis
- **Caution—**CrCl <30ml/min if treatment, N/V, diarrhea

Maternal Considerations

This is a fixed combination agent. Falciparum malaria has a higher risk of morbidity and mortality during pregnancy. There are no adequate reports or well-controlled studies of **atovaquone-proguanil** in pregnant women. At full term, both oral clearance (Cl/F) and the total apparent volume of distribution (V_d/F) estimates for both drugs were roughly 2× and plasma concentrations ½ that reported in healthy nonpregnant patients and those with acute malaria. Proguanil biotransformation into active antimalarial metabolites may be impaired during late pregnancy. These findings suggest the dosing regimen may need

to be increased during pregnancy to ensure efficacy and minimize the risk of resistance. (See comments under **atovaquone**.)
Side effects include pancytopenia, thrombocytopenia, neutropenia, phototoxicity, abdominal pain, N/V, diarrhea, dizziness, pruritus, rash, tinnitus, mouth ulcerations, and increased LFTs.

Fetal Considerations

There are no adequate and well-controlled studies in human fetuses. It is unknown whether **atovaquone-proguanil** crosses the human placenta. The clinical experience is reassuring.
Atovaquone crosses the rodent placenta, reaching an F:M ratio approximating 0.3. Rodent studies of **atovaquone** are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically. Rodent studies for proguanil too are reassuring, revealing no evidence of teratogenicity or IUGR, but the doses used have been insufficient to provide confidence in the conclusion. Though maternal and placental parasitemia is reduced by maternal pharmacotherapy, there is as yet no detectable reduction in perinatal mortality.

Breastfeeding Safety

There are no adequate reports or well-controlled studies in nursing women. It is unknown whether **atovaquone** enters human breast milk. It is excreted into rodent milk, achieving an M:P ratio of about one third. Trace amounts of proguanil are found in human breast milk. Perhaps in response to the inadequate study, the CDC recommends that breastfeeding women with infants <11kg should use **mefloquine** for malaria prophylaxis.

Drug Interactions

See **atovaquone**.
Slowed and diminished absorption of **cloxacillin** has been reported when given with proguanil. Caution should be taken to avoid subtherapeutic levels of **cloxacillin,** which can lead to treatment failure and facilitate drug resistance.

References

Babalola CP, Iwheye GB, Olaniyi AA. J Clin Pharm Ther 2002; 27:461-4.
Garner P, Gulmezoglu AM. Cochrane Database Syst Rev 2006; (4):CD000169.
Luzzi GA, Peto TE. Drug Saf 1993; 8:295-311.
McGready R, Ashley EA, Moo E, et al. J Infect Dis 2005; 192:846-53.
McGready R, Stepniewska K, Edstein MD, et al. Eur J Clin Pharmacol 2003; 59:545-52.
McGready R, Stepniewska K, Seaton E, et al. Eur J Clin Pharmacol 2003; 59:553-7.

Summary

Pregnancy Category: C
Lactation Category: S (if >11kg)

- **Atovaquone-proguanil** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk. The dose should probably be increased if used during late pregnancy.
- Proguanil is sold commercially as Paludrine and is not available in the U.S.
- The CDC recommends that breastfeeding women with infants <11kg use **mefloquine** for malaria prophylaxis.

Atracurium—(Tracrium)

International Brand Name—Acrium (Korea); Aculex (Korea); Genso (Taiwan); Mycurium (Israel); Relatrac (Colombia, Peru); Tracrium (Argentina, Chile, Costa Rica, Dominican Republic, Ecuador, El Salvador, Guatemala, Honduras, Mexico, Nicaragua, Panama, Paraguay, Uruguay); Tracur (Brazil); Tracurix (Argentina)

Drug Class

Anesthesia, adjunct; Musculoskeletal agents; Neuromuscular blockers, nondepolarizing

Indications

Surgical paralysis

Mechanism

Antagonizes ACh motor end plate receptors; nondepolarizing

Dosage with Qualifiers

Surgical paralysis—0.4-0.5mg/kg IV; may supplement with 0.08-0.10mg/kg q15-25min

- **Contraindications**—hypersensitivity to drug or class
- **Caution**—hepatic or renal dysfunction, hypotension, CV disease, electrolyte abnormalities

Maternal Considerations

Atracurium is an intermediate-duration curare derivative producing effective surgical paralysis. There are no adequate reports or well-controlled studies of **atracurium** in pregnant women. The clearance and clinical duration of **atracurium** are unaltered during pregnancy. In contrast, the clearance of **pancuronium** is increased 27% during cesarean section, and the mean onset time and clinical duration of **cisatracurium** are significantly reduced.
Side effects include CV collapse, tachycardia, hypotension, rash, flushing, and urticaria, all due to histamine release and hypertension.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. **Atracurium** has been used in lieu of **pancuronium** to facilitate fetal procedures. While small amounts are shown to cross the human placenta, its use during cesarean section is not associated with neonatal sequelae. In theory, fetal toxicity could be a risk if used for long-term paralysis of a critically ill pregnant woman.

Breastfeeding Safety

There are no adequate reports or well-controlled studies in nursing women. It is unknown whether **atracurium** enters human breast milk. Considering its application, **atracurium** is unlikely to affect the breastfeeding newborn. While some rodent studies report an increase in malformations, they are confounded by the profound respiratory depression associated with the drug.

Drug Interactions

Drugs that enhance the neuromuscular blocking action of **atracurium** include **enflurane, isoflurane,** and **halothane;** certain antibiotics, especially the aminoglycosides and polymyxins; **lithium;** magnesium salts; **procainamide;** and **quinidine**.
The prior administration of **succinylcholine** does not enhance duration, but quickens the onset and possibly the depth of neuromuscular blockade. **Atracurium** should not be given until a patient has recovered from **succinylcholine**.

References

Atherton DP, Hunter JM. Clin Pharmacokinet 1999; 36:169-89.
Guay J, Grenier Y, Varin F. Clin Pharmacokinet 1998; 34:483.

Mouw RJ, Klumper F, Hermans J, et al. Acta Obstet Gynecol Scand 1999; 78:763-7.
Pan PH, Moore C. J Clin Anesth 2001; 13:112-7.

Summary

Pregnancy Category: C
Lactation Category: U
- **Atracurium** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Atropine—(Atro Ofteno; Atropair; Atropen; Atropinol; Atropisol; Borotropin; Dosatropine; Isopto Atropine; Isotic cycloma; I-Tropine; Liotropina; Minims-Atropine; Ocu-Tropine; Sal-Tropine; Spectro-Atropine)

International Brand Name—Atrop (Malaysia); Atropin (Germany, Sweden); Atropina (Italy); Atropina Llorens (Spain); Atropin ''Dak'' (Denmark); Atropin Dispersa (Switzerland); Atropine (Greece); Atropine Dispersa (Hong Kong); Atropine Martinet (France); Atropine Sulfate Tablets (England); Atropini Sulfas (Bulgaria); Atropin Minims (Norway); Atrospan (Israel); Bellpino-Artin (India); Cendo Tropine (Indonesia); Chibro-Atropine (France); Ciba Vision Atropine (Thailand); Isopto (England); Isopto Atropin (Sweden); Isopto Atropina (Argentina, Ecuador); Isopto Atropine (Belgium, Canada, Malaysia, Philippines, Thailand); Minims Atropine Sulfaat (Netherlands); Minims Atropine Sulfate (England, Israel, Hong Kong); Skiatropine (Switzerland); Ximex Optidrop (Indonesia)

Drug Class

Anesthesia, adjunct; Antiarrhythmics; Antidotes; Cycloplegics; Mydriatics; Ophthalmics

Indications

Symptomatic bradycardia, organophosphate poisoning, adjunct to anesthesia to reduce secretions

Mechanism

Antagonizes ACh receptors

Dosage with Qualifiers

Symptomatic bradycardia—0.5-1mg IV q3-5min prn, max 2mg
Organophosphate poisoning—1-2mg IM/IV q20-30min until muscarinic symptoms resolve
Adjunct to anesthesia—0.4mg IM/SC 30-60min preoperatively to dry oral secretions before expected difficult airway management. Also given with anticholinesterase (**atropine** plus **neostigmine**) when reversing neuromuscular paralysis at the end of surgery.

*NOTE: may be combined with difenoxin, diphenoxylate, or **hyoscyamine, scopolamine,** and **phenobarbital** (Donnatal).*

- **Contraindications**—hypersensitivity to drug or class, narrow-angle glaucoma, paralytic ileus, asthma, myasthenia gravis
- **Caution**—unknown

Maternal Considerations

There are no adequate reports or well-controlled studies of **atropine** in pregnant women.
Side effects include paradoxical bradycardia (usually doses <0.3mg), tachycardia, palpitations, blurred vision, headache, N/V, dizziness, dry mouth, restlessness, delirium, tremor, and hot dry skin.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. **Atropine** rapidly crosses the human placenta, and the fetus will respond to the direct administration of **atropine**.

Breastfeeding Safety

There are no adequate reports or well-controlled studies in nursing women. It is unknown whether **atropine** enters human breast milk.

Drug Interactions	The signs of atropinization (flushing, mydriasis, tachycardia, dryness of the mouth and nose) may occur earlier than expected when used with **pralidoxime**.
References	Graf JL, Paek BW, Albanese CT, et al. J Pediatr Surg 2000; 35:1388-9. Kanto J, Lindberg R, Pihlajamaki K, Scheinin M. Pharmacol Toxicol 1987; 60:108-9.
Summary	**Pregnancy Category: C** **Lactation Category: U** • **Atropine** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Attapulgite

International Brand Name—None identified.

Drug Class	Antidiarrheals
Indications	Diarrhea
Mechanism	Unknown
Dosage with Qualifiers	Diarrhea—30ml PO prn, max 6×/d, alternatively 1.2-1.5g after each bowel movement (refer to each manufacturer's dosing formulations) • **Contraindications**—hypersensitivity to drug or class, bowel obstruction • **Caution**—fever, volume depletion
Maternal Considerations	There are no adequate reports or well-controlled studies of **attapulgite** in pregnant women. **Attapulgite** was formerly part of the Kaopectate formulation, but was removed in 2003. ***Side effects*** include constipation, dyspepsia, flatulence, and N/V.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **attapulgite** crosses the human placenta.
Breastfeeding Safety	There is no published experience in nursing women. It is unknown whether **attapulgite** will alter breast milk.
Drug Interactions	**Attapulgite** may alter absorption of a wide variety of drugs if taken together.
References	There are no relevant publications.
Summary	**Pregnancy Category: B** **Lactation Category: U** • There is no published experience in pregnant women, but a long clinical experience supports its occasional use during pregnancy.

Auranofin—(Ridaura)

International Brand Name—Aktil (Thailand); Auropan (Hungary); Crytion (Uruguay); Goldar (India); Ridaura (Brazil, Canada, China, Japan, Korea, Taiwan); Ridauran (France); Ridaura Tiltab (Hong Kong, Malaysia)

Drug Class	Antiarthritics; Gold compounds
Indications	Rheumatoid arthritis
Mechanism	Unknown
Dosage with Qualifiers	Rheumatoid arthritis—3mg PO bid; may increase to 9mg stepwise after 4-6mo • **Contraindications**—hypersensitivity to drug or class, gold toxicity, pulmonary fibrosis, dermatitis, bone marrow aplasia, necrotizing enterocolitis • **Caution**—hepatic or renal dysfunction
Maternal Considerations	There is no published experience with **auranofin** during pregnancy. ***Side effects*** include seizures, nephritic syndrome, renal failure, thrombocytopenia, ulcerative colitis, aplastic anemia, pneumonitis, pulmonary fibrosis, diarrhea, rash, itching, nausea, abdominal pain, conjunctivitis, hematuria, anemia, and anorexia.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **auranofin** crosses the human placenta. Rodent studies reveal an increased risk of embryo and fetal toxicity, gastroschisis, and umbilical hernia.
Breastfeeding Safety	There are no adequate reports or well-controlled studies in nursing women. It is unknown whether **auranofin** enters human breast milk. Gold is excreted into rodent milk.
Drug Interactions	A single case report suggests **auranofin** may have increased **phenytoin** blood levels.
References	No relevant publications.
Summary	**Pregnancy Category: C** **Lactation Category: U** • **Auranofin** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk. • There are usually alternative agents for which there is more experience during pregnancy and lactation.

Azatadine maleate—(Optimine)

International Brand Name—Idulamine (Colombia, Czech Republic, Mexico); Idulian (Bulgaria, Italy); Lergocil (Spain); Nalomet (Greece); Optimine (Belgium, Canada, England, Ireland); Verben (Denmark); Zadine (Hong Kong, Indonesia, Malaysia, Taiwan)

Drug Class	Antihistamines, H_1
Indications	Allergic rhinitis, urticaria
Mechanism	Unknown

Dosage with Qualifiers	Allergic rhinitis—1-2mg PO bid Urticaria—1-2mg PO bid • **Contraindications**—hypersensitivity, MAOI within 14d, urinary retention, prostatic hypertrophy • **Caution**—asthma, glaucoma
Maternal Considerations	**Azatadine** is an antihistamine with antiserotonergic, anticholinergic, and sedative effects. There is no published experience during pregnancy. ***Side effects*** include agranulocytosis, thrombocytopenia, anaphylaxis, dry mouth, nausea, abdominal pain, urinary retention, headache, constipation, and weight gain.
Fetal Considerations	There are no adequate reports or well-controlled studies of **azatadine** in human fetuses. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically.
Breastfeeding Safety	There are no adequate reports or well-controlled studies in nursing women. It is unknown whether **azatadine** enters human breast milk.
Drug Interactions	MAOIs prolong and intensify the anticholinergic and sedative effects of antihistamines. Additive effects may occur from the concomitant use of antihistamines with TCAs.
References	There is no published experience in pregnancy or during lactation.
Summary	**Pregnancy Category: B** **Lactation Category: U** • There are alternative agents for which there is more experience during pregnancy and lactation.

Azathioprine—(Imuran)

International Brand Name—Azafalk (Germany); Azahexal (Australia); Azamedac (Germany); Azamun (Hong Kong, New Zealand, Taiwan); Azamune (England); Azanin (Japan); Azapin (Australia); Azapress (South Africa); Azaprine (Korea); Aza-Q (Germany); Azarex (Germany); Azathiodura (Germany); Azathioprine (Israel); Azatioprina (Peru); Azatrilem (Mexico); Azopi (Israel); Azoran (India); Colinsan (Germany); Immuthera (Korea); Imunen (Brazil); Imuprin (Finland, Israel, Puerto Rico, South Africa); Imuran (Argentina, Belgium, Brazil, Bulgaria, Canada, Chile, Colombia, Czech Republic, Ecuador, England, Greece, Hungary, Ireland, Mexico, Netherlands, Paraguay, Poland, Portugal, Uruguay); Imurek (Austria, Germany, Switzerland); Imurel (Denmark, Finland, France, Norway, Spain, Sweden); Imuren (Norway); Transimune (India); Zytrim (Germany)

Drug Class	Immunosuppressants
Indications	Transplant rejection prophylaxis; immune disorders such as SLE, inflammatory bowel disease, and rheumatoid arthritis
Mechanism	A purine analog that inhibits T-cell activity
Dosage with Qualifiers	Transplant rejection—begin 3-5mg/kg/d PO/IV qd; maintenance 1-3mg/kg/d; transplant protocols vary Crohn's disease and ulcerative colitis—begin 50mg PO qd, increasing to 150-250mg PO qd; max 2.5mg/kg/d Rheumatoid arthritis—begin 1mg/kg PO qd; increase 0.5mg/kg/d after 6-8w; max 2.5mg/kg/d

NOTE: monitor CBC weekly; renal dosing if CrCl <50ml/h.

- **Contraindications**—hypersensitivity to drug or class
- **Caution**—pregnancy, lactation

Maternal Considerations

Azathioprine is metabolized to **6-mercaptopurine**. There are no adequate reports or well-controlled studies of **azathioprine** in pregnant women. Immune-related disorders are fairly common in reproductive-age women. Women with quiescent inflammatory bowel disease are likely to have an uncomplicated pregnancy, whereas women with active disease are more likely to have complications such as spontaneous abortions, miscarriages, stillbirths, and exacerbation of the disease. Most pregnancies treated with **azathioprine** end successfully, even in transplant patients. It has been used successfully for the treatment of autoimmune hepatitis during pregnancy.
Side effects include pancreatitis, fever, leukopenia, bone marrow suppression, immunosuppression, hepatotoxicity, risk of neoplasm, N/V, diarrhea, abdominal pain, rash, increased LFTs, myalgias, and arthralgia.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. **Azathioprine** crosses the human placenta; though the kinetics are unclear, it appears to reach equilibrium. The limited human experience (approximately 6 studies) is reassuring, and the drug should not be withheld if medically indicated. While no clear pattern of malformation is detectable in the large number of pregnant women exposed, isolated skeletal defects are reported. All immunosuppressants cross the placenta, and their long-term impact on the child later in life is unknown. There are also reports in neonates of reduced IgG and IgM, and leukopenia. It is unclear whether the reported increase in IUGR reflects disease or drug. Heightened immune responses were reported during the pregnancy of a woman whose mother had been treated with **azathioprine** throughout pregnancy. **Azathioprine** is teratogenic in rodents treated with human-equivalent doses, producing a constellation of malformations that are both skeletal and visceral.

Breastfeeding Safety

Azathioprine is excreted into breast milk, but the pharmacokinetics remain to be elucidated. In two women taking 75mg a day, the milk **6-mercaptopurine** was <20mcg/L, suggesting the breastfed neonate would ingest <0.5% of the maternal dose. There are no well-documented instances of neonatal effect.

Drug Interactions

Allopurinol inhibits the principal pathway for **azathioprine** detoxification. Women receiving both agents should have their dose of **azathioprine** reduced by ⅓ to ¼ the usual dose.
Drugs that may affect leukocyte production, including **co-trimoxazole,** may lead to exaggerated leukopenia, especially in renal transplant recipients.
The use of ACEIs in patients on **azathioprine** may induce severe leukopenia.
Azathioprine may inhibit the anticoagulant effect of **coumadin**.

References

Armenti VT, Moritz MJ, Davison JM. Drug Saf 1998; 19:219-32.
de Boer NK, Jarbandhan SV, de Graaf P, et al. Am J Gastroenterol 2006; 101:1390-2.
Heneghan MA, Norris SM, O'Grady JG, et al. Gut 2001; 48:97-102.
Khamashta MA. Best Pract Res Clin Rheumatol 2006; 20:685-94.
Scott JR, Branch DW, Holman J. Transplantation 2002; 73:815-6.
Sgro MD, Barozzino T, Mirghani HM, et al. Teratology 2002; 65:5-9.

Vroom F, de Walle HE, van de Laar MA, et al. Drug Saf 2006; 29:845-63.
Williamson RA, Karp LE. Obstet Gynecol 1981; 58:247-50.

Summary

Pregnancy Category: D
Lactation Category: U

- **Azathioprine** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.
- Consideration should be given to either switching to a different agent with a more reassuring safety profile, or reducing the dose to the minimum required for the control of symptoms.
- When required, the long-term clinical experience is reassuring.

Azithromycin—(Aruzilina; Zithromax)

International Brand Name—Aruzilina (Costa Rica, Dominican Republic, El Salvador, Guatemala, Honduras, Nicaragua, Panama); Atizor (Chile); Azadose (France); Azenil (Israel); Azimin (Colombia); Azithral (India); Azitrocin (Italy, Mexico); Azitromax (Norway, Sweden); Aziwok (India, South Africa); Azomyne (Israel); Azro (Israel); Aztrin (Indonesia); Forcin (Chile); Inedol (Peru); Kromicin (Colombia); Macrozit (Peru); Mezatrin (Indonesia); Octavax (Brazil); Setron (Peru); Sumamed (Bulgaria, China, Czech Republic, Hungary, Poland); Tobyl (Colombia); Tromix (Colombia); Ultreon (Germany); Xithrone (Israel); Zaret (Colombia); Zarom (Indonesia); Zeto (Israel); Zibramax (Indonesia); Zifin (Indonesia); Zimericina (Colombia); Zistic (Indonesia); Zithromax (Austria, Canada, Chile, England, France, Germany, Ireland, Netherlands, Switzerland); Zitrim (Colombia); Zitrim U (Colombia); Zitrobifan (Colombia); Zitromax (Argentina, Belgium, Brazil, Colombia, Denmark, Ecuador, Italy, Peru, Spain, Uruguay, Venezuela); Zomax (Israel)

Drug Class

Antibiotics; Macrolides

Indications

PID, *Chlamydia*, chancroid, uncomplicated gonorrhea, and community-acquired pneumonia

Mechanism

Inhibits microbial protein synthesis by binding to the P site of the 50S ribosomal subunit

Dosage with Qualifiers

Bacterial infection—500mg PO load ×1, then 250mg PO qd ×6d
Chlamydia or chancroid—1g PO ×1
Uncomplicated gonorrhea—2g PO ×1 (or 1g PO ×1 plus **fluoroquinolone** or **ceftriaxone** or **cefixime**)
PID—500mg IV qd ×2d, then 250mg PO qd ×6d
Community-acquired pneumonia—500mg IV qd ×2-5d, then 500mg PO qd for a total 7-10d

- **Contraindications**—hypersensitivity to drug or class
- **Caution**—hepatic dysfunction, **astemizole** or **terfenadine** use

Maternal Considerations

Azithromycin has a short serum t/2 in term pregnant women. Prolonged t/2 and high tissue levels occur in myometrium, placenta, and adipose tissue. When combined with **doxycycline,** it reduces the risk of postcesarean endomyometritis. Interconceptional use of **azithromycin** plus **metronidazole** does not reduce the prevalence of preterm birth compared to placebo. Considering its efficacy against other STDs and convenient dosing regimen, **azithromycin** is probably the treatment of choice for *Chlamydia*. Single-dose **azithromycin** may be as effective as **penicillin G** for the treatment of early syphilis. Partner pharmacotherapy is cost-effective. **Azithromycin** has been used in combination with **artesunate** as malaria prophylaxis. It was ineffective treatment to reduce lower genital tract colonization with *Ureaplasma urealyticum* in women with preterm labor.

Azithromycin also improves pulmonary function in women with cystic fibrosis and in women who are chronically infected with *Pseudomonas aeruginosa.*
Side effects include angioedema, anaphylaxis, cholestatic jaundice, Stevens-Johnson syndrome, pseudomembranous colitis, diarrhea, nausea, vaginitis, rash, anorexia, and itching.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. Less than 3% of maternally administered **azithromycin** crosses the placenta. Not surprisingly, there have been no adverse effects reported in humans. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically.

Breastfeeding Safety

Azithromycin is excreted in breast milk in a dose-dependent fashion that would approximate 0.4mg/kg/d, a subclinical amount. No neonatal effects have been reported.

Drug Interactions

Aluminum- and magnesium-containing antacids reduce the peak serum levels but not the AUC of oral **azithromycin**.
Concurrent use of macrolides may increase in the serum concentration of **theophylline**. While a single oral dose of **azithromycin** does not alter **theophylline** pharmacokinetics, its effect after multiple doses on steady-state **theophylline** is not known. Until further data are available, prudent medical practice dictates careful monitoring of plasma **theophylline** levels in patients receiving both concurrently.
Concurrent use of macrolides and **coumadin** in clinical practice is associated with increased anticoagulant effects. While **azithromycin** does not affect the PT response to a single dose of **coumadin,** prudent medical practice dictates careful monitoring of PT in all patients treated with both.
Macrolides have been reported to elevate **digoxin** levels.
Macrolides have been reported to increase the pharmacologic effect of **triazolam** by decreasing the clearance.
Macrolides may interfere with drugs metabolized by the CYP system, and thus may elevate serum levels of **carbamazepine, terfenadine, cyclosporine, hexobarbital,** and **phenytoin**.

References

Andrews WW, Goldenberg RL, Hauth JC, et al. Am J Obstet Gynecol 2006; 194:617-23.
Andrews WW, Hauth JC, Cliver SP, et al. Obstet Gynecol 2003; 101:1183-9.
Heikkinen T, Laine K, Neuvonen PJ, Ekblad U. BJOG 2000; 107:770-5.
Jacobson GF, Autry AM, Kirby RS, et al. Am J Obstet Gynecol 2001; 184:1352-4.
Kelsey JJ, Moser LR, Jennings JC, Munger MA. Am J Obstet Gynecol 1994; 170:1375-6.
Ogasawara KK, Goodwin TM. J Matern Fetal Med 1999; 8:12-6.
Postma MJ, Welte R, van den Hoek JA, et al. Value Health 2001; 4:266-75.
Ramsey PS, Vaules MB, Vasdev GM, et al. Am J Obstet Gynecol 2003; 188:714-8.
Riedner G, Rusizoka M, Todd J, et al. N Engl J Med 2005; 353:1236-44.
Saiman L, Marshall BC, Mayer-Hamblett N, et al. JAMA 2003; 290:1749-56.
Sarkar M, Woodland CC, Koren G, Einarson AR. BMC Pregnancy Childbirth 2006; 6:18.

Summary

Pregnancy Category: B
Lactation Category: S (likely)
- **Azithromycin** is an effective antimicrobial agent for a variety of disorders complicating pregnancy.

Aztreonam—(Azactam)

International Brand Name—Azactam (Argentina, Brazil, Chile, China, Ecuador, Egypt, Hong Kong, Israel, Japan, Korea, Peru, Philippines, Singapore, Taiwan, Venezuela); Azenam (India); Squibb-Azactam (Colombia)

Drug Class

Antibiotics; Monobactams

Indications

Susceptible bacterial infections, including gonorrhea

Mechanism

Inhibits bacterial cell wall synthesis by binding with high affinity to the penicillin-binding protein 3

Dosage with Qualifiers

Bacterial infection—0.5-2g IV/IM q8-12h; max 8g/d
Gonorrhea—1g IM ×1

NOTE: renal dosing.

- **Contraindications**—hypersensitivity to drug or class
- **Caution**—renal dysfunction

Maternal Considerations

There are no adequate reports or well-controlled studies of **aztreonam** in pregnant women. It is one of many antibiotics of potential use during pregnancy. **Aztreonam** is as effective as **gentamicin** plus **clindamycin** for the treatment of puerperal endomyometritis.
Side effects include seizures, anaphylaxis, eosinophilia, pseudomembranous colitis, phlebitis, diarrhea, nausea, rash, and elevated LFTs.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. **Aztreonam** crosses the human placenta in therapeutic concentrations, suggesting it might be useful for antepartal chorioamnionitis. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically.

Breastfeeding Safety

There are no adequate reports or well-controlled studies in human fetuses. It is excreted into the breast milk at trace levels.

Drug Interactions

No drug interactions are reported in humans.

References

Clark P. Obstet Gynecol Clin North Am 1992; 19:519-28.
Fleiss PM, Richwald GA, Gordon J, et al. Br J Clin Pharmacol 1985; 19:509-11.
Greenberg RN, Reilly PM, Weinandt WJ, et al. Clin Ther 1987; 10:36-9.
Itakura A, Kurauchi O, Mizutani S, et al. Jpn J Antibiot 1995; 48:749-53.
Matsuda S, Oh K, Hirayama H. Jpn J Antibiot 1990; 43:700-5.

Summary

Pregnancy Category: B
Lactation Category: S
- **Aztreonam** is a good agent whose selection may be based more on cost and availability than any particular advantage.
- **Aztreonam** achieves therapeutic levels in the fetal compartment.

Bacitracin—(Ak-Tracin; Baci-IM; Baci-Rx; Bacticin; Ocutricin; Spectro-Bacitracin)

International Brand Name—Bacitracine Martinet (France)

Drug Class	Antibiotics, miscellaneous; Anti-infectives, ophthalmic; Anti-infectives, topical; Dermatologics; Ophthalmics
Indications	Gram-positive and -negative bacterial infection
Mechanism	Bactericidal, cyclic polypeptide that inhibits bacterial cell wall synthesis
Dosage with Qualifiers	Skin or wound infection—apply cream topically qd to tid *NOTE: use no longer than 1w; often combined with* ***neosporin*** *and* ***polymixin B.*** • **Contraindications**—hypersensitivity to drug or class • **Caution**—myasthenia gravis
Maternal Considerations	There is no published experience during pregnancy. **Bacitracin** enhances wound healing in nonpregnant surgical patients and reduces scarring compared to placebo. ***Side effects*** include contact dermatitis.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **bacitracin** crosses the human placenta. Considering the dose and route, it is unlikely the maternal systemic concentration will reach a clinically relevant level. Rodent teratogenicity studies have not been performed.
Breastfeeding Safety	There are no adequate reports or well-controlled studies in nursing women. It is unknown whether **bacitracin** enters human breast milk. However, considering the dose and route, it is unlikely the breastfed neonate would ingest clinically relevant amounts.
Drug Interactions	No drug interaction studies identified.
References	Smack DP, Harrington AC, Dunn C, et al. JAMA 1996; 276:972-7. Watcher MA, Wheeland RG. J Dermatol Surg Oncol 1989; 11:1188-95.
Summary	**Pregnancy Category: C** **Lactation Category: S** • **Bacitracin** promotes wound healing and reduces scarring. • The long clinical experience with topical administration is reassuring.

Baclofen—(Lioresal)

International Brand Name—Alpha-Baclofen (New Zealand); Backen (Korea); Baclan (Korea); Baclapone (Korea); Baclo (Australia); Baclofene (France); Baclon (Finland, Taiwan); Baclosal (Israel, Thailand); Bacofen (Korea); Bacron (Korea); Bafen (Thailand); Baklofen (Czech Republic, Denmark, Norway); Baropan (Korea); Bigafen (Korea); Clofen (Australia, Malaysia); Curofen (Korea); Espast (Peru); Lebic (Germany); Lioresal (Argentina, Brazil, Canada, Ecuador, Paraguay, Uruguay, Venezuela); Lioresyl (Chile); Liotec (Canada); Lyflex (England, Ireland); Onelaxant-R (Philippines); Pacifen (New Zealand, Taiwan); Spinax (China, Taiwan); Stelax (Australia)

Drug Class	Muscle relaxants
Indications	Control of the spasticity secondary to MS and other spinal cord diseases
Mechanism	GABA B receptor antagonist (central-acting muscle relaxant)
Dosage with Qualifiers	Muscle spasm—begin 5mg PO tid; increase by 15mg qd q3d based on response; max 80mg/d • **Contraindications**—hypersensitivity to drug or class • **Caution**—renal dysfunction, seizure disorder
Maternal Considerations	There are no adequate reports or well-controlled studies of **baclofen** in pregnant women. The published experience is mostly limited to case reports, mostly of intrathecal use in women with MS. For example, one documents successful intrathecal use for the treatment of severe tetanus, and another the long-term treatment of severe spasticity after a C5 fracture. **Baclofen** proved superior to placebo for the relief of abortal pain. ***Side effects*** include CNS depression, seizures, CV collapse, drowsiness, headache, dizziness, blurred vision and slurred speech, constipation, pruritus, urinary frequency, constipation, and rash.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **baclofen** crosses the human placenta. There is a single case report of neonatal convulsions at 7d of age. Rodent studies reveal an increased prevalence of omphalocele, incomplete ossification of the sternum, vertebral arch widening, and neural tube defects when given at 10× the MRHD.
Breastfeeding Safety	There are no adequate reports or well-controlled studies in nursing women. **Baclofen** reduces sucking-induced prolactin release, but milk ejection is unchanged. Only about 0.1% of the maternal dose is excreted into human breast milk.
Drug Interactions	No drug interaction studies identified.
References	Committee on Drugs, American Academy of Pediatrics. Pediatrics 1994; 93:137-50. Corli O, Roma G, Bacchini M, et al. Clin Ther 1984; 6:800-7. Dalton CM, Keenan E, Jarrett L, et al. Mult Scler 2008; 14:571-2. Engrand N, Van De Perre P, Vilain G, Benhamou D. Eur J Anaesthesiol 2001; 18:261-3. Eriksson G, Swahn CG. Scand J Clin Lab Invest 1981; 41:185-7. Munoz FC, Marco DG, Perez AV, Camacho M. Ann Pharmacother 2000; 34:956. Ratnayaka DM, Dhaliwal H, Watkin S. BMJ 2001; 323:85.
Summary	**Pregnancy Category: C** **Lactation Category: S** • **Baclofen** is rarely necessary during pregnancy and should be given only when the benefits exceed the potential risks.

Balsalazide—(Colazal)

International Brand Name—Benoquin (Argentina); Colazide (Austria, England); Premid (Denmark)

Drug Class	Gastrointestinals; Salicylates
Indications	Ulcerative colitis, acute
Mechanism	Exact mechanism unknown (central-acting muscle relaxant)
Dosage with Qualifiers	Ulcerative colitis—2.25g PO tid; max use 8w • **Contraindications**—hypersensitivity to drug or class • **Caution**—renal dysfunction, seizure disorder, antibiotic treatment, pyloric stenosis
Maternal Considerations	**Balsalazide** is a prodrug enzymatically cleaved in the colon to produce melsalamine. Though considered safe to use by some clinicians, there are no adequate reports or well-controlled studies of **balsalazide** in pregnant women. ***Side effects*** include angioedema, bradycardia, bronchospasm, colitis, N/V, diarrhea, abdominal pain, anemia, epistaxis, anxiety, depression, nephritis, arthralgia, alopecia, and dermatitis.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **balsalazide** crosses the human placenta. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically.
Breastfeeding Safety	There is no published experience in nursing women. It is unknown whether **balsalazide** enters human breast milk.
Drug Interactions	No drug interaction studies were identified. Oral antibiotics could theoretically interfere with the release of **mesalamine** in the colon.
References	Klotz U. Clin Pharmacokinet 1985; 10:285-302. Schroeder KW. Scand J Gastroenterol Suppl 2002; (236):42-7.
Summary	**Pregnancy Category: B** **Lactation Category: U** • **Balsalazide** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Basiliximab—(Simulect)

International Brand Name—Simulect (Argentina, Brazil, Canada, Chile, Colombia, Hong Kong, Israel, Malaysia, Mexico, Peru, Philippines, South Africa, Taiwan, Thailand, Uruguay); Simultec (Venezuela)

Drug Class	Immunosuppressants; Monoclonal antibodies
Indications	Renal transplant immunoprophylaxis
Mechanism	IL-2 receptor antagonist
Dosage with Qualifiers	Kidney transplant—20mg IV single dose *NOTE: **basiliximab** should be given only after it is determined the patient will receive a graft; a second dose should be administered with great caution.*

- **Contraindications**—hypersensitivity to drug or class
- **Caution**—unknown

Maternal Considerations	There are only case reports of **basiliximab** use during pregnancy. ***Side effects*** include constipation, diarrhea, nausea, hyperkalemia, hypokalemia, acne, insomnia, angina pectoris, headache, tremor, hypertension, dysuria, UTI, edema, fever, asthenia, and hypercholesterolemia.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **basiliximab** crosses the human placenta. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically.
Breastfeeding Safety	There is no published experience in nursing women. It is unknown whether **basiliximab** enters human breast milk. However, considering the indication and dosing, one-time **basiliximab** use is unlikely to pose a clinically significant risk to the breastfeeding neonate.
Drug Interactions	No drug interaction studies or reports were identified. It is considered best to avoid live vaccines.
References	Danesi R, Del Tacca M. Transplant Proc 2004; 36:705-7.
Summary	**Pregnancy Category: B** **Lactation Category: U** • **Basiliximab** should be given to pregnant women only when the benefits outweigh the potential risks.

Beclomethasone—(Beclovent; Beconase; Vanceril; Vanceril DS)

International Brand Name—Aerobec (Germany, Mexico, South Africa); Afifon (Israel); Alanase (New Zealand); Aldecin (Australia, Belgium, Bulgaria, China, Denmark, Hong Kong, Malaysia, Netherlands, Switzerland, Taiwan); Aldecina (Costa Rica, Dominican Republic, El Salvador, Guatemala, Honduras, Nicaragua, Panama, Portugal); Aldecin Hayfever Aqueous Nasal Spray (Australia); Anceron (South Africa); Andion (Denmark); Asmabec Clickhaler (France); Atomase (Malaysia, New Zealand, Singapore); Beceze (Israel); Beclate (India, South Africa); Beclazone (Israel, New Zealand); Beclazone CFC Free (Singapore); Beclo-Asma (Hong Kong, Singapore); Beclo-Asma CFC Free (Singapore); Beclocort Nasel (Poland); Becloforte (Israel, Hong Kong, New Zealand, South Africa); Beclomet (Bulgaria, Germany, Malaysia, Switzerland, Taiwan); Beclometasone (France); Beclomet Easyhaler (Indonesia, Korea, Thailand); Beclomet Nasal Aqua (Indonesia, Thailand); Beclone (France); Beclo-Rhino (France); Beclorhinol (Germany); Beclo Siozwo Nasenspray (Germany); Beclosol Aquoso (Brazil); Becloturmant (Germany); Becodisks (China); Beconase (Austria, Belgium, Bulgaria, Chile, China, Costa Rica, Dominican Republic, Ecuador, El Salvador, England, Finland, France, Guatemala, Honduras, Hong Kong, Hungary, Indonesia, Malaysia, Mexico, Netherlands, Nicaragua, Panama, Peru, Portugal, South Africa, Spain, Thailand, Venezuela); Becotide (Bangladesh, Bulgaria, Costa Rica, Dominican Republic, Ecuador, El Salvador, Germany, Guatemala, Honduras, India, Indonesia, Ireland, Israel, Japan, Korea, Malaysia, Mexico, New Zealand, Nicaragua, Pakistan, Panama, Paraguay, Peru, Poland, Slovenia, South Africa, Turkey, Uruguay); Belax (Taiwan); Bemedrex Easyhaler (France); Bronconox (Colombia); Bronconox Forte (Colombia); Clenil (Indonesia, Philippines, Singapore, South Africa, Taiwan); Clenil Forte (Indonesia, Philippines); Decomit (Singapore); Ecobec (France); Filair (Chile); Miflasone (France, New Zealand); Nasobec Aqueous (Korea); Nexxair (France); Nobec (South Africa); Q Var (Argentina, Costa Rica, El Salvador, Guatemala, Honduras, Hong Kong, Malaysia, New Zealand, Nicaragua, Panama, Philippines, Singapore, South Africa); Qvar Autohaler (Australia, France); Qvar Inhaler (Australia); RatioAllerg (Germany); Respocort (Malaysia, New Zealand, Philippines); Rhinocort (Israel); Rinaze (South Africa); Rino-Clenil (England); Rynconox (Colombia); Viarex (Israel); Viarox (Germany, South Africa); Xiten (Peru)

Drug Class	Corticosteroids
Indications	Treatment of asthma, rhinitis; nasal polyp prophylaxis

Mechanism

Anti-inflammatory mechanism unknown

Dosage with Qualifiers

Asthma—4-16 inhalations/d
Rhinitis—1-2 inhalations in each nostril qd; max 336mcg/d
Nasal polyp prophylaxis—1-2 inhalations in each nostril qd; max 336mcg/d

NOTE: each metered inhalation delivers 42mcg of aerosolized drug.

- **Contraindications**—hypersensitivity to drug or class
- **Caution**—local infection

Maternal Considerations

Asthma is associated with several complications during pregnancy. Inhaled corticosteroids are generally be considered the prophylactic medication of choice in pregnant women with persistent asthma, unless well controlled by either **cromolyn** or **nedocromil. Beclomethasone** effectiveness requires regular use. A recent randomized trial compared **beclomethasone** to oral **theophylline** for the treatment of moderate asthma. Thus, **beclomethasone** is considered a first-line agent along with **budesonide** during pregnancy.
Side effects include irritation of nasal mucous membranes, urticaria, edema, bronchospasm, headache, and nausea.

Fetal Considerations

There are no well-controlled studies of **beclomethasone** in human fetuses. It is unknown whether **beclomethasone** specifically crosses the human placenta. Hypoadrenalism may occur in newborns of women using **beclomethasone,** suggesting placental transfer. Rodent studies using up to 10× the MRHD revealed increased frequencies of fetal resorption, cleft palate, delayed ossification, agnathia, and embryocidal effect.

Breastfeeding Safety

There are no adequate reports or well-controlled studies in nursing women. It is unknown whether **beclomethasone** enters human breast milk. Other steroids are excreted in low amounts.

Drug Interactions

No drug interaction studies identified.

References

Beck SA. Allergy Asthma Proc 2001; 22:1-4.
Brown HM, Storey G. Postgrad Med J 1975; 51:59-64.
Dombrowski MP, Brown CL, Berry SM. J Matern Fetal Med 1996; 5:310-3.
Dombrowski MP, Schatz M, Wise R, et al; National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network; National Heart, Lung, and Blood Institute. Am J Obstet Gynecol 2004; 190:737-44.
Karinski DA, Balkundi D, Rubin LP, Padbury JF. Neonatal Netw 2000; 19:27-32.
Mazzotta P, Loebstein R, Koren G. Drug Saf 1999; 20:361-75.
Stenius-Aarniala B, Piirila P, Teramo K. Thorax 1988; 43:12-8.
Wendel PJ, Ramin SM, Barnett-Hamm C, et al. Am J Obstet Gynecol 1996; 175:150-4.

Summary

Pregnancy Category: C
Lactation Category: U

- **Beclomethasone** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.
- Fetal adrenal suppression may occur after prolonged maternal systemic steroid administration.

Belladonna—(Donnatal; Lomotil; Atropine Sulfate)

International Brand Name—None identified.

Drug Class	Analgesics, narcotic; Parasympatholytics
Indications	Adjunctive therapy for irritable bowel syndrome, acute enterocolitis, duodenal ulcer, cesarean section (to decrease secretions), fetal bradycardia
Mechanism	Anticholinergic; atropine is the active agent
Dosage with Qualifiers	Donnatal—0.0194mg/tab, 5ml/elixir (23% alcohol) Lomotil—0.025mg/tab, 5ml Atropine sulfate—0.1mg/ml *NOTE: individualize the dose; may be combined with either opium,* ***ergotamine, phenobarbital,*** *or* ***butabarbital.*** • **Contraindications—**hypersensitivity to drug or class • **Caution**—neuropathy, glaucoma, hepatic diseases, hyperthyroidism, coronary heart diseases, chronic lung diseases
Maternal Considerations	There are no well-controlled studies of **belladonna** in pregnant women. ***Side effects*** include xerostomia, taste change, blurred vision, bradycardia, palpitations, drowsiness, headache, and anaphylaxis.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. **Belladonna** rapidly crosses the placenta, producing a pharmacologic fetal vagotomy with subsequent tachycardia. It decreases fetal breathing. However, no adverse acute or chronic fetal effects are documented in women taking **atropine.** No association with malformations has been documented.
Breastfeeding Safety	No adequate well-controlled studies determined the passage of **belladonna** in the breast milk; it is generally considered safe for breastfeeding.
Drug Interactions	Caution is advised in the administration of **belladonna-butabarbital** to women using anticoagulant agents. **Belladonna-butabarbital** may decrease the systemic effects of exogenous or endogenous corticosteroids. The concomitant use of other CNS depressants, including sedatives or hypnotics, antihistamines, tranquilizers, or alcohol, may produce additive depressant effects.
References	Abboud T, Raya J, Sadry S, et al. Anesth Analg 1983; 62:426-30. Freeman JJ, Altieri RH, Baptiste HJ, et al. J Natl Med Assoc 1994; 86:704-8. Hellman LM, Filisti LP. Am J Obstet Gynecol 1965; 91:797-805.
Summary	**Pregnancy Category: C** **Lactation Category: S** • **Belladonna** is useful adjuvant therapy for GI symptoms related to irritable bowel syndrome, acute enterocolitis, and duodenal ulcer. • **Belladonna** decreases fetal breathing.

Benazepril—(Lotensin)

International Brand Name—Benace (India); Boncordin (Argentina); Cibace (South Africa); Cibacen (Austria, Belgium, Denmark, Finland, Germany, Greece, Indonesia, Israel, Italy, Japan, Korea, Netherlands, Philippines, Portugal, Spain, Sweden, Switzerland, Taiwan); Cibacen Cor (Germany); Cibacene (France); Lotensin (Brazil, Bulgaria, Canada, China, Czech Republic, Ecuador, Hungary, Mexico, Peru, Poland, Uruguay, Venezuela)

Drug Class	ACEI/A2R-antagonists; Antihypertensives
Indications	Hypertension, congestive heart failure
Mechanism	Angiotensin-converting enzyme inhibitor
Dosage with Qualifiers	Hypertension—begin 10mg qd, max 80mg/d Congestive heart failure—begin 5mg qd; lower doses when used with a diuretic *NOTE: renal dosing.* May be combined with **hydrochlorothiazide.** • **Contraindications**—hypersensitivity to drug or class, renal artery stenosis, pregnancy • **Caution**—renal dysfunction, hypovolemia, collagen vascular disease, severe CHF
Maternal Considerations	The published experience during pregnancy consists of case reports. However, this class of agents is associated with severe fetal renal toxicity. Once thought relatively safe in the 1st trimester, **benazepril** is now considered contraindicated throughout gestation. ***Side effects*** include angioedema, hypotension, renal failure, hyperkalemia, elevated BUN/Cr, pancreatitis, liver toxicity, agranulocytosis, dizziness, headache, dyspepsia, cough, rash, urticaria, fatigue, myalgia, diarrhea, and taste changes.
Fetal Considerations	**Benazepril** may cause embryonic, fetal, and neonatal morbidity and death. ACEIs during the 2nd and 3rd trimesters of pregnancy are associated with hypotension, neonatal skull hypoplasia, renal failure, and oligohydramnios. It is not known whether all ACEIs have the exact risks. **Benazepril** has in humans been associated with oligohydramnios that was reversible with discontinuation. Limited placental transfer is noted in the rat.
Breastfeeding Safety	There is no published experience in nursing women. Minimal amounts of **benazepril** enter the breast milk.
Drug Interactions	May cause hypotension in women on diuretics, especially if recently started. This risk can be minimized by either discontinuing the diuretic or increasing salt intake prior to initiation. If this is not possible, the starting dose should be reduced. May attenuate potassium loss caused by thiazide diuretics. Potassium-sparing diuretics (e.g., **spironolactone, amiloride, triamterene**) or potassium supplements increase the risk of hyperkalemia. Increased serum **lithium** and symptoms of **lithium** toxicity are reported in patients receiving ACEIs. Frequent monitoring of the serum **lithium** level is recommended.
References	Chisholm CA, Chescheir NC, Kennedy M. Am J Perinatol 1997; 14:511-3. Muller PR, James A. J Perinatol 2002; 22:582-4.

Waldmeier F, Schmid K. Arzneimittelforschung 1989; 39:62-7.
Yamamoto S, Takemori E, Hasegawa Y, et al. Arzneimittelforschung 1991; 41:913-23.

Summary

Pregnancy Category: C (1st trimester), **D** (2nd and 3rd trimesters)
Lactation Category: S (likely)
- **Benazepril** is a recognized human teratogen and is contraindicated throughout pregnancy.
- There are alternative agents with a higher safety profile for which there is more experience during pregnancy and lactation.

Bendroflumethiazide—(Bendrofluazide; Benzide; Corzide; Esberizid; Naturetin; Salural)

International Brand Name—Aprinox (England); Berkozide (England); Centyl (Denmark, Ireland, Norway, Sweden); Inderetic (Netherlands); Naturine (France); Neo-Naclex (New Zealand); Pluryl (Belgium, Netherlands); Pluryle (Greece, Israel, South Africa); Prestim (Netherlands); Salures (Sweden); Sinesalin (Austria, Germany, Switzerland)

Drug Class

Diuretics; Thiazides

Indications

Hypertension

Mechanism

Mechanism unknown; interferes with electrolyte resorption in the distal renal tubule

Dosage with Qualifiers

Diuretic—5mg PO qam
Hypertension—5-20mg PO qd
Hypertension (Corzide)—1 tab PO qd

*NOTE: Corzide: each tablet contains 5mg of **bendroflumethiazide** plus **nadolol** (40 or 80mg).*

- **Contraindications**—hypersensitivity to drug or class, AV block, sinus bradycardia, cardiogenic shock, bradycardia, hypotension, bronchospasm, dizziness, N/V, confusion, rash, photosensitivity, and electrolyte abnormalities
- **Caution**—renal dysfunction

Maternal Considerations

There is no published experience with **bendroflumethiazide** during pregnancy. Thiazide diuretics should be avoided during pregnancy except for the treatment of congestive heart disease. It has been suggested but not shown that diuretics in general may hinder placental perfusion by preventing normal plasma expansion. Thiazide diuretics are diabetogenic in some women. There are several reports of severe electrolyte imbalance in both mothers and newborns. Hemorrhagic pancreatitis has also been reported after thiazide exposure.
Side effects include CHF, thrombocytopenia, agranulocytosis, and exfoliative dermatitis.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **bendroflumethiazide** crosses the human placenta. Other thiazide agents readily cross. Fetal bradycardia associated with fetal hypokalemia has also been reported after maternal thiazide use. Though not associated with congenital defects, neonatal thrombocytopenia and hypoglycemia are reported.

Breastfeeding Safety

There is no published experience in nursing women. Many thiazide diuretics are excreted into breast milk, but in low concentrations. They are generally considered safe for breastfeeding women.

Drug Interactions

Alcohol, barbiturates, or narcotics may trigger orthostatic hypotension.
Amphotericin B, corticosteroids, or **corticotropin** (ACTH) may intensify electrolyte imbalance, particularly hypokalemia.
May decrease the effects of oral anticoagulants.
May potentiate the effects of other antihypertensive medications (e.g., ganglionic or peripheral adrenergic blocking agents).
Oral hypoglycemic agents and insulin dosages may need to be increased as thiazides may elevate blood glucose.
May increase the risk of digitalis toxicity due to hypokalemia.
Cholestyramine and **colestipol** may delay or decrease absorption of **bendroflumethiazide.**
May enhance **lithium** toxicity by decreasing lithium renal clearance.
Hypotensive effects are enhanced by MAOIs.
Nondepolarizing muscle relaxants, preanesthetics and anesthetics used in surgery may be potentiated.
In some patients, the administration of an NSAID can reduce the diuretic, natriuretic, and antihypertensive effect of loop, potassium-sparing, or thiazide diuretics.
May decrease the effectiveness of **methenamine** due to alkalinization of the urine.
May have hyperuricemic effects requiring an increase in **probenecid** or **sulfinpyrazone.**

References

Assoli NS. Clin Pharmacol Ther 1960; 1:48-52.
Beermann B, Fahraeus L, Groschisky-Grind M, Lindstrom B. Gynecol Obstet Invest 1980; 11:45-8.
Finnerty FA, Buchholz JH, Tuckman J. JAMA 1958; 166:1414.
Flowers CE, Grizzle JE, Easterling WE, Bonner OB. Am J Obstet Gynecol 1962; 84:919-29.
Goldman JA, Neri A, Ovadia J, et al. Am J Obstet Gynecol 1969; 105:556-60.
Minkowitz S, Soloway HB, Hall JE, Yermakov V. Obstet Gynecol 1964; 24:337-42.
[No authors]. Drug Ther Bull 2001; 39(5):37-40.
Pritchard JA, Waley PJ. Am J Obstet Gynecol 1961; 81:1241-4.
Rodriguez SU, Leikin SL, Hiller MC. N Engl J Med 1964; 270:881-4.
Sibai BM, Grossman RA, Grossman HG. Am J Obstet Gynecol 1984; 150:831-5.

Summary

Pregnancy Category: D
Lactation Category: S

- Thiazide diuretics are contraindicated during pregnancy except for the treatment of congestive heart disease.
- There are alternative agents with a higher safety profile during pregnancy for almost all indications.

Benzocaine—(Americaine; Anacaine; Otocain)

International Brand Name—Anaesthesin (Germany); Auralyt (Mexico); Octicaina (Colombia); Topicaine (Australia)

Drug Class	Anesthetics, local
Indications	Topical anesthetic, lubricant, relief of pain in acute congestive and serous otitis, acute swimmer's ear, production of anesthesia of mucous membrane
Mechanism	Stabilizes the neuronal membrane and alters its permeability to sodium ions
Dosage with Qualifiers	Topical anesthetic (e.g., episiotomy pain)—apply to affected area as needed Anesthetic lubricant—apply over the intratracheal catheters and pharyngeal and nasal airways with the purpose of attenuating local reflexes Congestive and serous otitis and acute swimmer's ear—supplied as eardrops Anesthesia of mucous membrane—supplied as topical gel or local spray; max 20mg *NOTE: combined with antipyrine for otic uses.* • **Contraindications**—hypersensitivity to drug or class, perforated tympanic membrane • **Caution**—not known
Maternal Considerations	There are no well-controlled studies of **benzocaine** during pregnancy. It provides relief from perineal pain associated with episiotomy, especially when associated with a corticosteroid. Some practitioners use it as an alternative to **lidocaine** for the symptomatic relief of perineal herpetic lesions. ***Side effects*** include contact dermatitis, burning, and pruritus.
Fetal Considerations	There are no well-controlled studies of **benzocaine** in human fetuses. It is unknown whether **benzocaine** crosses the human placenta. Considering the dose and route, it is unlikely the maternal systemic concentration will reach a clinically relevant level.
Breastfeeding Safety	There is no published experience in nursing women. However, considering the dose and route, it is unlikely the breastfed neonate would ingest clinically relevant amounts.
Drug Interactions	No drug interaction studies identified.
References	Goldstein PJ, Lipman M, Luebehusen J. South Med J 1977; 70:806-8.
Summary	**Pregnancy Category: C** **Lactation Category: U** • Postepisiotomy pain can be an annoying complication relieved by local anesthetic. • Although frequently used to relieve the pain secondary to genital herpetic lesion, there are no well-controlled trials in this clinical context.

Benzoyl peroxide—(Benzac; Brevoxyl; Desquam-E; Desquam-X10; Desquam-X 5)

International Brand Name—Acetoxy (Canada); Acnacyl (Hong Kong, Singapore); Acneclear (Hong Kong); Acne Derm (Israel); Acne Mask (Israel); Acnetick-10 (Colombia); Acnexyl (Thailand); Acnie (Taiwan); Akneroxid (Austria, Germany, Hungary, Netherlands, Switzerland); Aldoacne (Spain); Basiron (Denmark, Finland, Norway, Sweden); Benoxid (Finland); Benoxil (Venezuela); Benoxyl (Brazil, Canada, England, Ireland, Israel, New Zealand, Philippines, Puerto Rico, Venezuela); Benoxyl 5 Lotion (Taiwan); Benoxyl AQ AL (Mexico); Benzac AC (Australia, Dominican Republic, El Salvador, Guatemala, Hong Kong, Israel, Malaysia, Mexico, Peru, Singapore, Venezuela); Benzac-AC 5 (South Africa); Benzac W (Australia, Chile, Greece, Mexico, Peru, Philippines, Puerto Rico); Benzeperox (Germany); Benzihex (Argentina); Benzihex AC (Paraguay, Uruguay); Benzolac (Indonesia); Benzperox (Bulgaria); Boxazin (Chile); Brevoxyl (France, Germany, Singapore, Switzerland, Taiwan); Cutacnyl (Portugal); Eclaran (France); Ecuaderm (Venezuela); Effacne (France); Klinoxid (Germany); Mytolac (Sweden); Oxiderma (Spain); Oxy (Brazil); Oxy 5 (Israel); Oxy-5 (Netherlands); Oxy 10 (Israel); Oxyderm (Canada); Oxy Lotion (Korea); Oxy Sensitive Vanishing Gel (Israel); Oxy Wash (Israel); Panoxyl (Australia, Brazil, Canada, Colombia, England, Finland, France, Germany, Hong Kong, Malaysia, Norway, Philippines, Taiwan, Thailand); PanOxyl (Australia); Panoxyl AQ (Costa Rica, Dominican Republic, El Salvador, Guatemala, Honduras, Hong Kong, Nicaragua, Panama, Taiwan, Thailand); Panoxyl Preps (New Zealand); Panoxyl Wash Lotion (Mexico); Pansulfox (Chile); Pernox Gel (India); Peroxiben (Spain); Persol Gel (India); Pimplex (Indonesia); Scherogel (Austria); Ultra Clearasil (Philippines); Vixiderm (Argentina)

Drug Class	Anti-infectives, topical; Dermatologics; Keratolytics
Indications	Acne vulgaris
Mechanism	Drying agent
Dosage with Qualifiers	Acne vulgaris—apply to affected areas qd or bid *NOTE: also packaged with* ***clindamycin*** *or* ***erythromycin.*** • **Contraindications**—hypersensitivity to drug or class • **Caution**—not known
Maternal Considerations	**Benzoyl peroxide** is for external use only. It has been used for the treatment of acne since the 1930s. There are no well-controlled studies in pregnant women. ***Side effects*** include dryness, irritation, and pruritus.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **benzoyl peroxide** crosses the human placenta. Rodent teratogen studies have apparently not been conducted. Considering the dose and route, it is unlikely the maternal systemic concentration will reach a clinically relevant level.
Breastfeeding Safety	There is no published experience in nursing women. It is unknown whether **benzoyl peroxide** enters human breast milk.
Drug Interactions	No drug interaction studies identified.
References	Auffret N. Presse Med 2000; 29:1091-7. Ives TJ. Am Pharm 1992; NS32:33-8. Reeves JR. Med Times 1980; 108:82-6.
Summary	**Pregnancy Category: C** **Lactation Category: U** • It is unlikely this drying agent poses a significant risk to the perinate.

Benztropine—(Bensylate; Cogentin; Glycopyrrolate)

International Brand Name—Akitan (Finland); Apo-Benzthropine (Canada); Bentrop (Australia); Cogentin (Canada, England, Hong Kong, Ireland, Malaysia, Norway, Portugal, Sweden, Thailand)

Drug Class	Anticholinergics; Antihistamines; Antiparkinson agents; Parasympatholytics
Indications	Adjunct therapy for parkinsonism or for the treatment of extrapyramidal reactions
Mechanism	Antagonizes ACh and histamine receptors
Dosage with Qualifiers	Parkinsonism—begin 0.5-1mg PO qd, increase by 0.5mg q5d; max 6mg PO qd Extrapyramidal reactions—1-4mg PO qd or bid • **Contraindications**—hypersensitivity to drug or class, narrow-angle glaucoma, tardive dyskinesia, ileus • **Caution**—CV disease
Maternal Considerations	There are no adequate reports or well-controlled studies of **benztropine** in pregnant women. The published experience is limited to isolated case reports. ***Side effects*** include tachycardia, anticholinergic psychosis, dry mouth, constipation, tachycardia, sedation, N/V, flatulence, anorexia, rash, dizziness, headache, nervousness, tinnitus, edema, and blurred vision.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **benztropine** crosses the human placenta. Exposure to **benztropine** during the 1st trimester might be associated with CV defects. Neonatal paralytic ileus has been reported after **benztropine** use.
Breastfeeding Safety	There is no published experience in nursing women. It is unknown whether **benztropine** enters human breast milk. No adverse neonatal effects are reported with other parasympatholytics such as **atropine.**
Drug Interactions	May increase the effects of antipsychotic drugs such as phenothiazines, **haloperidol,** and TCAs.
References	Committee on Drugs, American Academy of Pediatrics. Pediatrics 1994; 93:137-50. Falterman CG, Richardson CJ. J Pediatr 1980; 97:308-10. Thornburg JE, Moore KE. Res Commun Chem Pathol Pharmacol 1973; 6:313-20.
Summary	**Pregnancy Category: C** **Lactation Category: U** • **Benztropine** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Bepridil—(Vascor)

International Brand Name—Bepricol (Japan); Cordium (Portugal); Cruor (Argentina); Unicordium (France)

Drug Class	Calcium channel blockers
Indications	Chronic stable angina
Mechanism	Inhibits calcium influx into myocardial and vascular smooth muscle
Dosage with Qualifiers	Chronic stable angina—begin 200mg PO qd; max 400mg qd • **Contraindications**—hypersensitivity to drug or class, cardiac insufficiency, sick sinus syndrome, 2nd or 3rd degree heart block, hypotension, arrhythmia, prolonged QT interval • **Caution**—electrolyte abnormalities, bradycardia, recent MI, hepatic or renal dysfunction
Maternal Considerations	There is no published experience with **bepridil** during human pregnancy. ***Side effects*** include ventricular arrhythmia, prolonged QT interval, CHF, agranulocytosis, interstitial pulmonary disease, weakness, dizziness, headache, dyspepsia, nausea, tremor, anxiety, drowsiness, dyspnea, dry mouth, paresthesias, insomnia, syncope, flu-like syndrome.
Fetal Considerations	There are no well-controlled studies during pregnancy. Decreased fetal weight and survival were reported in animals exposed to doses more than 30× the MRHD. No teratogenic effects were noted in laboratory animals at the same dosages.
Breastfeeding Safety	There is no published experience in nursing women. **Bepridil** is excreted into human breast milk, achieving an M:P ratio approximating 0.33 according to the manufacturer, but the kinetics remain to be clarified. Caution is indicated considering the long t/2 and high oral absorption.
Drug Interactions	The likelihood of a serious adverse effect is increased by concomitant use of antiarrhythmic agents such as **quinidine** and **procainamide,** cardiac glycosides, and TCAs. Antiarrhythmics and TCAs may exaggerate the prolongation of the QT interval. Cardiac glycosides may exaggerate the depression of AV nodal conduction.
References	No publications of use in human pregnancy.
Summary	**Pregnancy Category: C** **Lactation Category: U** • **Bepridil** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk. • There are alternative agents for which there is more experience during pregnancy and lactation.

β-Carotene—(Vitamin A)

International Brand Name—B-Tene (Australia); Carotaben (Austria, Germany, Netherlands, Switzerland); Natural Betacarotene (Australia); Solvin (Ecuador)

Drug Class	Vitamins/minerals
Indications	Nutritional supplementation
Mechanism	Antioxidant
Dosage with Qualifiers	Supplementation—8000-25000IU PO qd • **Contraindications**—malabsorption syndrome • **Caution**—unknown
Maternal Considerations	**β-Carotene** is an antioxidant, and consuming foods rich in **β-carotene** may help protect from free radical damage. Some studies suggest dietary intake of **β-carotene** may reduce the risk of heart disease and cancer. There are no adequate reports or well-controlled studies in pregnant women. It has been suggested that millions of pregnant women annually suffer night blindness because of a deficiency. The safety of doses exceeding 6000 USP units during pregnancy is not established. ***Side effects*** include acute toxicity (fatigue, malaise, lethargy, abdominal discomfort), skeletal malformations (cortical thickening, short bones), arthralgia, alopecia, and cracking of the lips.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. High doses of **β-carotene** are teratogenic (bone, heart). There is no evidence of teratogenicity in women consuming 8000-25,000IU per day. However, low levels in rodents is associated with a reduction in the number of nephrons.
Breastfeeding Safety	There is no published experience in nursing women. **β-Carotene** enters human breast milk and raises its vitamin A level.
Drug Interactions	No drug interaction studies identified.
References	Bahl R, Bhandari N, Wahed MA, et al. J Nutr 2002; 132:3243-8. Bhat PV, Manolescu DC. J Nutr 2008; 138:1407-10. Fairfield KM, Fletcher RH. JAMA 2002; 287:3116-26. Mills JL, Simpson JL, Cunningham GC, et al. Am J Obstet Gynecol 1997; 177:31-6. West KP Jr. Food Nutr Bull 2003; 24:S78-90. Yamini S, West KP Jr, Wu L, et al. Eur J Clin Nutr 2001; 55:252-9.
Summary	**Pregnancy Category: C** **Lactation Category: U** • **β-Carotene** should be used during pregnancy only if the benefit justifies the potential fetal risk. • Supplementation is commonplace during pregnancy.

Betamethasone—(Benoson; Betaderm; Betason; Celestone; Rinderon; Unicort)

International Brand Name—Becasone (Taiwan, Thailand); Benoson (500 mcg) (Indonesia); Betacorten (Singapore); Betason (500 mcg) (Indonesia); Betnelan (England); Betnelan (500 mcg) (India, Israel, Netherlands, Philippines, South Africa); Betnesol (Bulgaria, Greece); Celestamine (Germany); Celestan (Austria); Celestene (France); Celeston (Denmark, Finland, Norway, Sweden); Celestone (Argentina, Belgium, Greece, Italy, Spain, Switzerland); Celestone (500 mcg) (Argentina, Bolivia, Brazil, Chile, Hong Kong, Israel, Korea, Malaysia, Paraguay, Philippines, Puerto Rico, Uruguay, Venezuela); Cortixyl (Peru); Walacort (India)

Drug Class ..... Corticosteroids

Indications ..... Prevention of RDS in preterm neonates, joint inflammation, arthritis

Mechanism ..... Maturation of type II pneumocytes, enhanced pulmonary compliance, anti-inflammatory

Dosage with Qualifiers .....

Prevention of RDS after preterm birth in women with preterm labor <34w—12.5mg IM ×2 doses 24h apart
Bursitis/tendinitis—1ml into the tendon sheath or joint combined with a local anesthetic agent
Rheumatoid arthritis or osteoarthritis—0.5-2ml into the joint

- **Contraindications**—hypersensitivity to drug or class, sepsis, uncontrolled diabetes mellitus
- **Caution**—diabetes mellitus, concomitant tocolysis

Maternal Considerations .....

Betamethasone may increase the risk of maternal infection in women with PPROM, though most large studies reveal no increase. It can transiently cause an abnormal glucose tolerance test, will worsen existing diabetes mellitus, and is associated with pulmonary edema especially when given with a tocolytic agent in the setting of an underlying infection.
Side effects include adrenal insufficiency and pulmonary edema.

Fetal Considerations .....

Betamethasone crosses the human placenta and is one of the few drugs proven to improve perinatal outcome. Some of the beneficial effect on the lung may be lost if delivery occurs more than 14d after administration. Two courses more than a week apart significantly reduces perinatal morbidity following preterm birth. Outcomes at 2-3y of age after multiple courses are reassuring. About half of the drug is metabolized to inactive 11-ketosteroid derivatives. An increased risk of neonatal sepsis was suggested but not confirmed. Multiple courses of **betamethasone** are not recommended. Adverse effects noted in animal and human studies are magnified by repeated courses of steroids. They include a profound suppression of fetal breathing and movement, impaired myelination, IUGR, and microcephaly. **Betamethasone** is a potent agent, with at least short-term impact on a range of physiologic functions that include endocrine, immune, CV, and neurologic functions. The fetal heart rate pattern may become transiently nonreactive. Intellectual and motor development and school achievement are not adversely influenced by steroid treatment. Some suggest emotional stress during organogenesis might cause congenital defects by increasing the level of endogenous **cortisone.** Epidemiologic studies report an association between oral clefting and exposure to corticosteroids during organogenesis. After controlling for 4 confounding factors, it was concluded prenatal exposure increased

the risk for cleft lip with or without cleft palate 6-fold. IUGR and shortening of the head and mandible are also suggested as sequelae of chronic steroid use during pregnancy, though it is difficult to separate drug from disease impact. The Collaborative Perinatal Project followed women treated during the 1st trimester. While the number of exposures was limited, no increase in congenital malformations was detected. There was no increase in risk of anomalies when steroids were initiated after organogenesis. Women exposed to topical **cortisone** during pregnancy have no significant increase in birth defects. Female rats exposed to **cortisone** *in utero* exhibit premature vaginal opening. **Cortisone** accelerates fetal rat intestinal maturation, perhaps explaining why corticosteroids decrease the incidence of NEC. In sum, the evidence that **cortisone** is a human teratogen is weak.

Breastfeeding Safety

There are no adequate reports or well-controlled studies in breastfeeding women. **Cortisone** is present in human milk, but it is unclear whether maternal treatment with **betamethasone** increases the concentration.

Drug Interactions

No drug interaction studies identified.

References

Ahmad I, Beharry KD, Valencia AM, et al. Growth Horm IGF Res 2006; 16:267-75.

Crowther CA, Haslam RR, Hiller JE, et al. Lancet 2006; 367:1913-9.

Emgard M, Paradisi M, Pirondi S, et al. Neurobiol Aging 2007; 28:112-21.

Huang WL, Harper CG, Evans SF, et al. Int J Dev Neurosci 2001; 19:415-25.

Johnson JW, Mitzner W, London WT, et al. Am J Obstet Gynecol 1979; 133:677-84.

McEvoy C, Schilling D, Spitale P, et al. Pediatrics 2008; 121:e1032-8.

Miller SL, Chai M, Loose J, et al. Endocrinology 2007; 148:1288-95.

National Institutes of Health. Consensus Statement. JAMA 1995; 273:413-8.

Rotmensch S, Liberati M, Celentano C, et al. Acta Obstet Gynecol Scand 1999; 78:768-73.

Rotmensch S, Liberati M, Vishne TH, et al. Acta Obstet Gynecol Scand 1999; 78:493-500.

Sloboda DM, Newnham JP, Challis JR. J Endocrinol 2000; 165:79-91.

Summary

Pregnancy Category: C
Lactation Category: U

- **Betamethasone** reduces the incidence of RDS, IVH, and neonatal death.
- There is no convincing scientific evidence that **betamethasone** increases the incidence of maternal or neonatal infection.

Betamethasone topical—(Diprolene AF; Diprosone; Valisone)

International Brand Name—Alphacort (Indonesia); Antroquoril (Australia); Beavate (Malaysia); Bemon (Germany); Bennasone (Thailand); Benoson (Indonesia); Besone (Malaysia, Thailand); Bessasone (Thailand); Beta (Philippines, Thailand); Betacort (Israel); Betacorten (Israel); Beta cream (New Zealand); Betaderm (Canada, Hong Kong, Venezuela); Betagalen (Germany); Beta ointment (New Zealand); Beta Scalp (New Zealand); Betasone (Hong Kong, Thailand); Betasone DHA (Malaysia); Betaval (Israel); Betnelan (Netherlands); Betnelan V (Belgium); Betnesol V (Germany); Betneval (France); Betnosone (Malaysia); Betnovat (Denmark); Betnovate (Austria, Brazil, Bulgaria, Canada, Chile, Czech Republic, Ecuador, England, Hong Kong, India, Indonesia, Malaysia, Mexico, Peru, Philippines, Portugal, Puerto Rico, Spain, Switzerland, Thailand, Venezuela); Betnovate RD (Singapore); Betopic (Indonesia, Taiwan); Betsona (Peru); Bettamousse (Israel); Bipro (Thailand); Camnovate (Singapore); Celestan V (Germany); Celestoderm (Canada, Colombia, Finland, France, Netherlands); Celestoderm V (Argentina, Bulgaria, Italy, Mexico, Spain, Switzerland); Celestoderm-V (Hong Kong, Indonesia, Israel, Malaysia); Celestone-M (Australia); Celestone-V (Australia); Celeston Valerat (Denmark); Corsaderm (Indonesia); Cortipyren (Uruguay); Cortival (Australia); Crinex (Paraguay); Dendri (Korea); Dermasole (Malaysia); Dermasone (Singapore); Dermobet (Brazil); Derzid (Hong Kong, Singapore); Ectosone (Canada, Hong Kong); Hexoderm (Paraguay); Inflacor (Colombia); Lenovate (South Africa); Medobeta (Taiwan); Polynovate (Thailand); Repivate (South Africa); Topivate (South Africa); Valezone (Philippines); Valisone (Canada); Varol (Korea); Vason (Indonesia)

Drug Class	Dermatologics
Indications	Steroid-responsive dermatitis
Mechanism	Anti-inflammatory through an unknown mechanism
Dosage with Qualifiers	Dermatitis—apply to affected area qd or bid (0.05-0.01% cream or ointment) *NOTE: may be combined with* ***clotrimazole.*** • **Contraindications**—hypersensitivity to drug or class • **Caution**—unknown
Maternal Considerations	The absorption level of topical **betamethasone** is unlikely to have significant systemic effect when applied topically in small amounts. ***Side effects*** include adrenal insufficiency, burning, itching, dryness, folliculitis, hypertrichosis, acne, dermatitis, skin atrophy, telangiectasia, and hypopigmentation.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. Considering the dose and route, it is unlikely the maternal systemic concentration will reach clinically relevant level.
Breastfeeding Safety	There is no published experience with topical **betamethasone** in pregnancy. However, considering the dose and route, it is unlikely the breastfed neonate would ingest clinically relevant amounts.
Drug Interactions	No drug interaction studies identified.
References	Perucca E, Franchi P, Dezerega V, et al. Rev Chil Obstet Ginecol 1995; 60:125-7.
Summary	**Pregnancy Category: C** **Lactation Category: U** • Administration of topical **betamethasone** likely poses little additional risk to mother or fetus.

Betaxolol—(Betoptic; Kerlone)

International Brand Name—Abaxon (Argentina); Alcon Betoptic (Philippines); Beof (Ecuador); Betac (Taiwan); Betarun (Taiwan); Betasel (Argentina); Betoptic (Brazil, Chile, Costa Rica, Ecuador, El Salvador, Guatemala, Honduras, Malaysia, Nicaragua, Panama, Paraguay, Peru, Taiwan, Thailand); Betoptic S (Brazil, Bulgaria, Canada, Chile, China, Colombia, Hong Kong, Israel, Korea, Mexico, Philippines, Poland, Singapore, South Africa, Taiwan, Thailand, Venezuela); Betoptima (Germany, Indonesia); Betoquin (Australia); Kerlon (Belgium, Denmark, Finland, Italy, Netherlands, Sweden, Switzerland); Kerlone (Belgium, Bulgaria, China, France, Germany, Greece, Israel, Korea, Malaysia, Paraguay, Philippines, Portugal, Spain, Taiwan); Kerlong (Japan); Lokren (Poland); Optibet (Indonesia); Optipress (India); Tonobexol (Argentina)

Drug Class ..... Adrenergic antagonists, β-Blocker; Antihypertensives

Indications ..... Hypertension, glaucoma

Mechanism ..... β_1-Adrenergic receptor antagonist

Dosage with Qualifiers ..... Hypertension—10-20mg PO qd; renal disease, begin 5mg PO qd
Glaucoma—1 drop in the affected eye bid; therapy is individualized

- **Contraindications**—hypersensitivity to drug or class, sinus bradycardia, 2nd or 3rd degree AV block, CHF
- **Caution**—unknown

Maternal Considerations ..... **Betaxolol** is a cardioselective β_1-adrenergic blocker. There are no adequate reports or well-controlled studies in pregnant women. Clearance is not affected by pregnancy.
Side effects include CHF, bronchospasm, bradycardia, headache, arthralgia, dyspepsia, fatigue, chest pain, edema, pharyngitis, rhinitis, and insomnia.

Fetal Considerations ..... There are no adequate reports or well-controlled studies in human fetuses. **Betaxolol** crosses the human placenta rapidly, achieving an F:M ratio approaching unity. A similar concentration is found in the amniotic fluid. There is a negative correlation between gestational age and **betaxolol** clearance. In rats, **betaxolol** is associated with miscarriage, IUGR, skeletal and visceral abnormalities, and incomplete descent of the testes.

Breastfeeding Safety ..... **Betaxolol** is excreted in the breast milk according to the manufacturer, which reports one nursing infant with side effects. Though the kinetics remain to be elucidated, caution should be exercised when administered in nursing mothers.

Drug Interactions ..... Catecholamine-depleting drugs (e.g., **reserpine**) may have an additive effect. Patients should be observed closely for hypotension or marked bradycardia.
β-Blockers, if discontinued, should be stopped slowly over several days before the gradual withdrawal of **clonidine.**
β-Blockers can interfere with the regulation of allergic reaction, leading to an increased severity and/or frequency of attacks.

References .....
Boutroy MJ, Morselli PL, Bianchetti G, et al. Eur J Clin Pharmacol 1990; 38:535-9.
Morselli PL, Boutroy MJ, Bianchetti G, Thenot JP. Dev Pharmacol Ther 1989; 13:190-8.
Morselli PL, Boutroy MJ, Bianchetti G, et al. Eur J Clin Pharmacol 1990; 38:477-83.

Summary .....
Pregnancy Category: C
Lactation Category: U

- **Betaxolol** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.
- There are alternative agents for which there is more experience during pregnancy and lactation.

Bethanechol—(Duvoid; Myocholine; Myotonachol; Myotonine; Urecholine)

International Brand Name—Duvoid (Canada); Liberon (Brazil); Miotonoachol (Argentina); Muscaran (Belgium); Myocholine Glenwood (Switzerland); Myocholine-Glenwood (Austria); Myo Hermes (Spain); Myotonin (Korea); Myotonine Chloride (England, Ireland, Uruguay); Mytonoachol (Canada); Ucholine (Thailand); Uninechol (Korea); Urecholine (Finland, South Africa); Urocarb (Australia); Urotone (India); Urotonine (India); Wecoli (Taiwan)

Drug Class	Cholinergics; Genitourinary
Indications	Acute, nonobstructive, postoperative or postpartum urinary retention; neurogenic atony of the bladder
Mechanism	Stimulates cholinergic receptors
Dosage with Qualifiers	Urinary retention—10-50mg PO tid or qid • **Contraindications**—hypersensitivity to drug or class, cystitis, mechanical obstruction, hyperthyroidism, peptic ulcer disease, asthma, parkinsonism, seizures • **Caution**—unknown
Maternal Considerations	There are no adequate reports or well-controlled studies of **bethanechol** in pregnant women. It has been used for decades for the treatment of postpartum urinary retention. ***Side effects*** include bronchospasm, chest pain, diarrhea, headache, flushing, N/V, hypotension, urgency, tachycardia, sweating, and miosis.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **bethanechol** crosses the human placenta.
Breastfeeding Safety	There is no published experience in nursing women. It is unknown whether **bethanechol** enters human breast milk.
Drug Interactions	May cause hypotension if given with a ganglion-blocking compound. Severe abdominal symptoms typically precede such a fall in the BP.
References	Gentili A, Migliorini P. Minerva Ginecol 1979; 31:689-92.
Summary	**Pregnancy Category: C** **Lactation Category: U** • **Bethanechol** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Biperiden—(Akineton; Bicamol; Tasmolin)

International Brand Name—Akineton (Argentina, Australia, Austria, Belgium, Brazil, Bulgaria, Canada, Colombia, Costa Rica, Czech Republic, Denmark, Dominican Republic, Ecuador, Egypt, El Salvador, Finland, Germany, Greece, Guatemala, Honduras, Hungary, Italy, Jordan, Lebanon, Mexico, Netherlands, Nicaragua, Norway, Panama, Paraguay, Peru, Philippines, Poland, Portugal, South Africa, Spain, Sweden, Switzerland, Taiwan, Uruguay, Venezuela); Akineton Retard (Argentina, Austria, Colombia, Costa Rica, Dominican Republic, Ecuador, El Salvador, France, Germany, Guatemala, Honduras, Mexico, Nicaragua, Panama, Peru, Portugal, Spain); Benzum 2 (Peru); Berofin (Argentina); Biperen (Taiwan); Biperin (Korea); Bipiden (Taiwan); Desiperiden (Germany); Dyskinon (India); Kinex (Mexico)

Drug Class	Anticholinergics; Antiparkinson agents
Indications	Adjunct therapy for parkinsonism; control of extrapyramidal disorders secondary to neuroleptic drugs
Mechanism	Antagonizes ACh receptors
Dosage with Qualifiers	Parkinsonism—2mg PO tid or qid; max 16mg qd Extrapyramidal disorder—2mg IM/IV q30min; max 4 doses/d • **Contraindications**—hypersensitivity to drug or class, narrow-angle glaucoma, bowel obstruction • **Caution**—epilepsy, arrhythmia
Maternal Considerations	There are no adequate reports or well-controlled studies of **biperiden** in pregnant women. ***Side effects*** include dry mouth, blurred vision, dizziness, urinary retention, constipation, hematuria, drowsiness, dyspepsia, agitation, and orthostatic hypotension.
Fetal Considerations	There are no adequate reports or well-controlled studies in animal or human fetuses. **Biperiden** apparently crosses the human placenta, though the kinetics remain to be elucidated.
Breastfeeding Safety	There is no published experience in nursing women. It is unknown whether **biperiden** enters human breast milk.
Drug Interactions	The central anticholinergic syndrome may occur when anticholinergics are given with drugs that have secondary anticholinergic actions (e.g., certain narcotic analgesics such as **meperidine,** the phenothiazines and other antipsychotics, TCAs, certain antiarrhythmics such as **quinidine,** antihistamines).
References	Kuniyoshi M, Inanaga K. Kurume Med J 1985; 32:199-202.
Summary	**Pregnancy Category: C** **Lactation Category: U** • **Biperiden** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Bismuth subsalicylate—(Pepto-Bismol)

International Brand Name—None identified.

Drug Class	Antidiarrheals
Indications	Diarrhea, heartburn, nausea
Mechanism	Works topically on the gastric mucosa to inhibit secretion, bind bacterial toxins, and direct antimicrobial activity
Dosage with Qualifiers	Diarrhea—30ml or 2 tab q30min to 1h; max 8 doses in 24h • **Contraindications**—hypersensitivity to drug or class • **Caution**—hepatic or renal dysfunction, oral anticoagulant or hypoglycemic agents
Maternal Considerations	There are no adequate reports or well-controlled studies of **bismuth subsalicylate** in pregnant women. Stool darkening should not be confused with melena. The long clinical experience with this OTC agent is reassuring. ***Side effects*** include anxiety, loss of hearing, confusion, severe constipation, diarrhea (severe or continuing), difficulty in speaking or slurred speech, dizziness or light-headedness, drowsiness, and fast or deep breathing.
Fetal Considerations	**Bismuth subsalicylate** is minimally absorbed across the gastric mucosa. Bismuth ion is not transported across the placenta. No adverse fetal outcomes have been reported.
Breastfeeding Safety	Bismuth ion is not excreted into breast milk to any significant degree. Excretion of large amounts of **bismuth subsalicylate** is unlikely considering the lack of systemic absorption.
Drug Interactions	Bismuth may enhance the hypoglycemia in women taking salicylates or **aspirin, probenecid,** or **sulfinpyrazone.** **Tetracycline** absorption may be reduced.
References	Krachler M, Rossipal E, Micetic-Turk D. Eur J Clin Nutr 1999; 53:486-94. [No authors]. JAMA 1985; 253:2700-4.
Summary	**Pregnancy Category: C** **Lactation Category: S** (likely) • The long clinical experience with this OTC agent is reassuring.

Bisoprolol fumarate—(Biconor; Concor Plus; Lodoz; Ziak)

International Brand Name—Bicor (Australia); Biso (Germany); Biso 5 (Taiwan); BisoABZ (Germany); Biso-BASF (Germany); Bisobloc (Netherlands); Bisolol (Israel); Bisomerck (Germany); Cardensiel (France); Cardiloc (Israel); Cardiocor (France); Concor (Argentina, Austria, Brazil, Bulgaria, Chile, China, Colombia, Costa Rica, Czech Republic, Dominican Republic, Ecuador, Egypt, El Salvador, Germany, Guatemala, Honduras, Hong Kong, India, Indonesia, Israel, Italy, Korea, Malaysia, Mexico, Nicaragua, Panama, Poland, Portugal, Switzerland, Taiwan, Thailand); Concor COR (Germany); Concore (Philippines); Corbis (Argentina); Cordalin (Germany); Corentel (Paraguay, Peru, Uruguay); Detensiel (France); Emconcor (Belgium, Denmark, Finland, Spain, Sweden); Emcor (England, Netherlands); Euradal (Spain); Fondril (Germany); Isoten (Belgium); Jutabis (Germany); Maintate (Indonesia, Japan); Monocor (Canada, Denmark, England, Taiwan); Pactens (Greece); Soprol (France)

Drug Class	Adrenergic antagonists, β-Blockers; Antihypertensives
Indications	Hypertension
Mechanism	β_1-Selective adrenoceptor antagonist
Dosage with Qualifiers	Hypertension—2.5-40mg PO qd *NOTE: additive effect with thiazide diuretics.* • **Contraindications**—hypersensitivity to drug or class, cardiogenic shock, AV block, sinus bradycardia, anuria • **Caution**—cardiac failure, arterial insufficiency, asthma, thyrotoxicosis, hepatic or renal dysfunction
Maternal Considerations	There is limited published experience with **bisoprolol** during pregnancy. ***Side effects*** include bradycardia, diarrhea, asthenia, and fatigue.
Fetal Considerations	There is a single case report of a child with cleft lip/palate and hypoplastic toes born to a woman ingesting multiple agents during pregnancy, including **bisoprolol, naproxen,** and **sumatriptan.** It is unknown whether **bisoprolol** crosses the human placenta. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically.
Breastfeeding Safety	There is no published experience in nursing women. It is unknown whether **bisoprolol** enters human breast milk.
Drug Interactions	**Bisoprolol** should not be combined with other β-blocking agents. Women taking catecholamine-depleting drugs, such as **reserpine** or **guanethidine,** should be closely monitored, as the added β-adrenergic blocking action may produce excessive reduction of sympathetic activity. In women receiving concurrent therapy with **clonidine,** it is suggested that **bisoprolol** be discontinued for several days before the **clonidine** if therapy is to be discontinued. **Rifampin** increases the metabolic clearance of **bisoprolol.** However, initial dose modification is generally not necessary. Women with a history of anaphylactic reaction may be more reactive to repeat challenge while taking β-blockers. Such patients may be unresponsive to the usual doses of **epinephrine** used to treat allergic reactions.
References	Kajantie E, Somer M. Clin Dysmorphol 2004; 13:195-6. Soucek M, Prasek J, Spinarova L. Vnitr Lek 1993; 39:541-8. Striuk RI, Brytkova IaV, Bukhonkina IuM, Pavlova LN. Kardiologia 2008; 48:29-33.

Summary	**Pregnancy Category: C** **Lactation Category: U** • **Bisoprolol** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk. • There are alternative agents for which there is more experience during pregnancy and lactation.

Bleomycin—(Blenoxane)

International Brand Name—Bileco (Argentina); Blanoxan (Mexico); Blenamax (Australia, Thailand); Blenoxane (Brazil, Canada, Ecuador, Egypt, Philippines, South Africa); Bleo (Hong Kong); Bleocin (Bulgaria, Czech Republic, Egypt, Greece, Hong Kong, Hungary, India, Indonesia, Malaysia, Portugal, Taiwan, Thailand); Bleocina (Uruguay); Bleocris (Paraguay); Bleolem (Mexico, Thailand); Bleomicina (Italy, Peru, Spain); Bleomycine (Belgium, France); Bleomycinum (Germany); Blexit (Chile); Bloicin-S (Philippines)

Drug Class	Antibiotics; Antineoplastics
Indications	Palliative treatment of squamous cell carcinoma (neck, tongue, cervix, vulva), lymphoma, and associated pleural effusion
Mechanism	Inhibition of DNA, RNA, and protein synthesis
Dosage with Qualifiers	Cancer—varies based on type of neoplasm; most regimens recommend 0.25-0.50U/kg (10-20U/m^2) • **Contraindications**—hypersensitivity to drug or class • **Caution**—hepatic or renal dysfunction
Maternal Considerations	There are no adequate reports or well-controlled studies in pregnant women. Neutropenia is an important risk. Long-term effects of **bleomycin** on reproductive function are insufficiently studied. Several studies concluded that subsequent fertility is clinically unaffected after treatment. ***Side effects*** include impairment of the pulmonary function (pulmonary fibrosis), rash, urticaria, alopecia, and stomatitis.
Fetal Considerations	There are no adequate reports or well-controlled studies in the human fetus. It is unknown whether **bleomycin** crosses the human placenta. Neonatal leukopenia has been reported shortly after delivery. Long-term follow-up of children exposed *in utero* has not revealed abnormalities. **Bleomycin** is teratogenic in rodents (skeletal malformations, hydroureter, vascular disruptions).
Breastfeeding Safety	There is no published experience in nursing women. It is unknown whether **bleomycin** enters human breast milk. For that reason, it is usually recommended the drug be discontinued in nursing women.
Drug Interactions	No drug interaction studies identified.
References	Aviles A, Neri N. Clin Lymphoma 2001; 2:173-7. de la Motte Rouge T, Pautier P, Duvillard P, et al. Ann Oncol 2008; 19:1435-41. Horbelt D, Delmore J, Meisel R, et al. Obstet Gynecol 1994; 84:662-4. Rajendran S, Hollingworth J, Scudamore I. Eur J Gynaecol Oncol 1999; 20:272-4. Yoshinaka A, Fukasawa I, Sakamoto T, et al. Arch Gynecol Obstet 2000; 264:124-7.

Summary	**Pregnancy Category: D** **Lactation Category: U** • **Bleomycin** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk. • No teratogenic human fetal effects are reported.

Bretylium—(Bretylol)

International Brand Name—Bretylate (Canada, Puerto Rico)

Drug Class	Antiarrhythmics, class III
Indications	Ventricular arrhythmia
Mechanism	Prolongs action potential
Dosage with Qualifiers	Ventricular arrhythmia—5-10mg/kg IM/IV ×1; repeat 1-2h prn until control, then q6h or infusion of 1-2mg/min Malignant ventricular arrhythmia—5mg/kg IV ×3; may increase to 10mg/kg and repeat prn, or infusion 1-2/mg/min • **Contraindications**—hypersensitivity to drug or class • **Caution**—rapid infusion, hepatic or renal dysfunction
Maternal Considerations	There are no adequate reports or well-controlled studies of **bretylium** in pregnant women. The one case report chronicled an uncomplicated course after chronic treatment of prolonged QT syndrome. ***Side effects*** include hypotension, N/V, diarrhea, hiccups, anxiety, and SOB.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **bretylium** crosses the human placenta.
Breastfeeding Safety	There are no adequate reports or well-controlled studies in nursing women. It is unknown whether **bretylium** enters human breast milk. The one case report noted no neonatal difficulties.
Drug Interactions	Digitalis toxicity may be aggravated by the initial release of **norepinephrine** triggered by **bretylium.** The pressor effects of catecholamines such as **dopamine** or **norepinephrine** are enhanced by **bretylium.**
References	Gutgesell M, Overholt E, Boyle R. Am J Perinatol 1990; 7:144-5.
Summary	**Pregnancy Category: C** **Lactation Category: U** • **Bretylium** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk. • There are alternative agents for which there is more experience during pregnancy and lactation.

Bromides—sodium, potassium salts

International Brand Name—None identified.

Drug Class	Anticonvulsants
Indications	Epilepsy, seborrheic dermatitis
Mechanism	Unknown
Dosage with Qualifiers	Epilepsy—loading dose 450mg/kg; maintenance dose 20-40mg/kg *NOTE: divide the 450mg/kg dose over 5d (90mg/kg/d) and add it to a maintenance dose of 20-40mg/kg (average of 30mg/kg) qd. Thus, a new patient will receive 120mg/kg of potassium bromide each day for 5d, and then return to 30mg/kg qd.* Seborrheic dermatitis—homeopathic doses • **Contraindications**—hypersensitivity to drug or class • **Caution**—unknown
Maternal Considerations	Oral or topical combinations of potassium and sodium bromide significantly improve seborrheic dermatitis and dandruff after 10 weeks. There are no adequate reports or well-controlled studies in pregnant women. ***Side effects*** include sedation, ataxia, increased urination, and rare skin disorders.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. IUGR, microcephaly, neonatal bromide intoxication (poor suck, weak cry, diminished Moro reflex, lethargy, hypotonia), rash, and sedation are reported after oral use. It is unlikely the maternal systemic concentration will reach a clinically relevant level after topical application.
Breastfeeding Safety	**Bromides** enter human breast milk. It is unlikely the breastfed neonate would ingest clinically relevant amounts after topical application. The American Academy of Pediatrics considers bromides compatible with breastfeeding.
Drug Interactions	No drug interaction studies identified.
References	Miller ME, Cosgriff JM, Roghmann KJ. Am J Obstet Gynecol 1987; 157:826-30. Ryan M, Baumann RJ. Pediatr Neurol 1999; 21:523-8. Smith SA, Baker AE, Williams JH Jr. Altern Med Rev 2002; 7:59-67.
Summary	**Pregnancy Category: D** **Lactation Category: S** • It is unlikely topically applied **bromides** pose a significant clinical risk to the perinate.

Bromocriptine—(Parlodel; Volbro)

International Brand Name—Alpha-Bromocriptine (New Zealand); Antilactin (Korea); Apo-Bromocriptine (New Zealand); Axialit (Argentina); Barlolin (Taiwan); Brameston (Puerto Rico); Brocaden (Thailand); Bromed (Austria); Bromergon (Denmark); Bromidine (Korea); Bromocorn (Poland); Bromocrel (Germany); Bromohexal (Australia); Bromokin (Finland); Bromo-Kin (France); Bromopar (Denmark); Butin (Malaysia, Singapore); Cryocriptina (Mexico); Deprolac (Taiwan); Diken (Mexico); Elkrip (Indonesia); Ergolactin (China); Kripton (Australia); Lactismine (Spain); Medocriptine (Hong Kong); Parilac (Israel); Parlodel (Argentina, Australia, Canada, Colombia, Ecuador, Mexico, Paraguay, Peru, Uruguay, Venezuela); Pravidel (Germany, Sweden); Provasyn (Philippines); Ronalin (Israel); Serocryptin (China, Greece, Hong Kong, India, Israel, Italy, Malaysia, Mexico, Peru, Switzerland); Suplac (Malaysia, Thailand); Umprel (Austria); Zolac (Malaysia)

Drug Class ..... Antiparkinson agents; Dopaminergics; Ergot alkaloids and derivatives

Indications ..... Parkinson's disease, amenorrhea, acromegaly

Mechanism ..... Dopamine agonist; stimulator of the dopaminergic receptors

Dosage with Qualifiers .....

Parkinson's disease—10-40mg PO qd
Amenorrhea—5-7.5mg PO qhs
Acromegaly—20-30mg PO qd

- **Contraindications**—hypersensitivity to drug or class, uncontrolled hypertension, CAD
- **Caution**—hypertension, hepatic or renal dysfunction

Maternal Considerations .....

Medical therapy with **bromocriptine** is the initial treatment of choice for infertility. When this is the primary indication for treatment, **bromocriptine** use has an extensive safety experience and is preferred by some clinicians. Indeed, most information regarding **bromocriptine** during pregnancy comes from women treated for infertility with an average duration of exposure of 28d. No special maternal considerations are reported. **Bromocriptine** is used in many countries for the suppression of breast engorgement after delivery. However, rebound engorgement is common after cessation. In 1994, the FDA withdrew approval for that indication after a series of reports describing severe vasospastic events including stroke, MI, cerebral edema, convulsions, and puerperal psychosis. Recent reports suggest a role in the treatment of peripartal cardiomyopathy and SLE. ***Side effects*** include seizures, stroke, MI, headache, dizziness, nausea, hypotension, cramps, fatigue, and constipation.

Fetal Considerations .....

There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **bromocriptine** crosses the human placenta. There are no reports of associated malformations after 1st trimester exposure. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically.

Breastfeeding Safety .....

Bromocriptine reduces lactation, and its use is generally considered contraindicated during breastfeeding.

Drug Interactions .....

Dopamine antagonists, butyrophenones, and certain other agents (e.g. phenothiazines, **haloperidol, metoclopramide, pimozide**) may decrease efficacy.
Concomitant use of **bromocriptine** with other ergot alkaloids is not recommended.

References .....

Ionescu O, Vulpoi C, Ungureanu MC, et al. Rev Med Chir Soc Med Nat Iasi 2001; 105:806-9.

Jana LJ, Cruz-Cruz P, Saavedna MA, et al. Ann NY Acad Sci 2007; 1110:297-304.
Randall S, Laing J, Chapman AJ, et al. Br J Obstet Gynaecol 1982; 89:20-33.
Ricci G, Giolo E, Nucera G, et al. Gynecol Obstet Invest 2001; 51:266-70.
Russell CS, Lang C, McCambridge M, Calhoun B. Obstet Gynecol 2001; 98:906-8.
Stefos T, Sotiriadis A, Tsirkas P, et al. Acta Obstet Gynecol Scand 2001; 80:34-8.
Turkalj I, Braun P, Krupp P. JAMA 1982; 247:1589-91.

Summary

Pregnancy Category: B
Lactation Category: NS

- **Bromocriptine** is contraindicated during breastfeeding and is not approved in the U.S. for the suppression of breast engorgement postpartum.

Bromodiphenhydramine—(Ambenyl; Ambophen; Bromanyl; Bromotuss w/Codeine; Mybanil; Myphetane DC)

International Brand Name—None identified.

Drug Class

Antihistamines

Indications

Antiallergic, anaphylaxis, dystonic reactions, antitussive, sedation, insomnia

Mechanism

Central and peripheral H_1 receptor antagonist

Dosage with Qualifiers

Antiallergic—1-2tsp PO q4-6h
Antitussive, sedation—1-2tsp PO q4-6h

*NOTE: combined with **codeine.***

- **Contraindications**—hypersensitivity to drug or class, newborns, lactation
- **Caution**—asthma, hyperthyroidism, CV disease

Maternal Considerations

Bromodiphenhydramine is a **diphenhydramine** derivative. There are no adequate reports or well-controlled studies in pregnant women. When combined with **droperidol, bromodiphenhydramine** has been advocated as effective in hospital treatment of severe hyperemesis. Overdose is associated with uterine contractions. It is inferior to **nalbuphine** for the relief of pruritus associated with intrathecal **morphine.**
Side effects include somnolence, dry mouth, headache, dizziness, and N/V.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. **Bromodiphenhydramine** crosses the human placenta, but the kinetics remain to be detailed. In sheep, transfer is rapid and directly dependent on gestational age. Maternal drug ingestion during rodent pregnancy may alter physical and reflex development. Rodent teratogenicity studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically.

Breastfeeding Safety — There are no adequate reports or well-controlled studies in nursing women. **Bromodiphenhydramine** is probably excreted into human breast milk.

Drug Interactions — No drug interaction studies identified.

References

Brost BC, Scardo JA, Newman RB. Am J Obstet Gynecol 1996; 175:1376-7.
Kumar S, Tonn GR, Riggs KW, Rurak DW. Drug Metab Dispos 2000; 28:279-85.
Nageotte MP, Briggs GG, Towers CV, Asrat T. Am J Obstet Gynecol 174:1801-5.
Yoo GD, Axelson JE, Taylor SM, Rurak DW. J Pharm Sci 1986; 75:685-7.

Summary

Pregnancy Category: B
Lactation Category: U

- **Bromodiphenhydramine** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Budesonide—(Budecort; Budeflam; Pulmicort; Rhinocort; Rhinocort Aqua)

International Brand Name—Allercort (Taiwan); Aquacort (Germany); B Cort (Colombia); Bebe Cream (Korea); Budecort (Korea, Thailand); Budecort Nasal (Philippines); Budecort NT (Philippines); Budeflam (South Africa); Budenase AQ (Hong Kong); Budenofalk (Germany, Hong Kong, Korea, Malaysia, Philippines, Singapore); Budeson (Argentina); Budeson 3 (Israel); Budicort Respules (Israel); Bunase (Thailand); Butacort (New Zealand); Butacort Aqueous (Malaysia); Clebudan (Chile, Colombia, Peru); Cycortide (Hong Kong); Desona Nasal (Korea); Duasma (Taiwan); Eltair (Malaysia, New Zealand, Singapore); Entocort (Brazil, Canada, Israel, Mexico, Singapore); Esonide (Singapore); Giona Easyhaler (Thailand); Inflammide (Colombia, Ecuador, Malaysia, Peru, Singapore); Inflanaze (South Africa); Miflonide (Germany, Israel); Miflonide Inhaler (New Zealand); Neo-Rinactive (Taiwan); Novopulmon (France, Germany); Numark (Mexico); Pulmicon Susp for Nebulizer (Korea); Pulmicort (Belgium, Brazil, Bulgaria, Canada, Chile, Colombia, Czech Republic, Denmark, El Salvador, England, Finland, France, Germany, Greece, Guatemala, Hungary, India, Mexico, Netherlands, Poland, Portugal, Spain, Sweden, Taiwan, Uruguay, Venezuela); Pulmicort Nasal (Taiwan); Pulmicort Nasal Turbohaler (China, Kenya, Korea, Mauritius, Nigeria); Pulmicort Turbuhaler (Kenya, Mauritius, Nigeria); PulmoLiseflam (Paraguay); Pulmotide (Israel); Rhinocort (Israel); Rhinocort Aqueous (Australia); Rhinocort Hayfever (Australia)

Drug Class — Corticosteroids; Corticosteroids, inhalation

Indications — Asthma, rhinitis

Mechanism — Anti-inflammatory by an unknown mechanism; potent glucocorticoid, weak mineralocorticoid

Dosage with Qualifiers

Asthma—0.5-1mg/d inhalation
Rhinitis—MDI 50mcg/puff inhalation

- **Contraindications**—hypersensitivity to drug or class, primary treatment of status asthmaticus
- **Caution**—infection, systemic steroids

Maternal Considerations — Asthma can be a serious problem during pregnancy. Inhaled corticosteroids should generally be considered the prophylactic medication of choice in pregnant women with persistent asthma, unless well controlled by either **cromolyn** or **nedocromil.** Although there are no adequate reports or well-controlled studies of **budesonide** during pregnancy, it is considered a first-line agent along with **beclomethasone.**

Side effects include allergic reaction, stridor, eczema, purpura, back pain, fracture, and myalgia.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **budesonide** crosses the human placenta. Epidemiologic study suggests **budesonide** is not a clinically significant teratogen. It appears, though, to cross the mouse placenta, where **budesonide** increases fetal loss, IUGR, and malformations. Rodents as a group are more susceptible to steroids than humans.

Breastfeeding Safety

There is no published experience in nursing women. It is unknown whether **budesonide** enters human breast milk. Considering <20% of the inhaled dose reaches the systemic circulation, it is unlikely clinically relevant concentrations will enter the breast milk and be absorbed orally.

Drug Interactions

The main route of metabolism of **budesonide** and other corticosteroids is via CYP3A4. The dose may need to be reduced when co-prescribing inhibitors of CYP3A4 activity (e.g., **ketoconazole, intraconazole, ritonavir, indinavir, saquinavir, erythromycin, itraconazole, clarithromycin**).
As with other drugs primarily metabolized through CYP3A4, grapefruit or grapefruit juice should be avoided.
Cimetidine, primarily an inhibitor of CYP1A2, slightly decreases **budesonide** clearance with a corresponding increase in oral bioavailability.

References

Andersson P, Appelgren LE, Ryrfeldt A. Acta Pharmacol Toxicol 1986; 59:392-402.
Kallen B, Rydhstroem H, Aberg A. Obstet Gynecol 1999; 93:392-5.
Kihlstrom I, Lundberg C. Arzneimittelforschung 1987; 37:43-6.
Mazzotta P, Loebstein R, Koren G. Drug Saf 1999; 20:361-75.
Rahimi R, Nikfar S, Abdollahi M. Hum Exp Toxicol 2006; 25:447-52.
The American College of Obstetricians and Gynecologists (ACOG) and The American College of Allergy, Asthma and Immunology (ACAAI). Ann Allergy Asthma Immunol 2000; 84:475-80.

Summary

Pregnancy Category: C
Lactation Category: S (likely)
- **Budesonide** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Bumetanide—(Bumex; Pendock; Segurex)

International Brand Name—Budema (Taiwan); Bumedyl (Mexico); Bumelex (Venezuela); Bumet (Dominican Republic, El Salvador, Guatemala, Honduras, Panama); Burinax (Brazil); Burinex (Austria, Belgium, Canada, Costa Rica, Denmark, Dominican Republic, El Salvador, England, France, Germany, Greece, Guatemala, Honduras, Hong Kong, Ireland, Malaysia, Netherlands, Nicaragua, Norway, Panama, Philippines, Puerto Rico, Sweden, Switzerland, Taiwan, Thailand); Busix (Taiwan); Butinat (Argentina); Butinon (Peru); Cambiex (Argentina); Drenural (Mexico); Farmadiuril (Spain); Fluxil (Brazil); Fontego (Italy); Fordiuran (Spain); Lunetoron (Japan); Miccil (Dominican Republic, El Salvador, Guatemala, Honduras, Mexico); Primex (Finland)

Drug Class

Diuretics, loop

Indications

Heart failure

Mechanism	Inhibits chloride resorption in the loop of Henle, and in the distal and proximal convoluted tubule
Dosage with Qualifiers	Heart failure—0.5-2mg/d PO; alternatively, 0.5-1mg IM/IV ×1 • **Contraindications**—hypersensitivity to drug or class, volume and electrolyte depletion, hypokalemia, ototoxicity • **Caution**—electrolyte abnormalities, hepatic coma, hyperuricemia, anuria
Maternal Considerations	There is no published experience with **bumetanide** during pregnancy. ***Side effects*** include renal failure, muscle cramps, impaired hearing, ECG changes, dry mouth, upset stomach, thrombocytopenia, vertigo, chest pain, and ototoxicity.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **bumetanide** crosses the human placenta. No teratogenic effects were noted in rodent studies. **Bumetanide** alters *in vitro* Na^{2+} and Cl^- transport across placental membranes.
Breastfeeding Safety	There is no published experience in nursing women. It is unknown whether **bumetanide** enters human breast milk.
Drug Interactions	Parenterally administered **bumetanide** should be avoided when aminoglycoside antibiotics are being used, especially in the presence of impaired renal function, except in life-threatening conditions. **Lithium** should generally not be given with diuretics because they reduce renal clearance and create a high risk of **lithium** toxicity. **Probenecid** should not be administered as it reduces both the natriuresis and hyperreninemia produced by **bumetanide** due to its inhibitory effect on renal tubular secretion of **bumetanide.** **Indomethacin** should not be co-prescribed since it blunts the increases in urine volume and sodium excretion and inhibits the **bumetanide**-induced increase in plasma renin activity. May potentiate the effect of various antihypertensive drugs, necessitating a reduction in the dose of these drugs.
References	McClain RM, Dammers KD. J Clin Pharmacol 1981; 21:543-54. Prieve BA, Yanz JL. Acta Otolaryngol 1984; 98:428-38.
Summary	**Pregnancy Category: D** **Lactation Category: U** • **Bumetanide** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Bupivacaine—(Bupivacaine HCl; Marcaine; Sensorcaine)

International Brand Name—Bucaine (Israel); Bupicaina (Argentina); Bupinex (Paraguay, Uruguay); Bupirop (Colombia, Ecuador); Bupirop simple sin preservantes (Peru); Bupivan (Peru); Buvacaina (Mexico); Buvacainas (Colombia); Carbostesin (Austria, Germany, Switzerland); Chirocaina (Venezuela); Duracaine (Chile); Kamacaine (Israel); Macaine (South Africa); Marcain (Denmark, England, Finland, Hungary, India, Indonesia, Ireland, Italy, Malaysia, Norway, Sweden); Marcaina (Brazil, El Salvador, Guatemala); Marcaine (Belgium, Bulgaria, Canada, Czech Republic, Greece, Hong Kong, Korea, Netherlands, Poland, Taiwan, Thailand); Marcaine Plain (South Africa); Picain (Finland); Senpivac (Philippines); Sensorcaine (Philippines); Sensoricaine (Canada)

Drug Class	Anesthetics, local
Indications	Conduction and local anesthesia

Mechanism

Inhibits nerve impulses by stabilizing neuronal membranes

Dosage with Qualifiers

Conduction anesthesia—varies; recommend consulting a specialty text
Local anesthesia—varies; max 2mg/kg, 400mg/d; onset 2-10min, duration 3-6h

*NOTE: available with **epinephrine** and in a preservative-free solution.*

- **Contraindications**—hypersensitivity to drug or class
- **Caution**—acutely ill patients, hepatic or renal dysfunction, heart block, hypovolemia, hypotension

Maternal Considerations

Bupivacaine is a very popular agent used for neuraxial anesthesia (epidural or spinal) during labor and delivery alone or in combination with either local anesthetic or narcotic agents. Because of its long duration, it is contraindicated for paracervical block.
Side effects include CNS toxicity, myocardial depression, heart block, bradycardia, ventricular arrhythmias, cardiac arrest, convulsions, respiratory arrest, unconsciousness, hypotension, N/V, paresthesias, fever, chills, pruritus, dizziness, restlessness, anxiety, and tremor.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. **Bupivacaine** crosses the human placenta, with transfer ratios (agent/antipyrine) *in vitro* approximating 0.4%. Transfer rate increases as the fetal pH declines. It does cross the rodent placenta (F:M ratio approximating 0.3), and decreased pup survival was reported after treatment with high concentrations.

Breastfeeding Safety

Bupivacaine and its major metabolite are found at clinically irrelevant levels after epidural administration. Though it has not been studied after local infiltration, one-time use is unlikely to pose a clinically significant risk to the breastfeeding neonate.

Drug Interactions

The administration of local anesthetic agents containing **epinephrine** or **norepinephrine** to women receiving MAOIs or TCAs may produce severe, prolonged hypertension. Concurrent use of these agents should be avoided.
Co-administration of vasopressor drugs and of ergot-type oxytocic drugs may cause severe, persistent hypertension or CVAs. Phenothiazines and butyrophenones may reduce or reverse the pressor effect of **epinephrine.**

References

Johnson RF, Cahana A, Olenick M, et al. Anesth Analg 1999; 89:703-8.
Morishima HO, Ishizaki A, Zhang Y, et al. Anesthesiology 2000; 93:1069-74.
Ortega D, Viviand X, Lorec AM, et al. Acta Anaesthesiol Scand 1999; 43:394-7.

Summary

Pregnancy Category: C
Lactation Category: S

- **Bupivacaine** is a popular agent for conduction anesthesia during labor.
- It is contraindicated for paracervical block.

Buprenorphine—(Buprenex; Subutex)

International Brand Name—Anorfin (Denmark); Buprex (Peru, Portugal, Spain); Buprine (Thailand); Lepetan (Japan); Norphin (India); Pentorel (India); Prefin (Spain); Subutex (Australia, France, Germany, Hong Kong, Israel, Malaysia, Singapore); Temgesic (Argentina, Bolivia, Bulgaria, Canada, Chile, Colombia, Ecuador, Greece, Honduras, Hong Kong, Israel, Malaysia, New Zealand, Paraguay, Peru, Poland, Portugal, Slovenia, South Africa, Spain, Taiwan, Thailand, Turkey, Uruguay); Transtec (England, Ireland)

Drug Class	Analgesics, narcotic
Indications	Pain, moderate-severe
Mechanism	Opiate receptor agonist-antagonist
Dosage with Qualifiers	Pain—300mcg IM/IV q4-6h; max 600mcg/dose *NOTE: 300mcg should be given IM; larger doses should be given IV over 2min.* • **Contraindications—**hypersensitivity to drug or class • **Caution—**impaired hepatic function
Maternal Considerations	There is extensive information in the addiction medicine literature concerning the use of opioids in recovering pregnant addicts. **Buprenorphine, methadone,** and **morphine** have been used to treat women seeking recovery from opioids, and closely monitored neonatal outcomes have been reassuring. ***Side effects*** include respiratory depression and or arrest, hypotension, bradycardia, N/V, sedation, miosis, euphoria, hallucinations, dysphoria, dry mouth, pruritus, blurred vision, sweating, and constipation.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. **Buprenorphine** crosses the human placenta poorly by a mechanism that does not involve P-glycoprotein. The majority of newborns born to opioid-dependent women show signs of opioid withdrawal. **Buprenorphine** substitution therapy has been used to prevent neonatal abstinence syndrome (NAS) and poor neurodevelopmental outcome in these infants, and may be less severe than that with **methadone,** perhaps because of a low placental transfer rate. The NAS associated with **buprenorphine** appears 12-48h after birth, peaks in 72-96h, and lasts for 120-168h. Time of last drug use and frequency of use during the 3rd trimester are important factors associated with drug-positive meconium specimens where concentrations may predict the onset and frequency of NAS. **Buprenorphine** has no apparent teratogenic effects. Some exposed children may present with transient motor abnormalities, though most probably resolve completely in 85% of cases.
Breastfeeding Safety	There are no adequate reports or well-controlled studies in nursing women. **Buprenorphine** is excreted into human breast milk in low concentrations (peak 0.18ng/ml for **buprenorphine** and 0.20ng/ml for norbuprenorphine). In one woman, the daily amount ingested by the neonate was very low (<4mcg), and no withdrawal signs were noted after breastfeeding was abruptly interrupted.
Drug Interactions	Care should be taken if used in combination with CNS depressant drugs. Care should be taken if used in combination with MAOIs. There are reports of respiratory and cardiovascular collapse in patients who received therapeutic doses of **diazepam**

and **buprenorphine.** There are a number of post-marketing reports of coma and death associated with the concomitant IV misuse of **buprenorphine** and benzodiazepines by addicts. In many cases, **buprenorphine** was misused by self-injection of crushed tablets.
A suspected interaction between **buprenorphine** and **phenprocoumon** has been reported resulting in purpura.
Drugs that inhibit CYP3A4 activity, such as macrolide antibiotics (e.g., **erythromycin**), azole antifungal agents (e.g., **ketoconazole**), and protease inhibitors (e.g., **ritanovir**), may cause decreased clearance of **buprenorphine.**
CYP inducers, such as **rifampin, carbamazepine,** and **phenytoin,** induce metabolism and may cause increased clearance of **buprenorphine.**

References

Grimm D, Pauly E, Poschl J, et al. Ther Drug Monit 2005; 27:526-30.
Johnson RE, Jones HE, Jasinski DR, et al. Drug Alcohol Depend 2001; 63:97-103.
Kayemba-Kay S, Laclyde JP. Addiction 2003; 98:1599-604.
Lejeune C, Simmat-Durand L, Gourarier L, Aubisson S; Groupe d'Etudes Grossesse et Addictions (GEGA). Drug Alcohol Depend 2006; 82:250-7.
Marquet P, Chevrel J, Lavignasse P, et al. Clin Pharmacol Ther 1997; 62:569-71.
Nanovskaya T, Deshmukh S, Brooks M, et al. J Pharmacol Exp Ther 2002; 300:26-33.
Nekhayeva IA, Nanovskaya TN, Hankins GD, Ahmed MS. Am J Perinatol 2006; 23:423-30.
Schindler SD, Eder H, Ortner R, et al. Addiction 2003; 98:103-10.
Wunsch MJ, Stanard V, Schnoll SH. Clin J Pain 2003; 19:148-55.

Summary

Pregnancy Category: C
Lactation Category: S (likely)

- **Buprenorphine** is an effective option for the treatment of pain during pregnancy.
- It may offer some advantage to **methadone** for women seeking recovery from opioid addiction.

Bupropion—(Wellbutrin; Zyban)

International Brand Name—Buxon (Chile); Odranal (Argentina, Colombia); Quomen (Thailand); Well (Korea); Wellbutrin SR (Argentina, Canada, Chile, Colombia, Korea, Paraguay, Peru, Singapore, Uruguay); Zyban (Brazil, Bulgaria, Canada, Denmark, England, France, Germany, Hong Kong, India, Ireland, Israel, New Zealand, Singapore); Zyban LP (France); Zyban Sustained Release (Australia)

Drug Class

Antidepressants; SSRIs

Indications

Depression, smoking cessation

Mechanism

Unknown mechanism of action; weak blocker of serotonin uptake

Dosage with Qualifiers

Depression—100mg PO tid; max dose 150mg PO tid
Smoking cessation—150-300mg PO bid; patient quits smoking after 5-7d of treatment; 2nd dose should not be later than 6pm and at least 8h after 1st dose

- **Contraindications**—hypersensitivity to drug or class, seizure disorder, use of MAOIs within 14d, bulimia, anorexia nervosa

- **Caution**—agitation, insomnia, psychosis, confusion, altered appetite, weight change

Maternal Considerations

There are no adequate reports or well-controlled studies in pregnant women. **Bupropion** is an effective adjunct for smoking cessation therapy and may be superior to the nicotine patch. It also appears useful for the treatment of postpartum depression. Glaxo-Wellcome maintains an international registry to follow women treated during pregnancy, and caregivers are encouraged to register treated patients.
Side effects include arrhythmias, 3rd degree heart block, Stevens-Johnson syndrome, depression, rash, rhabdomyolysis, dysphagia, vaginal irritation, mania/hypomania, N/V, anorexia, sedation, weight loss, weight gain, bronchitis, stomatitis, ataxia, seizure, constipation, and confusion.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **bupropion** crosses the human placenta. One prospective comparative study of 136 pregnant women taking **bupropion** conducted 4mo and 1y after delivery revealed no increase in adverse pregnancy outcomes except for an increase in 1st trimester losses. Another study looked at 1200 1st trimester exposures and concluded there was no increase in congenital malformations compared to control. Rodent studies too are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically.

Breastfeeding Safety

Bupropion is excreted into human breast milk, achieving M:P ratios of 2.5-8.6. However, the neonatal concentration was below the level of detection in the 3 newborns studied. Confirmatory studies are needed.

Drug Interactions

Bupropion is primarily metabolized by CYP2B6 to hydroxybupropion. Thus, the potential exists for interactions with drugs that affect CYP2B6 (e.g., **orphenadrine, cyclophosphamide**).
Though not well studied, some drugs may induce **bupropion** metabolism (e.g., **carbamazepine, phenobarbital, phenytoin**).
Bupropion and hydroxybupropion are inhibitors of CYP2D6 *in vitro.* Many drugs, including most antidepressants (SSRIs and many TCAs, including **nortriptyline, imipramine, desipramine, paroxetine, fluoxetine,** and **sertraline**), β-blockers (e.g., **metoprolol**), type 1C antiarrhythmics (e.g., **propafenone, flecainide**), and antipsychotics (e.g., **haloperidol, risperidone, thioridazine**) are metabolized by CYP2D6 and should be initiated at the lower end of the dose range. The dose of an original medication metabolized by CYP2D6 may need to be reduced if **bupropion** is added.
The acute toxicity of **bupropion** in animals is enhanced by the MAOI **phenelzine.**
Limited clinical data suggest a higher prevalence of adverse reactions in patients taking **bupropion** with either **levodopa** or **amantadine.** Use small doses initially and increase gradually.
Concurrent administration of **bupropion** XL tablets and agents that lower seizure threshold (e.g., antipsychotics, other antidepressants, **theophylline,** systemic steroids) should be undertaken with extreme caution. Use small doses initially and increase gradually.
There are rare reports of adverse neuropsychiatric events or reduced alcohol tolerance in patients drinking alcohol during treatment. Alcohol consumption should be avoided.

Physiologic changes resulting from smoking cessation itself, with or without **bupropion,** may alter the pharmacokinetics of some concomitant medications. Blood concentrations of medications that are extensively metabolized, such as **theophylline** and **warfarin,** may be expected to increase after smoking cessation due to the de-induction of liver enzymes.

References

Ahluwalia JS, Harris KJ, Catley D, et al. JAMA 2002; 288:468-74.
Baab SW, Peindl KS, Piontek CM, Wisner KL. J Clin Psychiatry 2002; 63:910-1.
Briggs GG, Samson JH, Ambrose PJ, Shroder DH. Ann Pharmacother 1993; 27:431-3.
Cole JA, Modell JG, Haight BR, et al. Pharmacoepidemiol Drug Saf 2007; 16:474-84.
Chan B, Einarson A, Koren G. J Addict Dis 2005; 24(2):19-23.
Chun-Fai-Chan B, Koren G, Fayez I, et al. Am J Obstet Gynecol 2005; 192:932-6.
Kotlyar M, Hatsukami DK. J Dent Educ 2002; 66:1061-73.
Nonacs RM, Soares CN, Viguera AC, et al. Int J Neuropsychopharmacol 2005; 8:445-9.
Weintraub M, Evan P. Hosp Form 1989; 24:254-9.
West R, McNeill A, Raw M. Thorax 2000; 55:987-99.

Summary

Pregnancy Category: B
Lactation Category: S (likely)

- **Bupropion** is an adjuvant agent for smoking cessation.
- Caregivers are encouraged to register treated women with the Glaxo-Wellcome Bupropion International Registry.
- **Bupropion** should be used during pregnancy and lactation only when the potential benefit justifies the potential perinatal risks.

Buspirone—(Ansiced; BuSpar)

International Brand Name—Actium (Paraguay); Ansial (Argentina, Spain); Ansitec (Brazil); Anxinil (Taiwan); Anxiolan (Thailand); Anxiron (Israel); Anxut (Germany); Bespar (Germany, Greece); Biron (New Zealand); Buspar (Brazil, Canada, Ecuador, Hong Kong, Indonesia, Korea, Mexico, South Africa, Taiwan); Busparium (Uruguay); Buspin (India); Buspirex (Canada); Buspirone (Greece); Bustab (Canada); Dalpas (Venezuela); Kalmiren (Hong Kong); Narol (Spain); Nerbet (Chile); Normaton (Guatemala, Honduras); Pasrin (South Africa); Paxon (Chile); Relac (Taiwan); Relax (Ecuador); Sburol (Korea); Sepirone (Taiwan); Seron (Korea); Sorbon (Israel); Spamilan (Poland); Spitomin (Bulgaria); Tran-Q (Indonesia); Xiety (Indonesia)

Drug Class

Sedatives

Indications

Anxiety

Mechanism

Mechanism of action is currently unclear; 5-HT_{1A} receptor agonist.

Dosage with Qualifiers

Anxiety—begin 7.5mg PO bid; increase by 5mg/d q3d until max 60mg/d

- **Contraindications**—hypersensitivity to drug or class
- **Caution**—use of MAOIs, hepatic or renal dysfunction

Maternal Considerations

There is no published experience with **buspirone** during pregnancy. **Buspirone** interacts with numerous other drugs. ***Side effects*** include dizziness, N/V, insomnia, rash, headache, fatigue, dry mouth, diarrhea, decreased concentration, hostility, depression, blurred vision, diarrhea, abdominal pain, numbness, and weakness.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **buspirone** crosses the human placenta. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically. *In vitro,* **buspirone** reduces neuronal apoptosis after exposure to alcohol.

Breastfeeding Safety

There is no published experience in nursing women. It is unknown whether **buspirone** enters human breast milk. **Buspirone** is excreted into rodent breast milk.

Drug Interactions

It is recommended that **buspirone** *not* be used concomitantly with MAOIs.

After addition of **buspirone** to a **diazepam** dosing regimen, nordiazepam increased about 15% associated with minor adverse clinical effects (dizziness, headache, and nausea).

Concomitant administration of **buspirone** and **haloperidol** to healthy control subjects resulted in increased serum **haloperidol** concentrations. The clinical significance is not clear.

The concomitant administration of **buspirone** with most other psychotropic drugs has not been studied; use with other CNS-active drugs should be approached cautiously.

Buspirone is metabolized *in vitro* by CYP3A4. This finding is consistent with the *in vivo* interactions observed between buspirone and the following:

Diltiazem *and* ***Verapamil****:* In one study, administration of **buspirone** (10mg) with **verapamil** (80mg tid) or **diltiazem** (60mg tid) increased plasma **buspirone** (**verapamil** increased AUC and C_{max} of **buspirone** 3.4-fold while **diltiazem** increased AUC and C_{max} 5.5-fold and 4-fold, respectively). Adverse events to **buspirone** may be more likely with either **diltiazem** or **verapamil.** Subsequent dose adjustment may be necessary.

Erythromycin*:* In one study, administration of **buspirone** (10mg) with **erythromycin** (1.5g/d for 4d) increased plasma **buspirone** (5-fold increase in C_{max} and 6-fold increase in AUC) in association with an increased incidence of side effects attributable to **buspirone.** If the two drugs are to be used in combination, a low dose of **buspirone** (e.g., 2.5mg bid) is recommended. Subsequent dose adjustment of either drug should be based on clinical assessment.

Grapefruit Juice: In one study, administration of **buspirone** (10mg as a single dose) with grapefruit juice (200ml double-strength tid for 2d) increased plasma **buspirone** (4.3-fold increase in C_{max}; 9.2-fold increase in AUC). Patients receiving **buspirone** should be advised to avoid drinking grapefruit juice.

Itraconazole*:* In one study, administration of **buspirone** (10mg) with **itraconazole** (200mg/d for 4d) increased plasma buspirone (13-fold increase in C_{max} and 19-fold increase in AUC) in association with an increased incidence of side effects attributable to **buspirone.** If the two drugs are to be used in combination, a low dose of **buspirone** (e.g., 2.5mg qd) is recommended. Subsequent dose adjustment of either drug should be based on clinical assessment.

Nefazodone*:* In one study, administration of **buspirone** (2.5 or 5mg bid) with **nefazodone** (250mg bid) increased plasma **buspirone** (increases up to 20-fold in C_{max} and up to 50-fold in AUC) and decreased (about 50%) plasma concentrations of the buspirone metabolite 1-PP. Subjects receiving **buspirone** 5mg bid and **nefazodone** 250mg bid experienced light-headedness, asthenia, dizziness, and somnolence, adverse events also observed with either drug alone. If the two drugs are to be used in combination, a low dose of **buspirone** (e.g., 2.5mg qd) is

recommended. Subsequent dose adjustment of either drug should be based on clinical assessment.
Rifampin: In one study, administration of **buspirone** (30mg as a single dose) with **rifampin** (600mg/day for 5d) decreased the plasma concentrations (83.7% decrease in C_{max}; 89.6% decrease in AUC) and pharmacodynamic effects of **buspirone.** If the two drugs are to be used in combination, the dosage of **buspirone** may need adjusting to maintain anxiolytic effect.
Other Inhibitors and Inducers of CYP3A4: Substances that inhibit CYP3A4, such as **ketoconazole** or **ritonavir,** may inhibit **buspirone** metabolism and increase plasma concentrations, while substances that induce CYP3A4, such as **dexamethasone** or certain anticonvulsants (**phenytoin, phenobarbital, carbamazepine**), may increase the rate of **buspirone** metabolism. If a patient has been titrated to a stable dosage on **buspirone,** a dose adjustment of **buspirone** may be necessary to avoid adverse events attributable to **buspirone** or diminished anxiolytic activity.

References

Druse M, Tajuddin NF, Gillespie RA, Le P. Brain Res Dev Brain Res 2005; 159:18-28.
Kim JA, Druse MJ. Brain Res Dev Brain Res 1996; 92:190-8.

Summary

Pregnancy Category: B
Lactation Category: U
- **Buspirone** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Busulfan—(Citosulfan; Leukosulfan; Misulban; Myleran)

International Brand Name—Busulfex (Canada, Hong Kong, Israel, Korea); Mablin (Japan); Myleran (Argentina, Brazil, Canada, Chile, China, Ecuador, Hong Kong, India, Mexico, Peru, Singapore, Taiwan, Thailand, Uruguay)

Drug Class

Alkylating agents; Antineoplastics

Indications

Leukemia, myelofibrosis

Mechanism

Alkylates and cross-links DNA

Dosage with Qualifiers

Leukemia—varies based on the type of neoplasm
Myelofibrosis—2-4mg PO 2-3×/w

- **Contraindications**—hypersensitivity to drug or class, resistance to prior treatment, blast crisis, acute lymphocytic leukemia
- **Caution**—bone marrow depression, seizures

Maternal Considerations

There are no adequate reports or well-controlled studies in pregnant women. **Busulfan** has been used successfully to treat leukemia and essential polycythemia during pregnancy.
Side effects include myelosuppression, pulmonary fibrosis, pericardial fibrosis, seizures, and hyperpigmentation.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **busulfan** crosses the human placenta. No pattern of anomalies can be discerned. There are reports of IUGR fetuses born to women who were treated with **busulfan** during pregnancy. In rodents, there is a high incidence of carpal and tarsal bone anomalies after small doses of antiproliferatives such as **cytosine arabinoside, mitomycin C,** or **busulfan.** Further, infertility may be increased in the offspring of treated rats.

Breastfeeding Safety

There is no published experience in nursing women. It is unknown whether **busulfan** enters human breast milk.

Drug Interactions

Itraconazole decreases **busulfan** clearance by up to 25%, and may produce AUCs >1500 μM/min in some patients.
Phenytoin increases the clearance of **busulfan** by 15% or more, possibly due to the induction of glutathione-S-transferase.
Because **busulfan** is eliminated from the body via glutathione conjugation, use of **acetaminophen** in the prior <72h or concurrently with **busulfan** may result in reduced clearance.
Busulfan may cause additive myelosuppression when used with other myelosuppressive drugs.
Bulsulfan-induced pulmonary toxicity may be additive to the effects of other cytotoxic agents.
The concomitant use of **metronidazole** and high-dose **busulfan** may result in increased trough levels of **busulfan** and is not recommended.

References

Diamond I, Anderson MM, McCreadie SR. Pediatrics 1960; 25:85-90.
Dobbing J. Lancet 1977; 1:1155.
Ozumba BC, Obi GO. Int J Gynaecol Obstet 1992; 38:49-50.
Rahman ME, Ishikawa H, Watanabe Y, Endo A. Reprod Toxicol 1996; 10:485-9.
Wright CA, Tefferi A. Eur J Haematol 2001; 66:152-9.

Summary

Pregnancy Category: D
Lactation Category: U

- Limited reports indicate **busulfan** can be used during pregnancy without apparent adverse fetal effects.
- **Busulfan** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Butalbital—(Butal compound; Farbital; Fioricet; Fiorinal; Fiormor; Fiortal; Fortabs; Idenal; Isollyl; Laniroif; Lanorinal; Tecnal; Trianal)

International Brand Name—None identified.

Drug Class

Barbiturates; Sedatives/hypnotics

Indications

Sedation, insomnia, preoperative sedation, tension headache

Mechanism

Alters sensory cortex, cerebellar, and motor activities

Dosage with Qualifiers

Sedation—15-30mg PO tid or qid
Insomnia—50-100mg PO qhs (short term)
Preoperative sedation—50-100mg PO 30-60min preoperatively
Tension headache—1-2 tabs Fioricet PO q4h

*NOTE: each Fioricet tab contains **butalbital** 50mg, **acetaminophen** 325mg, caffeine 40mg; max 6 tabs/d.*

- **Contraindications**—hypersensitivity to drug or class, porphyria, bronchopneumonia, pulmonary insufficiency
- **Caution**—hepatic or renal dysfunction, history of drug abuse

Maternal Considerations	There are no adequate reports or well-controlled studies of **butalbital** in pregnant women. ***Side effects*** include thrombocytopenia, Stevens-Johnson syndrome, drowsiness, sedation, constipation, dyspnea, N/V, SOB, and abdominal pain.
Fetal Considerations	There are no adequate reports or well-controlled studies in animal and human fetuses. It is unknown whether **butalbital** crosses the human placenta. Other barbiturates do cross. Withdrawal seizures have been reported in neonates whose mothers used **butalbital** during pregnancy.
Breastfeeding Safety	There is no published experience in nursing women. It is unknown whether **butalbital** enters human breast milk. Other barbiturates enter human breast milk, but the kinetics are poorly described.
Drug Interactions	No specific interaction studies identified. See **phenobarbital**.
References	Ostrea EM Jr. Am J Obstet Gynecol 1982; 143:597-8.
Summary	**Pregnancy Category: C** **Lactation Category: U** • **Butalbital** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Butorphanol—(Stadol)

International Brand Name—Bunol (Korea); Busphen (Korea); Butrum (India); Stadol (Ecuador, Japan, Philippines); Stadol NS (Canada, Chile)

Drug Class	Analgesics, narcotic agonist-antagonists
Indications	Labor pain management, anesthesia
Mechanism	Binds to opiate receptors producing agonist-antagonist effects
Dosage with Qualifiers	Pain—0.5-2mg IV q3-4h prn pain; begin 1mg IV or 2mg IM Preoperative sedation—2mg IV before induction Epidural anesthesia—consult a specialty text • **Contraindications**—hypersensitivity to drug or class, acute MI, coronary insufficiency • **Caution**—hepatic or renal dysfunction, CNS depression, biliary surgery, substance abuse, impaired pulmonary function, head injury
Maternal Considerations	There are no adequate reports or well-controlled studies in pregnant women prior to 37w. **Butorphanol** provides better initial analgesia than **fentanyl** during labor with fewer patient requests for more medication or epidural analgesia. In one well-designed study, it was less effective than **meperidine** for the relief of affective pain during labor. Acute psychosis has been reported after usage. ***Side effects*** include drowsiness, hypotension, respiratory depression, sedation, dizziness, N/V, sweating, headache, euphoria, confusion, nervousness, anorexia, and constipation.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. **Butorphanol** crosses the human placenta, achieving an F:M ratio approximating unity. Its use during labor is associated with a transient (90-120min) sinusoidal fetal heart rhythm. The addition of **butorphanol, fentanyl,** or **sufentanil** to epidural **bupivacaine** (0.25%) does not alter FHR short- or long-term variability. Neonatal respiratory depression may occur after parenteral maternal administration. No teratogenic effects are identified in rodents.

Breastfeeding Safety

There are no adequate reports or well-controlled studies in nursing women. **Butorphanol** is excreted into human breast milk, but it is estimated the unsupplemented neonate would ingest 4mcg/d if the woman was receiving an analgesic dose (2mg IM or 8mg PO) 4×/d.

Drug Interactions

Use with CNS depressants (e.g., alcohol, barbiturates, tranquilizers, antihistamines) may result in increased effects. When used concurrently with such drugs, the dose of **butorphanol** should be the smallest effective dose and the frequency of dosing reduced as much as possible.
The analgesic effect of **butorphanol** may be diminished if given shortly after **sumatriptan** nasal spray.
It is unknown if the effects of **butorphanol** are altered by other medications that affect hepatic metabolism of drugs (**erythromycin, theophylline,** etc.), but physicians should be alert to the possibility that a smaller initial dose and longer intervals between doses may be needed.
The fraction of **butorphanol** absorbed is unaffected by the concomitant administration of a nasal vasoconstrictor (**oxymetazoline**), but the rate of absorption is decreased. Therefore, a slower onset can be anticipated.

References

Atkinson BD, Truitt LJ, Rayburn WF, et al. Am J Obstet Gynecol 1994; 171:993-8.
Davis A, Yudofsky B, Quidwai S. J Neuropsychiatry Clin Neurosci 1998; 10:236-7.
Nelson KE, Eisenach JC. Anesthesiology 2005; 102:1008-13.
Pittman KA, Smyth RD, Losada M, et al. Am J Obstet Gynecol 1980; 138:797-800.
St. Amant MS, Koffel B, Malinow AM. Am J Perinatol 1998; 15:351-6.

Summary

Pregnancy Category: C
Lactation Category: S (likely)

- **Butorphanol** is a popular agent for labor analgesia given either parenterally or as part of conduction anesthesia.
- **Butorphanol** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Cabergoline—(Dostinex)

International Brand Name—Cabaser (Australia, Israel)

Drug Class	Antiparkinson agents; Dopaminergics; Ergot alkaloids and derivatives; Hormones/hormone modifiers
Indications	Hyperprolactinemia, lactation suppression
Mechanism	Stimulates D_2 dopamine receptors
Dosage with Qualifiers	Hyperprolactinemia—begin 0.25mg 2×/w, then increase 0.25mg/w qmo; max 1mg 2×/w; monitor prolactin level • **Contraindications**—hypersensitivity to drug or class, uncontrolled hypertension • **Caution**—hepatic dysfunction
Maternal Considerations	There are no adequate reports or well-controlled studies in pregnant women. **Cabergoline** is better tolerated and more effective in inducing a complete biochemical response than **bromocriptine.** Women become pregnant in 1-37mo (mean 12.4mo) with **cabergoline** therapy. It has been used successfully throughout pregnancy to treat a macroprolactinoma; most tumors disappear with therapy. **Cabergoline** is also effective in women resistant or poorly responsive to **bromocriptine.** Prolactin typically trends lower after delivery or 3mo after breastfeeding. **Cabergoline** is used in several countries to prevent postpartum lactation (1mg PO ×1) or block established lactation (0.25mg PO q12h ×4). ***Side effects*** include N/V, headache, dizziness, constipation, fatigue, abdominal pain, vertigo, hot flashes, dry mouth, depression, and hypotension.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **cabergoline** crosses the human placenta. First trimester exposure is not associated with adverse perinatal outcome. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically.
Breastfeeding Safety	There is no published experience in nursing women. It is unknown whether **cabergoline** enters human breast milk. **Cabergoline** effectively suppressed lactation in some studies, with less rebound than **bromocriptine.** It should be avoided if breastfeeding is desired.
Drug Interactions	Cabergoline should not be administered with D_2 antagonists, such as phenothiazines, butyrophenones, thioxanthines, or **metoclopramide.**
References	Bozhinova S, Porozhanova V, Penkov V. Akush Ginekol 2001; 40:11-4. Ciccarelli E, Grottoli S, Razzore P, et al. Endocrinol Invest 1997; 20:547-51. Colao A, Sarno AD, Pivonello R, et al. Expert Opin Investig Drugs 2002; 11:787-800. Delgrange E, Maiter D, Donckier J. Eur J Endocrinol 1996; 134:454-6.

Liu C, Tyrrell JB. Pituitary 2001; 4:179-85.
Molitch ME. J Reprod Med 1999; 44:1121-6.
Ricci E, Parazzini F, Motta T, et al. Reprod Toxicol 2002; 16:791-3.
Webster J. Drug Saf 1996; 14:228-38.

Summary

Pregnancy Category: B
Lactation Category: U

- Preliminary data suggests no increase in adverse fetal outcomes secondary to **cabergoline** use during pregnancy.
- **Cabergoline** should be avoided if breastfeeding is desired.

Caffeine

Drug Class

Analeptics; CNS stimulants; Xanthines

Indications

Migraine, tension headache, cluster headache, prematurity apnea

Mechanism

Most of the effects reflect antagonism of A1 and A2 adenosine receptors.

Dosage with Qualifiers

*NOTE: may be combined with **ergotamine** (Cafergot), or other analgesics such as ASA or **acetaminophen.***

- **Contraindications**—hypersensitivity to drug or class, peptic ulcer disease, porphyria
- **Caution**—history of abuse

Maternal Considerations

There is no clear evidence **caffeine** at moderate ingestion levels has an adverse effect on pregnancy. Toxicity occurs only in very high dosages (e.g., 25 tablets of Fiorinal [**ASA, butalbital, caffeine**]).
Side effects include tachycardia and anxiety. In combination with other drugs, **caffeine** it may cause anaphylaxis, toxic epidermal necrolysis, bone marrow suppression, GI bleeding, and Stevens-Johnson syndrome.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. **Caffeine** crosses the placenta, achieving an F:M ratio near unity. Cardiac arrhythmias are associated with maternal **caffeine** use in excess of 500mg/d. There is no substantive evidence that **caffeine** is either a teratogen or causes IUGR in humans. In rodents, high and sustained doses are associated with a small increase in the prevalence of cleft palate. Despite the fact that many epidemiologic studies observed a positive association between maternal **caffeine** intake and the risk of spontaneous abortion, the evidence is still equivocal given the biases likely present and the fact that most of the potential biases would overestimate any association.

Breastfeeding Safety

Though it enters human breast milk in small amounts, **caffeine** is generally considered safe for breastfeeding women.

Drug Interactions

Ergotamine and **caffeine** tablets should not be given with other vasoconstrictors.
Sympathomimetics (pressor agents) may cause extreme elevation of blood pressure.

Propranolol may potentiate the vasoconstrictive actions of **ergotamine** and **caffeine** by blocking the vasodilating property of epinephrine.
Nicotine may provoke vasoconstriction in some patients, predisposing to a greater ischemic response to ergot therapy.
The blood levels of ergotamine-containing drugs associated with vasospastic reactions are reported to be increased by the co-administration of macrolide antibiotics.

References

Browne ML. Epidemiology 2006; 17:324-31.
Clausson B, Granath F, Ekbom A, et al. Am J Epidemiol 2002; 155:429-36.
Cnattingius S, Signorello LB, Anneren G, et al. N Engl J Med 2000; 343:1839-45.
Grosso LM, Rosenberg KD, Belanger K, et al. Epidemiology 2001; 12:447-55.
Koren G. Can Fam Physician 2000; 46:801-3.
Pollard I, Locquet O, Solvar A, Magre S. Reprod Fertil Dev 2001; 13:435-41.
Signorello LB, McLaughlin JK. Epidemiology 2004; 15:229-39.
Signorello LB, Nordmark A, Granath F, et al. Obstet Gynecol 2001; 98:1059-66.

Summary

Pregnancy Category: C
Lactation Category: S
- **Caffeine** is one of the most frequently used drugs during pregnancy, often in combination with products containing **aspirin, acetaminophen,** and **codeine.**
- No teratogenic, carcinogenic, or mutagenic effects are known in humans.

Caffeine plus ergotamine—(Cafatine; Cafergot; Cafermine; Cafetrate; Ercaf; Ercatab; Ergo-Caff; Gotamine; Micomp-Pb; Migergot; Secadol; Wigraine)

International Brand Name—Avamigran (Thailand); Cafergot (Argentina, Austria, Belgium, Canada, Denmark, England, Indonesia, Ireland, Italy, Japan, Korea, Malaysia, Mexico, Netherlands, Norway, Russia, Spain, Sweden, Switzerland, Taiwan, Thailand); Cafergot N (Germany); Craming (Korea); Degran (Thailand); Ergocaf (Mexico); Ergofein (Czech Republic); Ergoffin (Germany); Ergokoffin (Denmark); Ergotamini Tartras Coffeinum (Netherlands); Ergoton (Taiwan); Ericaf (Indonesia); Gynergene Cafeine (France); Migranil (India); Polygot (Thailand); Trinergot (Mexico)

Drug Class

Adrenergic antagonists; CNS stimulants; Ergot alkaloids; Xanthines

Indications

Migraine, tension headache, cluster headache

Mechanism

Combination—see individual drugs

Dosage with Qualifiers

Headache—1-2 tabs/suppositories PO/PR q30min prn; max 6mg **ergotamine** qd

*NOTE: available in tablet or rectal suppository (100mg caffeine + 1mg **ergotamine** per tablet, 100/2 per suppository).*

- **Contraindications**—hypersensitivity, pregnancy, peptic ulcer disease, porphyria
- **Caution**—elderly patients, pediatric patients, history of abuse

Maternal Considerations	There are only scattered case reports of Cafergot use during pregnancy. This combination is contraindicated due to the oxytocic effects of **ergotamine.** See **caffeine** and **ergotamine** individually. ***Side effects*** include tachycardia and anxiety. In combination with other drugs, Cafergot may cause anaphylaxis, toxic epidermal necrolysis, bone marrow suppression, GI bleeding, and Stevens-Johnson syndrome.
Fetal Considerations	See **caffeine** and **ergotamine** individually. Jejunal atresia was reported in the child of a woman who ingested Cafergot in 5 consecutive pregnancies. The other 4 ended in spontaneous abortion.
Breastfeeding Safety	There is no published experience in nursing women. See **caffeine** and **ergotamine** individually.
Drug Interactions	**Ergotamine** and **caffeine** tablets should not be given with other vasoconstrictors. Sympathomimetics (pressor agents) may cause extreme elevation of blood pressure. **Propranolol** may potentiate the vasoconstrictive actions of **ergotamine** and **caffeine** by blocking the vasodilating property of epinephrine. **Nicotine** may provoke vasoconstriction in some patients, predisposing to a greater ischemic response to ergot therapy. The blood levels of ergotamine-containing drugs associated with vasospastic reactions are reported to be increased by the co-administration of macrolide antibiotics.
References	Browne ML. Epidemiology 2006; 17:324-31. Graham JM, Marin-Padilla M, Hoefnagel D. Clin Pediatr 1983; 22:226-8.
Summary	**Pregnancy Category: X** **Lactation Category: NS** • Contraindicated during pregnancy due to the oxytocic effects of **ergotamine.** • There are alternative agents with a higher safety profile for which there is more experience during pregnancy and lactation.

Calcifediol—(Dical-D; Calcijex)

International Brand Name—None identified.

Drug Class	Vitamins/minerals
Indications	Vitamin D deficiency, hypoparathyroidism, osteoporosis, hypocalcemia
Mechanism	Active form of vitamin D stimulates intestinal absorption of calcium and phosphorus.
Dosage with Qualifiers	Vitamin deficiency—50-100mcg PO qd Hypoparathyroidism—0.2-1mg PO qd Osteoporosis—0.6mg PO qd • **Contraindications**—hypersensitivity to drug or class, hypercalcemia, hypervitaminosis D • **Caution**—renal failure, renal stones, hyperphosphatemia

Maternal Considerations

Vitamin D supplementation is recommended during pregnancy. **Calcifediol** is converted in the kidney to an active form of vitamin D, calcitriol. There are no adequate reports or well-controlled studies in pregnant women. Veiled or dark-skinned pregnant women have an increased risk of vitamin D deficiency, which is associated with disease.
Side effects include hypercalcemia, elevated creatinine, polydipsia, nausea, and convulsion.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. There is a weak association between vitamin D levels and gestational age and fetal heel length. It is unknown whether **calcifediol** crosses the human placenta, though the placenta synthesizes active vitamin D. **Calcifediol** is reportedly teratogenic in some rodents.

Breastfeeding Safety

There is no published experience in nursing women. It is unknown whether **calcifediol** enters human breast milk, but supplementation has little effect on milk vitamin D levels.

Drug Interactions

No interactions have been reported.

References

Brunvand L, Quigstad E, Urdal P, Haug E. Early Hum Dev 1996; 45:27-33.
Cancela L, Le Boulch N, Miravet L. J Endocrinol 1986; 110:43-50.
Grover SR, Morley R. Med J Aust 2001; 175:251-2.
Kuoppala T, Tuimala R, Parviainen M, et al. Hum Nutr Clin Nutr 1986; 40:287-93.
Mallet E, Gugi B, Brunelle P, et al. Obstet Gynecol 1986; 68:300-4.
Morley R, Carlin JB, Pasco JA, Wark JD. J Clin Endocrinol Metab 2006; 91:906-12.

Summary

Pregnancy Category: B
Lactation Category: S

- Vitamin D supplementation is generally recommended during pregnancy.
- Most multivitamin supplements contain adequate quantities of vitamin D in one form or another.

Calcitonin—(Calcimar; Miacalcin)

International Brand Name—Biocalcin (Korea); Boncalmon (Korea); Cadens (France); Calcimar (Canada); Calcinin (Taiwan); Calcitoran (Japan); Calco (Singapore, Thailand); Calsynar (Brazil, South Africa, Taiwan); Caltine (Canada); Citonina (Argentina); Menocal (Korea, Singapore, Thailand); Miacalcic (Brazil, Chile, China, Colombia, Costa Rica, Dominican Republic, Ecuador, El Salvador, Guatemala, Honduras, Hong Kong, Indonesia, Israel, Malaysia, Mexico, New Zealand, Nicaragua, Panama, Peru, Philippines, Singapore, Taiwan, Thailand); Oseum (Mexico); Salmocalcin (Argentina); Salmotonin (Japan); Tonocalcin (Indonesia, Malaysia, Mexico); Zycalcit (India)

Drug Class

Hormones

Indications

Osteoporosis, Paget's disease, hypercalcemia

Mechanism

Unknown

Dosage with Qualifiers

Osteoporosis—100IU SC or IM qod or 200IU NAS qd
Paget's disease—begin 100IU SC or IM qd, then 50IU qod
Hypercalcemia—4IU/kg SC or IM q12h

- **Contraindications**—hypersensitivity to drug or class
- **Caution**—renal failure or stones, hyperphosphatemia

Maternal Considerations	**Calcitonin** regulates calcium homeostasis. There are no adequate reports or well-controlled studies in pregnant women. ***Side effects*** include rhinitis, back pain, epistaxis, nasal irritation, and headache.
Fetal Considerations	There are no adequate reports or well-controlled studies in pregnant women. **Calcitonin** does not cross the placenta. The mechanism by which high doses of **calcitonin** produce IUGR in rabbits is unknown.
Breastfeeding Safety	There is no published experience in nursing women. **Calcitonin** inhibits lactation in animals. It is unknown whether **calcitonin** enters human breast milk, though the high molecular weight argues against it. Further, any **calcitonin** in the milk would be destroyed by gastric acid. Procalcitonin is a normal constituent of human breast milk.
Drug Interactions	In patients with Paget's disease, prior diphosphonate use appears to reduce the antiresorptive response to **calcitonin**.
References	Kovarik J, Woloszczuk W, Linkesch W, Pavelka R. Lancet 1980; 1:199-200. Lafond J, Goyer-O'Reilly I, Laramee M, Simoneau L. Endocrine 2001; 14:285-94. Seki K, Makimura N, Mitsui C, et al. Am J Obstet Gynecol 1991; 164:1248-52. Woloszczuk W, Kovarik J, Pavelka P. Gynecol Obstet Invest 1981; 12:272-6.
Summary	**Pregnancy Category: C** **Lactation Category: S** (likely) • **Calcitonin** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Calcitriol—(Rocaltrol)

International Brand Name—Bocatriol (Germany); Bonky (Korea); Cabone (Korea); Calcijex (Australia, China, England, Hong Kong, Indonesia, Malaysia, Taiwan); Caraben SC (Korea); Cicarol (Korea); Citrihexal (Australia); Decostriol (Germany); Ecatrol (Indonesia); Ecatrol F (Indonesia); Hitrol (Indonesia); Kolkatriol (Indonesia); Kosteo (Australia); Lemytriol (Mexico); Meditrol (Thailand); Neobon (Korea); Osteotriol (Germany); Poscal (Korea); Renatriol (Germany); Rexamat (Argentina); Rocaltrol (Brazil, Canada, Chile, China, Costa Rica, Dominican Republic, Ecuador, El Salvador, Ghana, Guatemala, Honduras, Hong Kong, Indonesia, Japan, Kenya, Korea, Mexico, Nicaragua, Panama, Peru, South Africa, Taiwan, Tanzania, Thailand, Uganda, Uruguay, Venezuela); Roical (Malaysia, Singapore); Rolsical (India); Silkis (England, France, Hong Kong, Ireland, Singapore); Sitriol (Australia); Tariol (Korea); Tirocal (Mexico); Triocalcit (Peru)

Drug Class	Vitamins/minerals
Indications	Hypoparathyroidism, osteoporosis, hypocalcemia, supplementation during pregnancy
Mechanism	Active form of vitamin D; stimulates intestinal absorption of calcium and phosphorus
Dosage with Qualifiers	Hypocalcemia—0.25-1mcg PO qd Hypoparathyroidism—0.25-2mcg/d IV; increase the dose every 2-4w as needed Supplementation during pregnancy—10mcg/d PO

- **Contraindications**—hypersensitivity to drug or class, hypercalcemia, hypervitaminosis D
- **Caution**—renal failure or stones, hyperphosphatemia

Maternal Considerations

Calcitriol is an active form of vitamin D. There are no adequate reports or well-controlled studies in pregnant women. **Vitamin D** supplementation is recommended during pregnancy. **Calcitriol** combined with calcium supplementation helps lower systolic BP in older women.
Side effects include N/V, anorexia, convulsion, dry mouth, bone pain, polydipsia, irritability, weight loss, increased LFTs, and conjunctivitis.

Fetal Considerations

There are no adequate reports or well-controlled studies of the effect of **calcitriol** in human fetuses. It is unknown whether **calcitriol** crosses the human placenta, though the placenta synthesizes active vitamin D. **Calcitriol** is reportedly teratogenic in rabbits but not rats.

Breastfeeding Safety

There are no adequate reports or well-controlled studies in nursing women. It is unknown whether **calcitriol** enters human breast milk, but supplementation has little effect on milk vitamin D levels.

Drug Interactions

Cholestyramine may reduce intestinal absorption of fat-soluble vitamins which includes **calcitriol.**
Phenytoin/phenobarbital does not affect plasma concentrations of **calcitriol,** but may reduce endogenous levels of $25(OH)D_3$ by accelerating metabolism. Higher doses of **calcitriol** may be necessary if these drugs are given simultaneously.
Thiazides are known to induce hypercalcemia by decreasing urine calcium excretion. Some reports observe that use with thiazides cause hypercalcemia. Caution is indicated.
Ketoconazole inhibits both synthetic and catabolic enzymes of **calcitriol.** Reduction in serum endogenous **calcitriol** was seen after 300-1200 mg/d **ketoconazole** for 7d. However, *in vivo* drug interaction studies of **ketoconazole** with **calcitriol** have not been investigated.
As **calcitriol** alters intestinal, renal, and bone phosphate transport, the dose of phosphate-binding agents must be adjusted to reflect the serum phosphate concentration.
As **calcitriol** is the most potent active metabolite of vitamin D_3, pharmacologic doses of vitamin D and its derivatives should be withheld during treatment with **calcitriol.**
Magnesium-containing preparations (e.g., antacids) may cause hypermagnesemia and should not be taken during therapy with **calcitriol** by patients on chronic renal dialysis.

References

Brunvand L, Quigstad E, Urdal P, Haug E. Early Hum Dev 1996; 45:27-33.
Cancela L, Le Boulch N, Miravet L. J Endocrinol 1986; 110:43-50.
Kuoppala T, Tuimala R, Parviainen M, et al. Hum Nutr Clin Nutr 1986; 40:287-93.
Mallet E, Gugi B, Brunelle P, et al. Obstet Gynecol 1986; 68:300-4.
Pfeifer M, Begerow B, Minne HW, et al. J Clin Endocrinol Metab 2001; 86:1633-7.

Summary

Pregnancy Category: B
Lactation Category: U
- **Calcitriol** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.
- Most multivitamin supplements contain adequate quantities of vitamin D in one form or another.

Calcium chloride

Drug Class	Electrolyte replacements; Vitamins/minerals
Indications	Hypocalcemia, hypermagnesemia
Mechanism	Modulator of cellular events (e.g., contraction, signaling) via specific membrane channels
Dosage with Qualifiers	Hypocalcemia—500-1000mg IV slow infusion; do not exceed 1000mg ×1 Hypermagnesemia—500mg IV slow infusion; follow patient for clinical signs of hypermagnesemia • **Contraindications**—VF, hypercalcemia, digitalis toxicity, liver dysfunction • **Caution**—CV defects, impaired respiratory function, acidosis
Maternal Considerations	**Calcium chloride** is lifesaving in women with hypermagnesemia. It provides approximately 3× more calcium than calcium gluconate. **Calcium chloride** reduces the incidence of parturient paresis in cows and transiently increases cardiac output in gravid ewes during hemorrhagic hypotension. ***Side effects*** include tissue destruction after extravasation, and hyperkalemia-related ECG disturbances.
Fetal Considerations	It is unlikely calcium administration increases the fetal concentration. **Calcium chloride** decreases the **aspirin** toxicity in pregnant rats.
Breastfeeding Safety	It is unknown whether **calcium chloride** supplementation increases calcium concentration in breast milk.
Drug Interactions	A digitalized patient should not receive IV calcium compounds unless the indications are clearly defined. Calcium salts should not generally be mixed with carbonates, phosphates, sulfates, or tartrates in parenteral admixtures.
References	Bohman VR, Cotton DB. Obstet Gynecol 1990; 76:984-6. Oetzel GR. J Am Vet Med Assoc 1996; 209:958-61. Ueno K, Shimoto Y, Yokoyama A, et al. Res Commun Chem Pathol Pharmacol 1983; 39:179-88. Vincent RD Jr, Chestnut DH, Sipes SL, et al. Anesth Analg 1992; 74:670-6.
Summary	**Pregnancy Category: C** **Lactation Category: U** • **Calcium chloride** may be lifesaving in preeclamptic or preterm laboring women with hypermagnesemia secondary to magnesium sulfate infusion.

Camphor—(found in Absorbine Arthritic Pain Lotion 10%; Act-On Rub Lotion 1.5%; Anabalm Lotion 3%; Avalgesic; Aveeno Anti-Itch Conc. Lotion 0.3%; Banalg Muscle Pain Reliever 2%; Ben Gay Children's Vaporizing Rub 5%; Campho-Phenique First Aid Gel 10.8%)

International Brand Name—None identified.

Drug Class	Anesthetics, local; Antipruritics
Indications	Cold relief symptoms, muscle strain
Mechanism	Unknown
Dosage with Qualifiers	Found in multiple topical preparations • **Contraindications**—hypersensitivity to drug or class • **Caution**—seizures
Maternal Considerations	The FDA states that OTC drug products may not exceed **camphor** concentrations of 11%. There are no adequate reports or well-controlled studies in pregnant women. ***Side effects*** include local irritation and burning sensation.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. **Camphor** crosses the placenta, but there is no evidence of embryo toxicity or teratogenicity.
Breastfeeding Safety	There is no published experience in nursing women. It is unknown whether **camphor** enters human breast milk. Considering the route and dose, it is unlikely the breastfeeding neonate would ingest a clinically significant amount.
Drug Interactions	No drug interactions reported after topical use.
References	American Academy of Pediatrics, Committee on Drugs. Pediatrics 1978; 62:404-6. Uc A, Bishop WP, Sanders KD. South Med J 2000; 93:596-8. Weiss J, Catalano P. Pediatrics 1973; 52:713-4.
Summary	**Pregnancy Category: C** **Lactation Category: S** • **Camphor** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Candesartan—(Atacand)

International Brand Name—Amias (England, Ireland); Atacand (Canada, Colombia, France, Germany, Israel, Mexico, Singapore, South Africa, Sweden); Bilaten (Chile); Blopress (Austria, Brazil, Colombia, Costa Rica, El Salvador, Germany, Guatemala, Honduras, Hong Kong, Indonesia, Israel, Italy, Japan, Malaysia, Mexico, Nicaragua, Panama, Peru, Philippines, Thailand, Venezuela); Blox (Chile); Candesar (India); Kenzen (France); Tiadyl (Argentina, Paraguay)

Drug Class	ACEI/A2R-antagonists; Antihypertensives

Indications

Hypertension

Mechanism

AT-1 receptor antagonist

Dosage with Qualifiers

Hypertension—begin 16mg PO qd and increase gradually; max 32mg qd

- **Contraindications**—hypersensitivity to drug or class, history of angioedema
- **Caution**—renal artery stenosis, hepatic or renal dysfunction, hyponatremia, heart failure

Maternal Considerations

The published experience for **candesartan** during pregnancy is limited to a few case reports. It is assumed the effects of **candesartan** are similar to other ACEI class agents. As such, it should be avoided throughout pregnancy unless there is no other option. The lowest dose effective should be used when **candesartan** is required for BP control during pregnancy.
Side effects include fetal and neonatal morbidity/death (see Fetal Considerations), hypovolemia, asthenia, fever, paresthesia, vertigo, dyspepsia, gastroenteritis, tachycardia, palpitation, leukopenia, hepatotoxicity, neutropenia, hyperkalemia, edema, diarrhea, chest pain, cough, increased LFTs, pruritus, and rash.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. **Candesartan** presumably crosses the human placenta since fetal renal effects are reported and other ACEIs cross. AT-1 receptors are expressed on many organs of the human fetus. ACEIs are considered both teratogenic and fetotoxic. They are contraindicated throughout pregnancy as all members of this class may cause cranial hypoplasia, reversible or irreversible renal failure, oligohydramnios, anuria, death, prematurity, IUGR, and patent ductus arteriosus.

Breastfeeding Safety

There is no published experience in nursing women. It is unknown whether **candesartan** enters human breast milk.

Drug Interactions

Reversible increases in serum lithium along with toxicity have been reported during administration of **lithium** and ACEIs, including **candesartan,** and with some A2R-antagonists. Careful monitoring of serum lithium is recommended.

References

Bald M, Holder M, Zieger M, et al. Pediatr Nephrol 2005; 20:1664-8.
Cooper WO, Hernandez-Diaz S, Arbogast PG, et al. N Engl J Med 2006; 354:2443-51.
Hinsberger A, Wingen AM, Hoyer PF. Lancet 2001; 357:1620.
Simonetti GD, Baumann T, Pachlopnik JM, et al. Pediatr Nephrol 2006; 21:1329-30.

Summary

Pregnancy Category: C (1st trimester), **D** (2nd and 3rd trimesters)
Lactation Category: U

- **Candesartan** and other ACEIs should be considered human teratogens.
- **Candesartan** and other inhibitors of angiotensin's effects should be avoided during pregnancy if possible.
- There are alternative agents for which there is more experience during pregnancy and lactation.
- When the mother's disease requires treatment with **candesartan,** the lowest dose should be used followed by close monitoring of the fetus.

Captopril—(Capoten; Tenofax)

International Brand Name—Ace-Bloc (Taiwan); Acenorm (Australia, Germany); Acepress (Indonesia, Italy); Acepril (England); Aceril (Israel); Aceten (India, South Africa); Adocor (Germany); Alopresin (Spain); Altran (Colombia); Apuzin (Taiwan); Asisten (Argentina); Capace (South Africa); Capocard (Hong Kong); Caposan (Peru); Capotena (Mexico); Capotril (Israel); Capril (Hong Kong, Korea, Taiwan); Captace (Philippines); Captensin (Indonesia); Capti (Israel); Captoflux (Germany); Captomax (South Africa); Captopren (Colombia); Captoprilan (Dominican Republic); Captoril (Japan); Captral (Mexico); Cardipril (Mexico); Catona (Mexico); Catoplin (Singapore); Cesplon (Spain); Cryopril (Mexico); Debax (Austria); Dexacap (Hong Kong, Indonesia); Ecapres (Dominican Republic); Ecaten (Mexico); Epicordin (Germany); Epsitron (Hong Kong, Thailand); Farmoten (Indonesia); Hiperil (Portugal); Hypopress (Israel); Hypotensor (Greece); Inhibace (Israel); Insucar (Colombia); Isopresol (Argentina); Katopil (Slovenia); Ketanine (Singapore); Keyerpril (Mexico); Locap (Indonesia); Lopirin (Austria, Germany, Switzerland); Lopril (Finland, France); Medepres (Argentina); Mereprine (Portugal); Midrat (Mexico); Nolectin (Peru); Oltens Ge (France); Petacilon (Singapore); Praten (Indonesia); Primace (Philippines); Rilcapton (Hong Kong, Singapore, Taiwan); Ropril (Hong Kong); Smarten (Taiwan); Tenofax (Indonesia); Tensicap (Indonesia); Tensiomen (Bulgaria, Hungary, Thailand); Tensobon (Germany); Tensoprel (Singapore); Tensoril (Philippines); Tenzib (Belgium); Topace (Australia); Toprilem (Mexico); Typril-ACE (Philippines); Vasosta (Philippines); Zapto (South Africa); Zorkaptil (Slovenia)

Drug Class	ACEI/A2R-antagonists; Antihypertensives
Indications	Hypertension, CHF surgery, diabetes, MI (acute)
Mechanism	Angiotensin-converting enzyme inhibitor
Dosage with Qualifiers	Hypertension—25-50mg PO tid CHF—12.5-50mg PO tid Diabetic nephropathy—25mg PO tid *NOTE: may be combined with* ***hydrochlorothiazide.*** • **Contraindications**—hypersensitivity to drug or class, renal artery stenosis • **Caution**—collagen vascular diseases, CHF, renal artery stenosis, hepatic or renal dysfunction, hyponatremia
Maternal Considerations	There are no adequate reports or well-controlled studies of **captopril** in pregnant women. ACEIs are contraindicated across gestation unless there is no option. Improved pregnancy outcome was noted in diabetic mothers treated prenatally with low doses of **captopril.** The lowest dose effective should be used when **captopril** is required during pregnancy. Close monitoring of AF and fetal well-being is recommended. ***Side effects*** include angioedema, hypotension, renal failure, hepatic toxicity, pancreatitis, proteinuria, neutropenia, rash, pruritus, hypotension, angioedema, cough, abdominal pain, N/V, diarrhea, anorexia, constipation, peptic ulcer, dizziness, headache, malaise, fatigue, insomnia, dry mouth, dyspnea, alopecia, and paresthesias.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. **Captopril** apparently crosses the human placenta, though the kinetics remain to be elucidated. ACEIs are considered both teratogenic and fetotoxic. They are contraindicated throughout pregnancy as all members of this class may cause cranial hypoplasia, reversible or irreversible renal failure, oligohydramnios, anuria, death, prematurity, IUGR, and patent ductus arteriosus. **Captopril** is embryocidal and causes stillbirths in a variety of animals (sheep, rabbits, rats).
Breastfeeding Safety	**Captopril** is excreted in breast milk at a very low concentration and is generally considered compatible with breastfeeding.

Drug Interactions

Patients on diuretics (especially if recently initiated), as well as those on severe dietary salt restriction or dialysis, may experience a precipitous drop in BP typically within an hour of receiving the initial dose of **captopril.** Proactive steps to avoid hypotension include discontinuing the diuretic or increasing the salt intake approximately 1w prior to initiating **captopril** or initiating therapy with small doses (6.25 or 12.5mg). If hypotension occurs, the patient should be placed in a supine position and, if necessary, receive an IV infusion of normal saline. Transient hypotension is not a contraindication to further doses.

Nitroglycerin or other nitrates (as used for management of angina) or other drugs having vasodilator activity should, if possible, be discontinued before starting **captopril.** If resumed during **captopril** therapy, such agents should be given cautiously, perhaps at a lower dose.

Enhanced by antihypertensive agents that cause renin release (e.g., thiazides).

Agents affecting sympathetic activity (e.g., ganglionic blocking agents or adrenergic neuron blocking agents) should be used with caution.

β-Adrenergic blocking agents are somewhat additive to **captopril,** but the overall response is less than the individual sum.

Serum potassium may rise since **captopril** decreases aldosterone production. Potassium-sparing diuretics such as **spironolactone, triamterene,** or **amiloride,** or potassium supplements, should be given only for documented hypokalemia, and then with caution. Salt substitutes containing potassium should also be used with caution.

Indomethacin may reduce the antihypertensive effect, especially in cases of low-renin hypertension. Other NSAIDs (e.g., **aspirin**) may have this effect.

Increased serum lithium levels and symptoms of toxicity are reported in patients receiving **lithium** and ACEI therapy. These drugs should be co-administered with caution.

References

August P, Mueller FB, Sealey JE, Edersheim TG. Lancet 1995; 345:896-7.

Bar J, Chen R, Schoenfeld A, et al. J Pediatr Endocrinol Metab 1999; 12:659-65.

Burrows RF, Burrows EA. Aust NZ J Obstet Gynaecol 1998; 38:306-11.

Cooper WO, Hernandez-Diaz S, Arbogast PG, et al. N Engl J Med 2006; 354:2443-51.

Easterling TR, Carr DB, Davis C, et al. Obstet Gynecol 2000; 96:956-61.

Summary

Pregnancy Category: C (1st trimester), **D** (2nd and 3rd trimesters)

Lactation Category: S

- **Captopril** and other ACEIs are considered human teratogens.
- **Captopril** and other inhibitors of angiotensin's effects should be avoided throughout pregnancy if possible.
- There are alternative agents for which there is more experience during pregnancy and lactation.
- Should the mother's disease require treatment with **captopril,** the lowest dose should be used followed by close monitoring of the fetus.

Carbachol—(Carbastat; Carboptic; Isopto; Miostat)

International Brand Name—Carbamann (Germany); Glaumarin (Japan); Isopto Karbakolin (Sweden); Karbakolin Isopto (Denmark)

Drug Class	Miotics; Ophthalmics; Parasympathomimetics
Indications	Glaucoma
Mechanism	Cholinergic receptor agonist; partial cholinesterase inhibitor
Dosage with Qualifiers	Glaucoma—2 gtt each eye tid *NOTE: no more than 0.5ml should be administered for satisfactory miosis.* • **Contraindications**—hypersensitivity to drug or class, acute iritis • **Caution**—cardiac failure, asthma, hyperthyroidism, GI spasm, parkinsonism, recent MI, hypertension
Maternal Considerations	There are no adequate reports or well-controlled studies of the effect of **carbachol** in pregnant women. **Carbachol** is a potent stimulator of myometrial contractility in rodents. Considering the dose and route, it is unlikely the maternal systemic concentration will reach a clinically relevant level. ***Side effects*** include stinging, burning, flushing, sweating, epigastric distress, abdominal cramps, tightness in urinary bladder, and headache.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **carbachol** crosses the human placenta. Considering the dose and route, it is unlikely the maternal systemic concentration will reach a clinically relevant level.
Breastfeeding Safety	There is no published experience in pregnancy. It is unknown whether **carbachol** enters human breast milk. However, considering the dose and route, it is unlikely the breastfed neonate would ingest a clinically relevant amount.
Drug Interactions	NSAIDs may decrease cholinergic efficacy.
References	Boxall DK, Ford AP, Choppin A, et al. Br J Pharmacol 1998; 124:1615-22. Garfield RE, Bytautiene E, Vedernikov YP, et al. Am J Obstet Gynecol 2000; 183:118-25. Luckas MJ, Taggart MJ, Wray S. Am J Obstet Gynecol 1999; 181:468-76.
Summary	**Pregnancy Category: C** **Lactation Category: U** • **Carbachol** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Carbamazepine—(Atretol; Convuline; Epitol; Macrepan; Tegretol)

International Brand Name—Apo-Carbamazepine (Canada, Malaysia); Camapine (Taiwan, Thailand); Carbatol (India); Carbazene (Thailand); Carbazep (Mexico); Carbazina (Mexico); Carmaz (India); Carpaz (South Africa); Carzepin (Malaysia); Carzepine (Thailand); Clostedal (Mexico); Degranol (South Africa); Epileptol (Korea); Epileptol CR (Korea); Eposal Retard (Colombia); Espa-lepsin (Germany); Foxalepsin (Germany); Foxalepsin Retard (Germany); Hermolepsin (Sweden); Karbamazepin (Sweden); Kodapan (Japan); Lexin (Japan); Mazetol (India, Malaysia); Neugeron (Costa Rica, Dominican Republic, Guatemala, Honduras, Mexico, Nicaragua, Panama); Neurotol (Finland); Neurotop (Austria, Hungary, Malaysia); Neurotop Retard (Malaysia); Nordotol (Denmark, Mexico); Panitol (Thailand); Sirtal (Germany); Tardotol (Denmark); Taver (Thailand); Tegol (Taiwan); Tegretal (Germany); Tegretol CR (Israel, Korea, New Zealand, South Africa); Tegretol-S (South Africa); Telesmin (Japan); Temporal Slow (Hungary); Temporol (Bulgaria, South Africa); Teril (Hong Kong, Israel, New Zealand, Taiwan); Timonil (Germany, Israel); Timonil Retard (Germany, Israel, Switzerland)

Drug Class	Anticonvulsants
Indications	Seizure disorder, trigeminal neuralgia
Mechanism	Unknown
Dosage with Qualifiers	Seizure disorder—400-600mg PO bid (or 12-25mg/kg/d); max 600mg PO bid Trigeminal neuralgia—200-400mg PO bid • **Contraindications**—hypersensitivity, MAOIs in the past 2w • **Caution**—hepatic or renal failure, bone marrow depression, history of blood dyscrasia, cardiac disease
Maternal Considerations	Anticonvulsant drugs should not be discontinued abruptly during pregnancy if used to prevent seizures, as there is a significant possibility of precipitating status epilepticus. There are no adequate reports or well-controlled studies of **carbamazepine** in pregnant women. It would seem advisable for women to continue medication during pregnancy using monotherapy at the lowest dose required to achieve seizure control. Polytherapy would seem best avoided where possible. ***Side effects*** include seizures, Stevens-Johnson syndrome, arrhythmias, agranulocytosis, thrombocytopenia, and hepatitis.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. **Carbamazepine** rapidly crosses the human placenta and accumulates in fetal organs, including the brain. Epidemiologic study suggests **carbamazepine** is a teratogen causing facial dysmorphism, spina bifida, distal phalange hypoplasia, and developmental delay. In prospective studies involving 1255 exposures, **carbamazepine** was associated with increased rates of neural tube, CV, urinary tract, and cleft palate anomalies. One overview (Cochrane) concluded the evidence is weak that **carbamazepine** is a teratogen as monotherapy. More recent epidemiologic evidence, however, concludes **carbamazepine** is a modest teratogen—less than **phenytoin,** but more than other anticonvulsant agents. The combination of **carbamazepine** with other antiepileptic drugs has a synergistic effect on the prevalence of birth defects. There is also concern that **carbamazepine** exposure increases the risk of neonatal intracranial hemorrhage. Rodent studies reveal an increased prevalence of talipes, cleft palate, and anophthalmos.
Breastfeeding Safety	**Carbamazepine** is excreted in human breast milk. Although it is generally considered safe for breastfeeding women, neonatal sequelae reported include cholestatic hepatitis. The infant should

be monitored for possible adverse effects, the drug given at the lowest effective dose, and breastfeeding avoided at times of peak drug levels.

Drug Interactions

Carbamazepine suspension should not be used with other liquid medicinal agents or diluents. Mixing it with either **chlorpromazine** solution or liquid **thioridazine** causes a precipitate.

CYP3A4 inhibitors inhibit **carbamazepine** metabolism and may increase plasma levels. Drugs that have been shown, or would be expected, to increase **carbamazepine** levels include **acetazolamide, cimetidine, clarithromycin, dalfopristin, danazol, delavirdine, diltiazem, erythromycin, fluoxetine,** grapefruit juice, **isoniazid, ketoconazole, loratadine, itraconazole,** macrolides, **niacinamide, nicotinamide, propoxyphene, terfenadine, troleandomycin, valproate,** and **verapamil.** If a patient has been on a stable dosage of **carbamazepine** and begins treatment with one of these inhibitors, it is reasonable to expect a dose reduction in **carbamazepine** may be necessary.

CYP3A4 inducers can increase **carbamazepine** metabolism. Drugs that have been shown, or would be expected, to decrease **carbamazepine** levels include **cisplatin, doxorubicin, felbamate, phenobarbital, phenytoin, primidone, rifampin, theophylline,** and **troleandomycin.**

Increases the plasma levels of **clomipramine, phenytoin,** and **primidone.**

Induces hepatic CYP activity (especially CYP3A4 or epoxide hydrolase) and either causes or would be expected to cause decreased levels of **acetaminophen, alprazolam, amitriptyline, bupropion, buspirone, citalopram, clobazam, clonazepam, clozapine, cyclosporine, delavirdine, desipramine, diazepam, dicumarol, doxycycline, ethosuximide, haloperidol, lamotrigine, levothyroxine, lorazepam, methadone, methsuximide, midazolam, mirtazapine, nortriptyline, olanzapine,** oral contraceptives, **phensuximide, phenytoin, quinine, theophylline, tiagabine, topiramate, valproate,** and **warfarin.**

Administration with **lithium** may increase the risk of neurotoxic side effects.

Altered thyroid function has been reported when combined with other anticonvulsant medications.

Breakthrough bleeding has been reported in women receiving oral and subdermal implant contraceptives, and their reliability may be adversely affected.

Phenytoin has been reported to increase. Careful monitoring of **phenytoin** after use with **carbamazepine** is advised.

Warfarin's anticoagulant effect may be reduced by **carbamazepine.**

Because of its primary CNS effect, caution should be used when **carbamazepine** is taken with other centrally acting drugs and alcohol.

References

Adab N, Tudur SC, Vinten J, et al. Cochrane Database Syst Rev 2004; (3):CD004848.

Bar-Oz B, Nulman I, Koren G, Ito S. Paediatr Drugs 2000; 2:113-26.

Burja S, Rakovec-Felser Z, Treiber M, et al. Wien Klin Wochenschr 2006; 118(Suppl 2):12-6.

Diav-Citrin O, Shechtman S, Arnon J, Ornoy A. Neurology 2001; 57:321-4.

Frey B, Braegger CP, Ghelfi D. Ann Pharmacother 2002; 36:644-7.

Holmes LB, Harvey EA, Coull BA, et al. N Engl J Med 2001; 344:1132-8.

Iqbal MM, Sohhan T, Mahmud SZ. J Toxicol Clin Toxicol 2001; 39:381-92.
Kaaja E, Kaaja R, Hiilesmaa V. Neurology 2003; 60:575-9.
Matalon S, Schechtman S, Goldzweig G, Ornoy A. Reprod Toxicol 2002; 16:9-17.
Meador KJ, Baker GA, Finnell RH, et al; NEAD Study Group. Neurology 2006; 67:407-12.
Samren EB, van Duijn CM, Christiaens GC, et al. Ann Neurol 1999; 46:739-46.

Summary

Pregnancy Category: C
Lactation Category: S (likely)

- **Carbamazepine** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk; other anticonvulsants are preferable.
- Monotherapy with the lowest effective quantity given in divided doses to minimize the peaks can minimize the risks.

Carbenicillin—(Geocillin)

International Brand Name—Carbachol (Poland); Carbamann (Germany); Glaumarin (Japan); Isopto Karbakolin (Sweden); Karbakolin Isopto (Denmark)

Drug Class

Antibiotics; Penicillins

Indications

Infections with *E. coli, P. mirabilis, Staphylococcus, Streptococcus, S. fecalis* (enterococci)

Mechanism

Inhibits synthesis of cell wall mucopeptide

Dosage with Qualifiers

Adult infection—2-4 tab qd (1 tab = 382mg carbenicillin)

- **Contraindications**—hypersensitivity to drug or class
- **Caution**—cephalosporin allergy, seizure disorder, renal dysfunction

Maternal Considerations

Carbenicillin is indicated for the treatment of acute and chronic infections of the upper and lower urinary tract. There are no adequate reports or well-controlled studies in pregnant women. ***Side effects*** include seizures, anaphylaxis, Stevens-Johnson syndrome, hemolytic anemia, neutropenia, nausea, urticaria, diarrhea, rash, and fever.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **carbenicillin** crosses the human placenta. Other penicillins do cross to varying degrees. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically.

Breastfeeding Safety

There is no published experience in nursing women. **Carbenicillin** is excreted into breast milk in low concentrations, but is generally considered safe during breastfeeding.

Drug Interactions

Carbenicillin blood levels may be increased and prolonged by administration with **probenecid.**

References

Davies BI, Mummery RV, Brumfitt W. Br J Urol 1975; 47:335-41.
Elek E, Ivan E, Arr M. Int J Clin Pharmacol 1972; 6:223-8.

Summary	**Pregnancy Category: B** **Lactation Category: S** • Penicillin-class drugs are generally considered safe during pregnancy.

Carbidopa—(Lodosyn)

International Brand Name—None identified.

Drug Class	Antiparkinson agents; Dopaminergics
Indications	Parkinson's disease
Mechanism	Inhibits peripheral dopamine decarboxylation, crosses blood-brain barrier and can serve as a dopamine precursor
Dosage with Qualifiers	Parkinson's disease—optimal dose is determined by careful titration whether given alone or in combination with **levodopa.** Most patients respond to a 1:10 proportion of **carbidopa** and **levodopa,** provided the daily dosage of **carbidopa** is 70mg or more/d; max 200mg PO qd *NOTE: may be combined with **levodopa** (Sinemet).* • **Contraindications**—hypersensitivity, glaucoma, melanoma • **Caution**—psychosis, asthma, gastric ulcer, renal failure
Maternal Considerations	There are no adequate reports or well-controlled studies of **carbidopa** in pregnant women. Pregnancy may exacerbate Parkinson's disease and have a long-term negative impact on the course of the illness. ***Side effects*** include suicidal ideation, hemolytic anemia, leukopenia, hepatic failure, agitation, headache, and anxiety.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. **Carbidopa** crosses the rat and human placenta, and the fetal blood-brain barrier. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically. Its use with **levodopa** is associated with visceral and skeletal malformations in rabbits.
Breastfeeding Safety	There are no adequate reports or well-controlled studies in nursing women. It is unknown whether **carbidopa** enters human breast milk.
Drug Interactions	Symptomatic postural hypotension may occur when **carbidopa-levodopa** is added to the antihypertensive treatment, and a dose adjustment of the antihypertensive agent may be required. There are rare reports of adverse reactions, including hypertension and dyskinesia, from the concomitant use of TCAs and a **carbidopa-levodopa** combination. Phenothiazines and butyrophenones may reduce the therapeutic effects of **levodopa.** The beneficial effects of **levodopa** in Parkinson's disease may be reversed by **phenytoin** or **papaverine.** Patients taking these drugs should be carefully observed for any loss of the therapeutic response to **carbidopa-levodopa.**
References	Merchant CA, Cohen G, Mytilineou C, et al. J Neural Transm Park Dis Dement Sect 1995; 9:239-42.

Shulman LM, Minagar A, Weiner WJ. Mov Disord 2000; 15:132-5.
Vickers S, Stuart EK, Bianchine JR, et al. Drug Metab Dispos 1974; 2:9-22.

Summary

Pregnancy Category: C
Lactation Category: U
- **Carbidopa** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Carbinoxamine—(Rondec: carbinoxamine/dextromethorphan/pseudoephedrine)

International Brand Name—Became (Malaysia, Taiwan); Congestrin (Costa Rica, Dominican Republic, El Salvador, Honduras); Kezintea (Taiwan); Rondec-T (Taiwan); Rondex (Puerto Rico)

Drug Class

Antihistamines

Indications

Cold symptoms

Mechanism

Nonselectively antagonizes central and peripheral H_1 receptors

Dosage with Qualifiers

Cold symptoms—5ml PO qid
- **Contraindications**—hypersensitivity to drug or class, MAOI usage
- **Caution**—glaucoma, hypertension, diabetes, asthma, COPD

Maternal Considerations

There is no published experience with **carbinoxamine** during pregnancy.
Side effects include arrhythmia, hypertension, coronary vasospasm, drowsiness, thickened secretions, and dry mouth.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **carbinoxamine** crosses the human placenta.

Breastfeeding Safety

There is no published experience in nursing women. It is unknown whether **carbinoxamine** enters human breast milk.

Drug Interactions

Antihistamines may enhance the effects of TCAs, barbiturates, alcohol, and other CNS depressants.
MAOIs prolong and intensify the anticholinergic effects of antihistamines.

References

There is no published experience in pregnancy or during lactation.

Summary

Pregnancy Category: C
Lactation Category: U
- **Carbinoxamine** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.
- There are alternative agents for which there is more experience during pregnancy and lactation.

Carboprost tromethamine—(Hemabate)

International Brand Name—Prostin 15m (Netherlands, New Zealand); Prostinfenem (Denmark, Sweden); Prostodin (India)

Drug Class

Abortifacients; Oxytocics; Prostaglandins; Stimulants, uterine

Indications

Pregnancy termination, uterine atony

Mechanism

Stimulates prostaglandin F receptors

Dosage with Qualifiers

Pregnancy termination—begin 100mcg IM test dose, then 250mcg IM q90-120min; max 12mg total or use no longer than 2d
Uterine atony—250mcg IM ×1, may repeat q15-90min; max 2mg

- **Contraindications**—hypersensitivity to drug or class; acute PID; acute renal, hepatic, or pulmonary insufficiency; symptomatic CAD
- **Caution**—hypertension, diabetes mellitus, asthma, hepatic or renal dysfunction, anemia, seizure disorder, uterine scar, chorioamnionitis

Maternal Considerations

Carboprost is an analog of 15-methylprostaglandin $PGF_{2\alpha}$. It is a second-line agent for the treatment of uterine atony refractive to **oxytocin** behind **methergine/ergotrate** because of the high incidence of GI complaints (21% vs <1%). Some suggest that it is more effective if given directly into the myometrium, but there are no trial data to support the practice. **Carboprost** has also been given both IM and intra-amniotically for pregnancy termination, though both misoprostil and PGE_2 are superior for this indication. It can speed cervical ripening (200mcg IM), but once administered may be difficult to control. Misoprostil is superior for preparation for a 1st trimester vacuum aspiration. ***Side effects*** include pulmonary edema, respiratory distress, bronchospasm, hematemesis, uterine rupture, diarrhea, N/V, fever, flushing, hypertension, cough, headache, and pain.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **carboprost** crosses the human placenta. The principal risk reflects that of hypoxia associated with uterine tachysystole.

Breastfeeding Safety

There is no published experience in nursing women. It is unknown whether **carboprost** enters human breast milk.

Drug Interactions

May augment the activity of other oxytocic agents. Use with other oxytocic agents is not recommended.

References

Dildy GA 3rd. Clin Obstet Gynecol 2002; 45:330-44.
Lamont RF, Morgan DJ, Logue M, Gordon H. Prostaglandins Other Lipid Mediat 2001; 66:203-10.
Perry KG Jr, Rinehart BK, Terrone DA, et al. Am J Obstet Gynecol 1999; 181:1057-61.
Su LL, Biswas A, Choolani M, et al. Am J Obstet Gynecol 2005; 193:1410-4.
Vimala N, Mittal S, Dadhwal V. Int J Gynaecol Obstet 2005; 88:134-7.

Summary

Pregnancy Category: C
Lactation Category: U

- **Carboprost** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Carisoprodol—(Caridolin; Chinchen; Flexartal; Mus-Lax; Neotica; Rela; Rotalin; Scutamil-C; Soma)

International Brand Name—Artifar (Greece); Carisoma (England, India); Myolax (Thailand); Somadril (Denmark, Norway, Sweden)

Drug Class	Muscle relaxants
Indications	Muscle spasm
Mechanism	Blocks interneuronal activity in the descending reticular formation and spinal cord
Dosage with Qualifiers	Muscle spasm—350mg PO tid and hs, or qid • **Contraindications**—hypersensitivity to drug or class, porphyria • **Caution**—hepatic or renal dysfunction
Maternal Considerations	The major metabolite of **carisoprodol** is **meprobamate.** There are no adequate reports or well-controlled studies in pregnant women. ***Side effects*** include anaphylaxis, erythema multiforme, drowsiness, orthostatic hypotension, vertigo, ataxia, vomiting, tremor, rash, angioedema, and headache.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. **Carisoprodol** crosses the human placenta and in limited study, does not appear to cause developmental toxicity. Rodent teratogenicity studies have not been performed.
Breastfeeding Safety	**Carisoprodol** is concentrated in breast milk. The absolute dose ingested by an exclusively breastfed infant was estimated at 1.9mg/kg/d, and the relative dose 4.1% of the weight-adjusted maternal dose. No adverse effects are reported.
Drug Interactions	Concurrent **azelastine** nasal or **dexmedetomidine** may increase the risk of CNS depression.
References	Briggs GA, Ambrose PJ, Nageotte MP, Padilla G. Ann Pharmacother 2008; 42:898-901. Grizzle TB, George JD, Fail PA, Heindel JJ. Fundam Appl Toxicol 1995; 24:132-9. Nordeng H, Zahlsen K, Spigset O. Ther Drug Monit 2001; 23:298-300.
Summary	**Pregnancy Category: C** **Lactation Category: NS** (possibly) • **Carisoprodol** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Carteolol—(Arteoptik; Cartrol; Ocupress; Optipress)

International Brand Name—Arteolol (Spain); Arteoptic (Czech Republic, Denmark, Germany, Hong Kong, Poland, Portugal, Switzerland, Taiwan, Thailand); Caltamol (Korea); Calte (Korea); Carteabak (France); Carteol (Belgium, France, Italy); Carteol LP (France); Catelon Eye drop (Korea); Elebloc (Argentina, Taiwan); Endak (Austria, Germany); Glauteolol (Argentina); Karol (Korea); Karteol (Taiwan); Mikelan (France, Hong Kong, India, Korea, Malaysia, Pakistan, South Africa, Thailand); Stobol (Bulgaria); Teoptic (England, Ireland, Netherlands, South Africa)

Drug Class	Adrenergic antagonists; β-Blockers; Ophthalmics

Indications

Hypertension, glaucoma

Mechanism

Antagonizes β_1- and β_2-adrenergic receptors

Dosage with Qualifiers

Hypertension—2.5-10mg PO qd
Chronic open-angle glaucoma and intraocular hypertension—1 gtt of 1% solution bid

NOTE: renal dosing.

- **Contraindications**—hypersensitivity to drug or class, asthma, COPD, bradycardia, AV block, CHF
- **Caution**—diabetes mellitus, hyperthyroidism

Maternal Considerations

There is no published experience with **carteolol** during pregnancy.
Side effects include bronchospasm, asthenia, paresthesia, edema, and back pain.

Fetal Considerations

There are no adequate reports or well-controlled studies of **carteolol** in human fetuses. Rodent studies are reassuring, revealing no evidence of teratogenicity despite the use of doses dramatically higher than those used clinically. There was, however, evidence of fetotoxicity and IUGR at these high doses.

Breastfeeding Safety

There is no published experience in nursing women. It is unknown whether **carteolol** enters human breast milk. It does enter rat milk.

Drug Interactions

Catecholamine-dependent drugs (e.g., **reserpine**) may have an additive effect. Patients treated with **carteolol** plus a catecholamine-depleting agent must be observed carefully for evidence of hypotension and/or excessive bradycardia, which may cause syncope or postural hypotension.
General anesthetics may exaggerate the hypotension.
NSAIDs may blunt the antihypertensive effect of β-blockers.
Calcium antagonists may be used with β-adrenergic blocking agents when heart function is normal, but should be avoided in women with impaired cardiac function. Hypotension is more likely when the calcium antagonist is a dihydropyridine derivative (e.g., **nifedipine**), while LV failure and AV conduction disturbances are more likely with either **verapamil** or **diltiazem.**
Use with **digitalis** and either IV **diltiazem** or **verapamil** may have additive effects in prolonging AV conduction time.
Use with oral antidiabetic agents or insulin may be associated with hypoglycemia or possibly hyperglycemia. The dose of the hypoglycemic agent should be adjusted accordingly.
Carteolol solution should be used with caution in women receiving an oral β-adrenergic blocking agent because of the potential for additive effects.

References

Tamagawa M, Numoto T, Tanaka N, Nishino H. J Toxicol Sci 1979; 4:59-77.
Tanaka N, Shingai F, Tamagawa M, Nakatsu I. J Toxicol Sci 1979; 4:47-58.

Summary

Pregnancy Category: C
Lactation Category: U

- **Carteolol** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.
- There are many alternative agents for the treatment of hypertension for which there is more experience during pregnancy and lactation.

Carvedilol—(Coreg)

International Brand Name—Cardivas (India); Carvedlol (Korea); Carvrol (Korea); Dilatrend (Austria, Colombia, Ecuador, Germany, Hong Kong, Italy, Korea, Malaysia, Mexico, Norway, Peru, Philippines, Taiwan, Thailand); Dilbloc (Indonesia); Eucardic (England, Ireland); Kredex (France); Querto (Germany); V-Bloc (Indonesia)

Drug Class	Adrenergic antagonists; Antihypertensives; β-Blockers
Indications	Hypertension, CHF
Mechanism	Selective α_1- and nonselective β-adrenergic receptor antagonists
Dosage with Qualifiers	Hypertension—6.25-12.5mg PO bid, re-evaluate in 2w; max 25mg bid CHF—3.125-50mg PO bid; max 25-50mg PO bid • **Contraindications**—hypersensitivity to drug or class, asthma, AV block, bradycardia, CHF (class IV) • **Caution**—hepatic or renal dysfunction
Maternal Considerations	There are no adequate reports or well-controlled studies of **carvedilol** in pregnant women. There are reports of its use for the treatment of peripartal cardiomyopathy. ***Side effects*** include AV block, bradycardia, thrombocytopenia, sudden death, bronchospasm, fatigue, N/V, orthostatic hypotension, bradycardia, headache, gout, and abdominal pain.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **carvedilol** crosses the human placenta. **Carvedilol** crosses the rodent placenta, and produces fetotoxicity and IUGR when given in doses that are multiples of the MRHD.
Breastfeeding Safety	There are no adequate reports or well-controlled studies in nursing women. It is unknown whether **carvedilol** enters human breast milk. It does enter the milk of some rodent species.
Drug Interactions	Strong inhibitors of CYP2D6 (e.g., **quinidine, fluoxetine, paroxetine, propafenone**) are unstudied, but would be expected to increase blood levels of the (*R*−) enantiomer. Retrospective analysis of side effects in clinical trials showed that poor 2D6 metabolizers had a higher rate of dizziness during up-titration. Patients taking a drug with β-blocking properties and a one that can deplete catecholamines (e.g., **reserpine,** MAOIs) should be observed closely for signs of hypotension and/or severe bradycardia. **Clonidine** may potentiate the antihypertensive effects of β-blocking agents. If the **clonidine** is to be terminated, the β-blocking agent should be discontinued first over several days. Mean trough **cyclosporine** levels are increased after **carvedilol** treatment in renal transplant patients suffering from chronic vascular rejection. In about 30%, the **cyclosporine** dose has to be reduced. Due to wide interindividual variability, it is recommended that **cyclosporine** concentrations be monitored closely after initiation of **carvedilol** therapy. **Digoxin** concentrations are increased by about 15%. Both **digoxin** and **carvedilol** slow AV conduction. Therefore, increased monitoring of **digoxin** is recommended when initiating, adjusting, or discontinuing **carvedilol.** **Rifampin** reduced plasma concentrations by about 70%. **Cimetidine** increased AUC by about 30% but caused no change in C_{max}.

Isolated cases of conduction disturbance (rarely with hemodynamic compromise) have been observed when **carvedilol** is co-administered with **diltiazem.**
β-Blocking drugs may enhance the blood glucose–reducing effect of **insulin** and oral hypoglycemics.

References

Sliwa K, Skudicky D, Candy G, et al. Eur J Heart Fail 2002; 4:305-9.

Summary

Pregnancy Category: C
Lactation Category: U

- **Carvedilol** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.
- There are alternative agents for which there is more experience during pregnancy and lactation.

Casanthranol—(Peri-Colace: casanthranol/docusate sodium)

International Brand Name—None identified.

Drug Class

Anthraquinones; Purgatives

Indications

Constipation

Mechanism

Stimulates peristalsis

Dosage with Qualifiers

Constipation—1-2 tab PO qd

- **Contraindications**—hypersensitivity to drug or class, constipation, appendicitis, acute abdomen, mineral oil
- **Caution**—N/V

Maternal Considerations

There are no adequate reports or well-controlled studies of **casanthranol** in pregnant women.
Side effects include bowel obstruction, abdominal cramps, rash, and electrolyte disorders.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **casanthranol** crosses the human placenta. It is not associated with an increased incidence of fetal malformations. Rodent teratogenicity studies have apparently not been performed.

Breastfeeding Safety

There is no published experience during pregnancy. It is unknown whether **casanthranol** enters human breast milk. A metabolite, anthraquinone, is excreted into breast milk and may increase the incidence of diarrhea in infants of nursing mothers. However, it is generally considered safe during breastfeeding.

Drug Interactions

Casanthranol may have an additive effect when given with mineral oil.

References

Greenleaf JO, Leonard HSD. Practitioner 1973; 210:259-63.
Heinonen OP, Slone D, Shapiro B. Birth Defects and Drugs in Pregnancy. Littleton, MA: Publishing Sciences Group, 1977.

Summary

Pregnancy Category: C
Lactation Category: S

- **Casanthranol** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Cefaclor—(Ceclor; Ceclor CD; Cefaclor)

International Brand Name—Aclor (Australia); Alfatil (France); Alfatil LP (France); Alphexine (France); Brelox (Philippines); Capabiotic (Indonesia); Castal (Hong Kong); CEC (South Africa); CEC 500 (Germany); Ceclex (Korea); Ceclobid (Philippines); Ceclor (Australia, Austria, Belgium, Brazil, Bulgaria, Canada, China, Costa Rica, Czech Republic, Dominican Republic, Ecuador, El Salvador, Greece, Guatemala, Honduras, Hong Kong, Hungary, Indonesia, Israel, Korea, Mexico, Netherlands, Nicaragua, Panama, Peru, Philippines, Poland, Portugal, Spain, Switzerland, Venezuela); Ceclor AF (Costa Rica, Dominican Republic, El Salvador, Guatemala, Honduras, Panama, Peru); Ceclor CD (Australia, Philippines); Ceclor MR (Hong Kong, South Africa); Ceclor Retard (Colombia, Spain); Cecrocin (Korea); Cecrun (Korea); Cefabac (Israel); Cefabiocin (Germany); Cefacle (Korea); Cefaclin (Korea); Cefaclostad (Germany); Cefalan (Mexico); Cefkor (Australia); Cefkor CD (Australia); Cefler (Korea); Cefral (Argentina); Celco (Thailand); Cephalodoc (Germany); Ceracl (Korea); Cero (Taiwan); Cesid (Korea); Cleancef (China, Korea, Singapore); Clex (Korea); Cloracef (Indonesia); Cloracef MR (Israel); Clorotir (New Zealand, Philippines, Thailand); Cyclor (Korea); Distaclor (England, Ireland, Malaysia, Thailand); DistaclorMR (Malaysia); Especlor (Indonesia); Faclor (Brazil); Haxifal (France); Hefaclor (Germany); Karlor CD (Australia); Kefaclor (Tanzania); Keflor (Australia, Chile, China, India, Taiwan); Keflor AF (Taiwan); Kefolor (Denmark, Finland, Sweden); Kefral (Japan); Kemocin (Korea); Kerfenmycin (Taiwan); Kindoplex (Philippines); Kloclor BD (South Africa); Kwicap (Argentina); Mediconcef (Indonesia); Medoclor (Hong Kong); Miclor (Korea); Newgenclor (Korea); Newporine (Korea); Panacef (Italy, Peru); Panacef RM (Peru); Panoral (Germany); Panoral Forte (Germany); Pharmaclor (Israel); Qualiceclor (Hong Kong); Qualiphor (Hong Kong); Serviclor (Mexico); Sifaclor (Thailand); Soficlor (Hong Kong, Malaysia, Singapore); Swiflor (Taiwan); Syntocor (Hong Kong); Teraclox (Mexico); Vefarol (Philippines); Vercef (Malaysia); Versef (Philippines); Xelent (Philippines); Xeztron (Philippines)

Drug Class	Antibiotics; Cephalosporins, 2nd-generation
Indications	Bacterial infections (gram-positive aerobes: *S. aureus*, *S. pneumoniae*, *S. pyogenes;* gram-negative anaerobes: *H. influenzae*)
Mechanism	Bactericidal—inhibits cell wall synthesis
Dosage with Qualifiers	Bacterial infection—375-500mg XR PO bid within 1h of eating, or 250-500mg tid *NOTE: renal dosing.* • **Contraindications**—hypersensitivity to drug or class • **Caution**—penicillin allergy, renal dysfunction, antibiotic-associated colitis, seizure disorder, concomitant use of nephrotoxic drugs
Maternal Considerations	Because of its antimicrobial spectrum, **cefaclor** is used to treat acute bronchitis, pharyngitis, and skin infections. It has poor activity against the anaerobes associated with bacterial vaginosis. There are no adequate reports or well-controlled studies in pregnant women. However, cephalosporins are usually considered safe during pregnancy. ***Side effects*** include anaphylaxis, seizures, pseudomembranous colitis, nephrotoxicity, leukopenia, thrombocytopenia, erythema multiforme, exfoliative dermatitis, and cholestatic jaundice.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **cefaclor** crosses the human placenta. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically.
Breastfeeding Safety	Most cephalosporins are excreted into breast milk. While there are no adequate reports or well-controlled studies in nursing women, **cefaclor** is generally considered compatible with breastfeeding.
Drug Interactions	Nephrotoxicity has been reported following co-administration of other cephalosporins and aminoglycosides.

Probenecid may decrease renal tubular secretion of cephalosporins, resulting in increased and more prolonged cephalosporin blood levels.

References

Committee on Drugs, American Academy of Pediatrics. Pediatrics 1994; 93:137-50.
Puapermpoonsiri S, Watanabe K, Kato N, Ueno K. Antimicrob Agents Chemother 1997; 41:2297-9.

Summary

Pregnancy Category: B
Lactation Category: S

- **Cefaclor** is used for the treatment of acute bronchitis, pharyngitis, and skin infections.

Cefadroxil—(Cedroxim; Droxicef; Duricef; Kefroxil; Nor-Dacef; Ultracef; Wincef)

International Brand Name—Adroxef (Chile); Alxil (Indonesia); Amben (Hong Kong); Ancefa (Indonesia); Baxan (England); Bidicef (Indonesia); Biodroxil (Bulgaria, Colombia, Hong Kong, Israel, Peru); Biodroxyl (Venezuela); Biofaxil (Portugal); Camex (Korea); Cedrox (Germany); Cedroxim (Costa Rica, Dominican Republic, El Salvador, Guatemala, Honduras, Nicaragua, Panama); Cefacar (Argentina); Cefacell (Korea); Cefadril (Italy, Thailand); Cefadrol (India); Cefadrox (South Africa); Cefalom (Greece); Cefamox (Brazil, Mexico, Philippines, Sweden, Uruguay); Cefaroxil (Korea); Cefat (Indonesia); Cefaxil (Taiwan); Ceforal (Portugal); Cefoxil (Korea); Cefra-Om (Portugal); Cefroxil (Spain); Cephos (Italy); Cepotec (Mexico); Cipadur (South Africa); Crenodyn (Italy); Curisafe (Israel); Cyclomycin-K (Greece); Dacef (South Africa); Doxef (Indonesia); Drocef (Brazil, Korea); Droxicef (Israel); Droxyl (India); Drozid (Philippines); Duracef (Austria, Belgium, Colombia, Costa Rica, Czech Republic, Dominican Republic, Ecuador, El Salvador, Finland, Guatemala, Honduras, Hong Kong, Hungary, Israel, Mexico, Nicaragua, Panama, Peru, Philippines, Poland, South Africa, Spain, Switzerland, Taiwan); Duricef (Canada, Korea, Singapore); Egobiotic (Argentina); Ethicef (Indonesia); Evacef (Korea); Fadrox (Colombia); Justum (Paraguay); Kefloxcin (Malaysia); Kelfex (Indonesia); Kleotrat (Greece); Konicef (Korea); Lapicef (Indonesia); Lesporina (Colombia); Likodin (Taiwan); Lydroxil (India); Medicefa (Korea); Moxacef (Belgium, Greece, Netherlands); Nefalox (Greece); Nor-Dacef (Dominican Republic, El Salvador, Guatemala, Honduras, Nicaragua); Odoxil (India); Omnidrox (Slovenia); Oracefal (France); Oradroxil (Italy); QCef (Indonesia); Qualidrox (Hong Kong); Rafemox (Chile); Sedral (Japan, Taiwan); Sofidrox (Malaysia, Singapore); Teroxina (Mexico); Ucefa (Taiwan); Ultracef (Ireland); Urocef (Korea); Vepan (India); Versatic (Argentina); Vidcef (Korea)

Drug Class

Antibiotics; Cephalosporins, 1st-generation

Indications

Bacterial infections (gram-positive aerobes: *S. aureus*, β_1-hemolytic streptococci; gram-negative aerobes: *E. coli*, *P. mirabilis*, *Klebsiella* species, *Moraxella catarrhalis*)

Mechanism

Bactericidal—inhibits cell wall synthesis

Dosage with Qualifiers

Bacterial infection—500-1000mg PO qd

NOTE: renal dosing.

- **Contraindications**—hypersensitivity to drug or class
- **Caution**—penicillin allergy, renal dysfunction, antibiotic-associated colitis, seizure disorder, concomitant use of nephrotoxic drugs

Maternal Considerations

Because of its antimicrobial spectrum, **cefadroxil** is used to treat UTIs and pharyngitis. There are no adequate reports or well-controlled studies in pregnant women. However, cephalosporins are usually considered safe during pregnancy.
Side effects include anaphylaxis, seizures, pseudomembranous colitis, nephrotoxicity, leukopenia, thrombocytopenia, erythema multiforme, exfoliative dermatitis, cholestatic jaundice, diarrhea, nausea, dyspepsia, urticaria, pruritus, and vaginal candidiasis.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **cefadroxil** crosses the human placenta. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically.

Breastfeeding Safety

Cefadroxil is excreted into breast milk in low concentrations; it is generally considered compatible with breastfeeding.

Drug Interactions

Nephrotoxicity has been reported following co-administration of other cephalosporins and aminoglycosides.
Probenecid may decrease renal tubular secretion of cephalosporins, resulting in increased and more prolonged cephalosporin blood levels.

References

Committee on Drugs, American Academy of Pediatrics. Pediatrics 1994; 93:137-50.
Shetty N, Shulman RI, Scott GM. J Hosp Infect 1999; 41:229-32.

Summary

Pregnancy Category: B
Lactation Category: S
- **Cefadroxil** is used for the treatment of acute bronchitis, pharyngitis, and skin infections.

Cefamandole—(Mandol)

International Brand Name—Cedol (Taiwan); Cefadol (Taiwan, Thailand); Cefam (Italy); Dardokef (Indonesia); Dofacef (Indonesia); Kefadol (England, Ireland); Kefandol (France); Kefdole (Japan, South Africa); Kepadol (England); Kertet (Thailand); Mancef (Korea); Mandokef (Austria, Bulgaria, Denmark, Finland, Germany, Hungary, Portugal, South Africa, Spain, Switzerland); Mandol (Belgium, Czech Republic, Egypt, Korea, Netherlands, Taiwan)

Drug Class

Antibiotics; Cephalosporins, 2nd-generation

Indications

Bacterial infections (gram-positive aerobes: *S. aureus, S. epidermidis, S. pneumoniae, S. pyogenes;* gram-negative aerobes: *E. coli, Klebsiella, Enterobacter, P. mirabilis, Morganella morganii;* anaerobic organisms: *Peptococcus, Peptostreptococcus, Clostridium, Bacteroides, Fusobacterium)*

Mechanism

Bactericidal—inhibits cell wall synthesis

Dosage with Qualifiers

Bacterial infection—500mg-1.0g IV q4-8h
Cesarean section prophylaxis—1g IV at umbilical cord clamping

- **Contraindications**—hypersensitivity to drug or class
- **Caution**—penicillin allergy, renal dysfunction, antibiotic-associated colitis, seizure disorder, concomitant use of nephrotoxic drugs

Maternal Considerations

Because of its antimicrobial spectrum, **cefamandole** is used to treat lower respiratory tract infections, UTIs, peritonitis, and septicemia and for post–cesarean section prophylaxis. For the latter, it has no advantage over any other cephalosporin. Though used by some for the treatment of group B streptococcus colonization, there is growing resistance. Cephalosporins are usually considered safe during pregnancy.
Side effects include anaphylaxis, seizures, pseudomembranous colitis, nephrotoxicity, leukopenia, thrombocytopenia, erythema multiforme, exfoliative dermatitis, and cholestatic jaundice.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **cefamandole** crosses the human placenta. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically.

Breastfeeding Safety

Cefamandole is excreted into breast milk in low concentrations; it is generally considered safe during breastfeeding.

Drug Interactions

Nephrotoxicity has been reported following co-administration of other cephalosporins and aminoglycosides.
Probenecid may decrease renal tubular secretion of cephalosporins, resulting in increased and more prolonged cephalosporin blood levels.

References

Committee on Drugs, American Academy of Pediatrics. Pediatrics 1994; 93:137-50.
Duff P, Gibbs RS, Jorgensen JH, Alexander G. Obstet Gynecol 1982; 60:409-12.
Ling FW, McNeeley SG Jr, Anderson GD, et al. Clin Ther 1984; 6:669-76.
Peterson CM, Medchill M, Gordon DS, Chard HL. Obstet Gynecol 1990; 75:179-82.
Simoes JA, Aroutcheva AA, Heimler I, Faro S. Infect Dis Obstet Gynecol 2004; 12:1-8.

Summary

Pregnancy Category: B
Lactation Category: S
- **Cefamandole** is used for the treatment of acute bronchitis, pharyngitis, and skin infections.

Cefazolin—(Ancef; Cefazolin; Kefzol; Zolicef)

International Brand Name—Anzolin (India); Basocef (Germany); Biozolin (Indonesia); Cefa (Taiwan); Cefacidal (Belgium, Ecuador, France, Peru, South Africa); Cefamezin (Argentina, Hong Kong, Indonesia, Israel, Japan, Korea, Portugal, South Africa, Spain, Thailand); Cefarad (Israel, South Africa); Cefazin (Taiwan); Cefazol (Bulgaria, Indonesia, Thailand); Cefazolina (Spain); Cefazoline Panpharma (France); Cezolin (Brazil); Faxilen (Philippines); Fazol (Philippines); Fazolin (Thailand); Fonvicol (Philippines); Gramaxin (Austria); Izacef (South Africa); Kefarin (Greece); Kefazin (Israel); Kefzol (Austria, Belgium, Canada, Chile, Czech Republic, Hungary, Ireland, Israel, Netherlands, Poland, Switzerland, Taiwan, Venezuela); Kofatol (Taiwan); Lupex (Philippines); Megacef (Philippines); Oricef (Taiwan); Orizolin (South Africa); Reflin (India); Sanzol (Philippines); Stancef (Philippines); Stazolin (Taiwan); Surzolin (India); Totacef (Israel); Uzolin (Taiwan); Zaconil (Philippines); Zolecef (Israel); Zolicef (Austria, Thailand); Zolidina (Paraguay, Uruguay); Zolin (Italy)

Drug Class

Antibiotics; Cephalosporins, 1st-generation

Indications

Bacterial infections (gram-positive aerobes: *S. aureus, S. epidermidis, S. pneumoniae;* gram-negative aerobes: *E. coli, Klebsiella, Enterobacter, P. mirabilis*)

Mechanism

Bactericidal—inhibits cell wall synthesis

Dosage with Qualifiers

Acute infection—25-100mg/kg/d IV/IM q8h
Cesarean section prophylaxis—1g IV at umbilical cord clamping
Bacterial endocarditis—1g IV/IM 30min before procedure

NOTE: renal dosing.

- **Contraindications**—hypersensitivity to drug or class
- **Caution**—penicillin allergy, renal dysfunction, antibiotic-associated colitis, seizure disorder, concomitant use of nephrotoxic drugs

Maternal Considerations

Because of its antimicrobial spectrum, **cefazolin** is used to treat lower respiratory tract infections, GU tract infections, skin infections, peritonitis, septicemia, and endocarditis; for post-cesarean section prophylaxis; and intrapartum for group B streptococcus. **Cefazolin** is superior to **clindamycin** and **erythromycin** for group B streptococcus prophylaxis in patients with a non-anaphylactic penicillin allergy. The prophylactic administration of **cefazolin** preoperatively, intraoperatively, or postoperatively reduces the incidence of post–cesarean section infection. The timing of administration does not significantly alter efficacy. For this indication, it has no clinical advantage over any other cephalosporin, and cost is often the deciding factor. Prophylaxis is usually discontinued within 24h of the surgical procedure. Cephalosporins are usually considered safe during pregnancy.

Side effects include seizures, pseudomembranous colitis, nephrotoxicity, leukopenia, thrombocytopenia, erythema multiforme, and Stevens-Johnson syndrome.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. **Cefazolin** rapidly crosses the human placenta, achieving concentrations greater than or equal to the 90% MIC for group B streptococcus maternal, fetal, and AF samples. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically.

Breastfeeding Safety

While there are no adequate reports or well-controlled studies in nursing women, **cefazolin** is apparently excreted into human breast milk. Though the kinetics remain to be elucidated, it is generally considered compatible with breastfeeding.

Drug Interactions

Nephrotoxicity has been reported following co-administration of other cephalosporins and aminoglycosides.

Probenecid may decrease renal tubular secretion of cephalosporins, resulting in increased and more prolonged cephalosporin blood levels.

References

Fiore Mitchell T, Pearlman MD, Chapman RL, et al. Obstet Gynecol 2001; 98:1075-9.

Millar LK, Wing DA, Paul RH, Grimes DA. Obstet Gynecol 1995; 86:560-4.

Philipson A, Stiernstedt G, Ehrnebo M. Clin Pharmacokinet 1987; 12:136-44.

Thigpen BD, Hood WA, Chauhan S, et al. Am J Obstet Gynecol 2005; 192:1864-8.

Wing DA, Hendershott CM, Debuque L, Millar LK. Obstet Gynecol 1998; 92:249-53.

Summary

Pregnancy Category: B

Lactation Category: S

- **Cefazolin** is superior to both **clindamycin** and **erythromycin** for group B streptococcus prophylaxis in patients with a non-anaphylactic penicillin allergy.

Cefdinir—(Omnicef)

International Brand Name—Cefzon (Japan); Omnicef (Austria, Korea, Thailand); Sefdin (India)

Drug Class

Antibiotics; Cephalosporins, 1st-generation

Indications

Bacterial infections (gram-positive aerobes: *S. aureus, S. epidermidis, S. pneumoniae;* gram-negative aerobes: *E. coli, Klebsiella, Enterobacter, P. mirabilis*)

Mechanism

Bactericidal—inhibits cell wall synthesis

Dosage with Qualifiers

Acute infection—600mg PO qd ×10d, or 300mg PO bid ×10d

- **Contraindications**—hypersensitivity to drug or class
- **Caution**—penicillin allergy, renal dysfunction, antibiotic-associated colitis, seizure disorder, concomitant use of nephrotoxic drugs

Maternal Considerations

There are no adequate reports or well-controlled studies of **cefdinir** in pregnant women. It appears effective and safe during pregnancy for the treatment of acute infections, but has no unique advantage over other cephalosporins for most indications. Cost is often a key decision factor.
Side effects include diarrhea, vaginal moniliasis, vaginitis, rash, N/V, headache, abdominal pain, dyspepsia, flatulence, anorexia, constipation, abnormal stools, asthenia, dizziness, insomnia, leukorrhea, pruritus, and somnolence.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **cefdinir** crosses the human placenta. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically.

Breastfeeding Safety

Most cephalosporins are excreted into breast milk. While there is no published experience in nursing women, **cefdinir** is generally considered compatible with breastfeeding.

Drug Interactions

30ml Maalox TC suspension reduces rate (C_{max}) and extent (AUC) of absorption of **cefdinir** by approximately 40%. The time to C_{max} is also prolonged by 1h. There are no significant effects on pharmacokinetics if the antacid is administered 2h before or 2h after.
Probenecid inhibits the renal excretion of **cefdinir,** causing an approximate doubling in AUC, a 54% increase in peak **cefdinir** plasma levels, and a 50% prolongation in the apparent elimination t/2.
An iron supplement containing 60mg of elemental iron (as FeSO4) or vitamins supplemented with 10mg of elemental iron reduce absorption by 80% and 31%, respectively. **Cefdinir** should be taken at least 2h before or after the supplement.

References

Guay DR. Rel Clin Ther 2002; 24:473-89.

Summary

Pregnancy Category: B
Lactation Category: S

- **Cefdinir** is used for the treatment of community-acquired pneumonia, acute bronchitis, maxillary sinusitis, and otitis media.
- There are other cephalosporins for which there is more experience regarding use during pregnancy and lactation.

Cefditoren—(Spectracef)

International Brand Name—Meiact (Indonesia)

Drug Class

Antibiotics; Cephalosporins, 1st-generation

Indications

Bacterial infections, hospital-acquired pneumonia

Mechanism

Bactericidal—inhibits cell wall synthesis

Dosage with Qualifiers

Acute infection—200-400mg PO with food bid ×10d
Hospital-acquired pneumonia—400mg PO with food bid ×14d

NOTE: renal dosing.

- **Contraindications**—hypersensitivity to drug or class, hypersensitivity to milk proteins, carnitine deficiency
- **Caution**—penicillin allergy, renal dysfunction, antibiotic-associated colitis, concomitant use of nephrotoxic drugs, seizures

Maternal Considerations

There is no published experience with **cefditoren** during pregnancy. Cephalosporins are generally considered safe during pregnancy.
Side effects include seizures, N/V, diarrhea, pseudomembranous colitis, abdominal pain, dyspepsia, flatulence, anorexia, constipation, abnormal stools, Stevens-Johnson syndrome, vaginal moniliasis, vaginitis, headache, asthenia, dizziness, insomnia, rash, leukorrhea, pruritus, and somnolence.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **cefditoren** crosses the human placenta. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically.

Breastfeeding Safety

Most cephalosporins are excreted into breast milk. While there is no published experience in nursing women, **cefditoren** is generally considered compatible with breastfeeding.

Drug Interactions

Antacids that contain magnesium (800 mg) and aluminum (900 mg) reduce oral absorption of **cefditoren** administered after a meal, as reflected by a 14% decrease in mean C_{max} and an 11% decrease in mean AUC.
Famotidine (20mg) reduces the oral absorption of **cefditoren** after a meal, as reflected in a 27% decrease in mean Cmax and a 22% decrease in mean AUC.
Probenecid produced a 49% increase in mean Cmax, a 122% increase in mean AUC, and a 53% increase in t/2 of **cefditoren.**

References

Guay DR. Rel Clin Ther 2002; 24:473-89.

Summary

Pregnancy Category: B
Lactation Category: S

- **Cefditoren** is used for the treatment of hospital-acquired pneumonia, acute bronchitis, maxillary sinusitis, and otitis media.
- There are other cephalosporins for which there is more experience regarding use during pregnancy and lactation.

Cefepime—(Maxipime)

International Brand Name—Axepim (France); Cefepim (Austria); Cefepitax (Brazil); Ceficad (India); Cepimax (Philippines); Forzyn Beta (Paraguay); Maxcef (Argentina, Israel, Uruguay); Maxfrom (Argentina); Maxipime (Austria, Belgium, Bulgaria, Canada, Chile, Colombia, Costa Rica, Czech Republic, Denmark, Ecuador, El Salvador, Germany, Guatemala, Honduras, Hong Kong, Hungary, Indonesia, Italy, Japan, Korea, Malaysia, Mexico, Netherlands, Nicaragua, Panama, Peru, Poland, Singapore, South Africa, Sweden, Taiwan, Thailand, Venezuela)

Drug Class

Antibiotics; Cephalosporins, 4th-generation

Indications

Bacterial infections (gram-positive aerobes: MRSA, *S. epidermidis, S. pneumoniae;* gram-negative aerobes: *E. coli, Klebsiella, Enterobacter, P. mirabilis, Pseudomonas aeruginosa)*

Mechanism

Bactericidal—inhibits cell wall synthesis

Dosage with Qualifiers

Bacterial infection—1-2g IV/IM q12h
Uncomplicated UTI—0.5-1g IV/IM q12h

NOTE: renal dosing.

- **Contraindications**—hypersensitivity to drug or class
- **Caution**—penicillin allergy, renal dysfunction, antibiotic-associated colitis, seizure disorder, concomitant use of nephrotoxic drugs

Maternal Considerations

Cefepime is used to treat lower respiratory tract infections, GU tract infections, skin infections, and neutropenic patients because of its antimicrobial spectrum. Limited study suggests it is effective as **cefotaxime** for the treatment of acute obstetric and gynecologic infections. Third- and 4th-generation cephalosporins (e.g., **cefotaxime, cefoperazone, ceftriaxone, ceftazidime, ceftizoxime**) are generally not recommended for surgical prophylaxis. Despite these recommendations, they have been accepted by the medical community for prophylaxis and are today commonly misused. Cephalosporins are usually considered safe during pregnancy.
Side effects include anaphylaxis, seizures, pseudomembranous colitis, nephrotoxicity, leukopenia, thrombocytopenia, erythema multiforme, exfoliative dermatitis, Stevens-Johnson syndrome, and cholestatic jaundice.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **cefepime** crosses the human placenta. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically.

Breastfeeding Safety

Most cephalosporins are excreted into breast milk. While there is no published experience in nursing women, **cefepime** is generally considered compatible with breastfeeding.

Drug Interactions

Renal function should be monitored if given with high doses of aminoglycosides because of the increased potential of nephrotoxicity and ototoxicity of aminoglycoside antibiotics. Nephrotoxicity has been reported following the administration of other cephalosporins with potent diuretics such as **furosemide.**

References

Kai S, Kohmura H, Ishikawa K, et al. Jpn J Antibiot 1992; 45:642-60.
Newton ER, Yeomans ER, Pastorek JG, et al. J Antimicrob Chemother 1993; 32(Suppl B):195-204.

Summary

Pregnancy Category: B
Lactation Category: S

- Third- and 4th-generation cephalosporins are generally not recommended for surgical prophylaxis.
- There are alternative agents for which there is more experience during pregnancy and lactation.

Cefixime—(NOTE: This drug has been withdrawn from the US market.)

International Brand Name—Aerocef (Austria); Cefirax (Korea); Cefix (Brazil, Israel, Korea); Cefixmycin (Taiwan); Cefspan (Chile, Indonesia, Japan, Taiwan, Thailand); Cephoral (Germany, Hungary, Poland, Switzerland); Ceracin (Korea); Cexima (Paraguay); Denvar (Costa Rica, Dominican Republic, Ecuador, El Salvador, Guatemala, Honduras, Mexico, Nicaragua, Panama, Peru, Spain); Devoxim (Colombia); Fixef (Indonesia); Fixim (Netherlands); Fixime (South Africa); Fixiphar (Indonesia); Fixx (India); Longacef (Venezuela); Maxpro (Indonesia); Necopen (Spain); Novacef (Argentina, Mexico); Oralcef (Uruguay); Oroken (France); Pocef (Korea); Sofix (Indonesia); Spancef (Indonesia); Spaxim (Indonesia); Starcef (Indonesia); Sucef (Korea); Sufixime (Korea); Supran (Israel); Suprax (Canada, Czech Republic, England, Germany, Ireland, Italy); Tergecef (Philippines); Tocef (Indonesia); Tricef (Chile, Sweden); Ultraxime (Philippines); Uro-cephoral (Germany); Zefral (Philippines)

Drug Class

Antibiotics; Cephalosporins, 3rd-generation

Indications

Bacterial infections (gram-positive aerobes: *S. pneumoniae, S. pyogenes;* gram-negative aerobes: *E. coli, Proteus, H. influenzae, Moraxella catarrhalis, N. gonorrhoeae*)

Mechanism

Bactericidal—inhibits cell wall synthesis

Dosage with Qualifiers

Bacterial infection—400mg PO qd
Gonorrhea (uncomplicated)—400mg PO ×1

NOTE: renal dosing.

- **Contraindications**—hypersensitivity to drug or class
- **Caution**—penicillin allergy, renal dysfunction, antibiotic-associated colitis, seizure disorder, concomitant use of nephrotoxic drugs

Maternal Considerations

Cefixime is used to treat lower respiratory tract infections, otitis media, pharyngitis, acute bronchitis, acute exacerbation of chronic bronchitis, gonorrhea, GU tract infections, skin infections, and neutropenic patients because of its antimicrobial spectrum. **Cefixime** is an effective and safe oral medication during pregnancy for the treatment of acute obstetric diseases and STDs such as gonorrhea. Third- and 4th-generation cephalosporins (e.g., **cefotaxime, cefoperazone, ceftriaxone, ceftazidime, ceftizoxime**) are generally not recommended for surgical prophylaxis. Despite these recommendations, they have been accepted by the medical community for prophylaxis and are today commonly misused. Cephalosporins are usually considered safe during pregnancy.
Side effects include anaphylaxis, seizures, pseudomembranous colitis, neutropenia, thrombocytopenia, erythema multiforme, exfoliative dermatitis, and cholestatic jaundice.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **cefixime** crosses the human placenta. Transfer across the rodent placenta is poor. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically.

Breastfeeding Safety

Most cephalosporins are excreted into breast milk. While there is no published experience in nursing women, **cefixime** is generally considered compatible with breastfeeding. Transfer into rodent milk occurs at low levels.

Drug Interactions

Elevated **carbamazepine** levels have been reported when given with **cefixime.**
Increased PT, with or without bleeding, has been reported when given to patients receiving **warfarin** or other anticoagulants.

References

Donders GG. Drugs 2000; 59:477-85.
Gray RH, Wabwire-Mangen F, Kigozi G, et al. Am J Obstet Gynecol 2001; 185:1209-17.
Halperin-Walega E, Batra VK, Tonelli AP, et al. Drug Metab Dispos 1988; 16:130-4.
Mahon BE, Rosenman MB, Graham MF, Fortenberry JD. Am J Obstet Gynecol 2002; 186:1320-5.
Ramus RM, Sheffield JS, Mayfield JA, Wendel GD Jr. Am J Obstet Gynecol 2001; 185:629-32.
Wilton LV, Pearce GL, Mann RD. Br J Clin Pharmacol 1996; 41:277-84.

Summary

Pregnancy Category: B
Lactation Category: S

- Third- and 4th-generation cephalosporins are generally not recommended for surgical prophylaxis.
- There are alternative agents for which there is more experience during pregnancy and lactation.

Cefmetazole—(Zefazone)

International Brand Name—None identified.

Drug Class

Antibiotics; Cephalosporins, 2nd-generation

Indications

Bacterial infection (gram-positive aerobes: *S. aureus, S. epidermidis, S. pneumoniae, S. pyogenes;* gram-negative aerobes: *E. coli, Klebsiella, Enterobacter, P. mirabilis, Morganella morganii;* anaerobic organisms: *Peptococcus, Peptostreptococcus, Clostridium, Bacteroides, Fusobacterium*)

Mechanism

Bactericidal—inhibits cell wall synthesis

Dosage with Qualifiers

Bacterial infection—2gm IV q6-12h for 5-14d
Perioperative prophylaxis—1-2g IV 30-90min prior to procedure; may be repeated in 8-16h

- **Contraindications**—hypersensitivity to drug or class
- **Caution**—penicillin allergy, renal dysfunction, antibiotic-associated colitis, seizure disorder, concomitant use of nephrotoxic drugs

Maternal Considerations

There are no adequate reports or well-controlled studies in pregnant women. **Cefmetazole** is highly effective against most causes of bacterial vaginosis during pregnancy. **Cefmetazole** appears equivalent to **cefoxitin** in reducing post–cesarean section endometritis. Cephalosporins are usually considered safe during pregnancy.
Side effects include anaphylaxis, Stevens-Johnson syndrome, renal failure, diarrhea, headache, hypotension, nausea, rash, pruritus,

	fever, epigastric pain, vaginitis, pleural effusion, dyspnea, and erythema.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. **Cefmetazole** rapidly crosses the human placenta, yielding fetal levels in excess of the typical MIC. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically.
Breastfeeding Safety	Only a scant amount of **cefmetazole** is excreted into human breast milk, and it is generally considered compatible with breastfeeding.
Drug Interactions	Nephrotoxicity has been reported following co-administration of other cephalosporins and aminoglycosides. **Probenecid** may decrease renal tubular secretion of cephalosporins, resulting in increased and more prolonged cephalosporin blood levels.
References	Cho N, Fukunaga K, Kunii K. Jpn J Antibiot 1981; 34:915-24. Crombleholme WR, Green JR, Ohm-Smith M, et al. J Antimicrob Chemother 1989; 23(Suppl D):97-104. Ninomiya K, Yoshimoto T, Hasegawa Y. Jpn J Antibiot 1984; 37:14-7. Puapermpoonsiri S, Watanabe K, Kato N, Ueno K. Antimicrob Agents Chemother 1997; 41:2297-9.
Summary	**Pregnancy Category: B** **Lactation Category: S** • **Cefmetazole** is an effective agent for the treatment of bacterial vaginosis and postpartum endometritis. • Selection is often based on cost.

Cefonicid—(Monocid)

International Brand Name—Lisa (Israel); Lisa IM (Taiwan); Monocef (Israel); Monocid (Belgium, China, Italy, Korea, Portugal, Spain)

Drug Class	Antibiotics; Cephalosporins, 2nd-generation
Indications	Bacterial infections (gram-positive aerobes: *S. aureus, S. epidermidis, S. pneumoniae;* gram-negative aerobes: *E. coli, Klebsiella, Enterobacter, P. mirabilis, Pseudomonas aeruginosa, N. gonorrhoeae;* gram-positive anaerobes: *C. perfringens, Peptostreptococcus, Peptococcus, Propionibacterium acnes;* gram-negative anaerobes: *Fusobacterium nucleatum*)
Mechanism	Bactericidal—inhibits cell wall synthesis
Dosage with Qualifiers	Bacterial infection—10-25mg/kg (or 1g) IV q24h Cesarean section prophylaxis—1g IV 30min prior to procedure • **Contraindications**—hypersensitivity to drug or class • **Caution**—penicillin allergy, renal dysfunction, antibiotic-associated colitis, seizure disorder, concomitant use of nephrotoxic drugs
Maternal Considerations	Because of its antimicrobial spectrum, **cefonicid** is used to treat lower respiratory tract infections, GU tract infections, skin

infections, and septicemia and for surgical prophylaxis. It appears effective and safe during pregnancy for the treatment of acute infections and post–cesarean section prophylaxis, but has no unique advantage over other cephalosporins for most indications. Cost is often a key decision factor. Cephalosporins are usually considered safe during pregnancy.
Side effects include anaphylaxis, seizures, neutropenia, pseudomembranous colitis, thrombocytopenia, erythema multiforme, exfoliative dermatitis, cholestatic jaundice, and positive Coombs' test.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **cefonicid** crosses the human placenta. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically.

Breastfeeding Safety

Cefonicid is excreted at low concentrations into human breast milk, but is generally considered compatible with breastfeeding.

Drug Interactions

Nephrotoxicity has been reported following co-administration of other cephalosporins and aminoglycosides.
Probenecid may decrease renal tubular secretion of cephalosporins, resulting in increased and more prolonged cephalosporin blood levels.

References

Duff P, Robertson AW, Read JA. Obstet Gynecol 1987; 70:718-21.
Faro S, Martens MG, Hammill HA, et al. Am J Obstet Gynecol 1990; 162:900-10.
Fejgin MD, Markov S, Goshen S, et al. Int J Gynaecol Obstet 1993; 43:257-61.
Lou MA, Wu YH, Jacob LS, Pitkin DH. Infect Dis 1984; 6(Suppl 4):S816-20.

Summary

Pregnancy Category: B
Lactation Category: S

- **Cefonicid** is effective and safe during pregnancy for the treatment of acute obstetric infection and surgical prophylaxis.
- A favorable cost profile is a key factor in its selection.

Cefoperazone—(Cefobid)

International Brand Name—Bifotik (Indonesia); Cefactam (Paraguay); Cefobactam (Korea); Cefobid (Argentina, Austria, Bulgaria, Chile, Colombia, Czech Republic, Egypt, Hong Kong, Hungary, Indonesia, Jordan, Korea, Malaysia, Oman, Poland, Portugal, Spain, Taiwan, Thailand, United Arab Emirates, Uruguay, Venezuela); Cefobis (Germany, Philippines, Switzerland); Cefogram (Italy); Cefolatam (Korea); Cefomycin (India); Cefopemax (Brazil); Cefoperazine (Japan); Ceforin (Korea); Cefozone (Singapore, Thailand); Ceperatam (Korea); Ceropid (Indonesia); CPZ (Taiwan); Dardum (Malaysia, Singapore); Ferzobat (Indonesia); Logafox (Indonesia); Magnamycin (India); Mediper (Italy); Medocef (Malaysia, Thailand); Peratam (Korea); Shinfomycin (Malaysia, Taiwan); Stabixin (India, Indonesia); Tomabef (Italy); Zoncef (Italy)

Drug Class

Antibiotics; Cephalosporins, 3rd-generation

Indications

Bacterial infections (gram-positive aerobes: *S. aureus, S. epidermidis, S. pneumoniae, S. pyogenes, Enterococcus;* gram-negative aerobes: *E. coli, Klebsiella, Enterobacter, Citrobacter, P. mirabilis, Pseudomonas aeruginosa, N. gonorrhoeae;* gram-positive anaerobes: *C. perfringens, Peptostreptococcus, Peptococcus, Propionibacterium acnes*)

Mechanism

Bactericidal—inhibits cell wall synthesis

Dosage with Qualifiers

Bacterial infection—1-2g IV/IM q12h
Cesarean section prophylaxis—1-2g IV

NOTE: may be combined with Sulbactam.

- **Contraindications**—hypersensitivity to drug or class
- **Caution**—penicillin allergy, renal dysfunction, antibiotic-associated colitis, seizure disorder, concomitant use of nephrotoxic drugs, altered hepatic function

Maternal Considerations

Because of its antimicrobial spectrum, **cefoperazone** is used to treat lower respiratory tract infections, GU tract infections, skin infections, and septicemia and for surgical prophylaxis. **Cefoperazone** appears effective and safe during pregnancy for the treatment of acute infections. Clearance is only modestly affected by pregnancy. Third- and 4th-generation cephalosporins (e.g., **cefotaxime, cefoperazone, ceftriaxone, ceftazidime, ceftizoxime**) are generally not recommended for surgical prophylaxis. Despite these recommendations, they have been accepted by the medical community for prophylaxis and are today commonly misused. ***Side effects*** include anaphylaxis, serum sickness, pseudomembranous colitis, neutropenia, rash, urticaria, thrombocytopenia, and nausea.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. **Cefoperazone** crosses the human placenta, but to a lower degree than **ceftizoxime.** Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically.

Breastfeeding Safety

Cefoperazone is excreted in small amounts into human breast milk, and is generally considered compatible with breastfeeding.

Drug Interactions

Nephrotoxicity has been reported following co-administration of other cephalosporins and aminoglycosides.
Probenecid may decrease renal tubular secretion of cephalosporins, resulting in increased and more prolonged cephalosporin blood levels.

References

Fortunato SJ, Bawdon RE, Maberry MC, Swan KF. Obstet Gynecol 1990; 75:830-3.
Geroulanos S, Marathias K, Kriaras J, Kadas B. J Chemother 2001; 13(1):23-6.
Gilstrap LC 3rd, St Clair PJ, Gibbs RS, Maier RC. Antimicrob Agents Chemother 1986; 30:808-9.
Gonik B, Feldman S, Pickering LK, Doughtie CG. Antimicrob Agents Chemother 1986; 30:874-6.
Matsuda S, Kashiwagura T, Hirayama H. Jpn J Antibiot 1985; 38:223-9.
Ng NK, Sivalingam N. Med J Malaysia 1992; 47:273-9.
Ogita S, Imanaka M, Matsumoto M, et al. Am J Obstet Gynecol 1988; 158:23-7.

Summary

Pregnancy Category: B
Lactation Category: S

- **Cefoperazone** appears effective and safe during pregnancy for the treatment of acute obstetric infection.
- Third- and 4th-generation cephalosporins are generally not recommended for surgical prophylaxis.

Ceforanide

Drug Class	Antibiotics; Cephalosporins, 2nd-generation
Indications	Bacterial infection, surgical prophylaxis
Mechanism	Bactericidal—inhibits cell wall synthesis
Dosage with Qualifiers	Bacterial infection—500mg-1g IV bid Surgical prophylaxis—500mg-1g IV ×1 • **Contraindications**—hypersensitivity to drug or class • **Caution**—penicillin allergy, renal dysfunction, antibiotic-associated colitis, seizure disorder, concomitant use of nephrotoxic drugs
Maternal Considerations	There are no adequate reports or well-controlled studies of **ceforanide** in pregnant women. It appears to have no unique advantage over other cephalosporins for most indications. Cephalosporins are usually considered safe during pregnancy. ***Side effects*** include anaphylaxis, serum sickness, pseudomembranous colitis, diarrhea, N/V, constipation, headache, and fever.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **ceforanide** crosses the human placenta. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically.
Breastfeeding Safety	Most cephalosporins are excreted into breast milk. While there is no published experience in nursing women, **ceforanide** is generally considered compatible with breastfeeding.
Drug Interactions	Nephrotoxicity has been reported following co-administration of other cephalosporins and aminoglycosides. **Probenecid** may decrease renal tubular secretion of cephalosporins, resulting in increased and more prolonged cephalosporin blood levels.
References	Saravolatz LD, Lee C, Drukker B. Obstet Gynecol 1985; 66:513-6.
Summary	**Pregnancy Category: B** **Lactation Category: S** • **Ceforanide** appears safe during pregnancy for the treatment of acute obstetric infections such as chorioamnionitis.

Cefotaxime—(Claforan; Zetaxim)

International Brand Name—Baxima (Indonesia); Benaxima (Mexico); Biocef (Indonesia); Biosint (Mexico); Biotax (India); Biotaxime (Thailand); Cefacolin (Argentina); Cefajet (China); Cefaxim (Mexico); Cefirad (Korea); Cefocam (Paraguay); Cefoclin (Mexico); Cefomic (China); Cefotax (Israel, Japan, Thailand); Cefpiran (Korea); Cetax (Taiwan); Cetaxima (Malaysia); Clacef (Indonesia, Singapore); Cladex (Philippines); Claforan (Brazil, Canada, China, Costa Rica, Dominican Republic, Ecuador, El Salvador, Guatemala, Honduras, Hong Kong, India, Indonesia, Japan, Malaysia, Nicaragua, Panama, Paraguay, Peru, Philippines, Taiwan, Thailand, Venezuela); Clafoxim (Philippines); Claraxim (Thailand); Clatax (Indonesia); Clavocef (Philippines); Clavox (Taiwan); Efotax (Indonesia); Fotax (Thailand); Fotexina (Colombia, Mexico); Goforon (Indonesia); Grifotaxima (Peru); Kalfoxim (Indonesia); Lancef (Indonesia); Lapixime (Indonesia); Lyforan (India); Molelant (Greece); Motaxim (Thailand); Naspor (Peru); Newtaxime (Korea); Omnatax (India); Oritaxime (Thailand); Pantaxin (Philippines); Primafen (Spain); Primocef (Indonesia); Ralopar (Portugal); Sepsilem (Mexico); Soclaf (Indonesia); Spirosine (Greece); Stoparen (Greece); Taporin (Mexico); Taximax (Indonesia); Taxime (Israel); Tirdicef (Indonesia); Tirotax (Mexico); Ultracef (Uruguay); Vantef (Philippines); Viken (Mexico); Zariviz (Italy); Zetaxim (India)

Drug Class

Antibiotics; Cephalosporins, 3rd-generation

Indications

Bacterial infections (gram-positive aerobes: *S. aureus, S. epidermidis, S. pneumoniae, S. pyogenes, Enterococcus;* gram-negative aerobes: *E. coli, Klebsiella, Enterobacter, Citrobacter, P. mirabilis, Pseudomonas aeruginosa, N. gonorrhoeae;* gram-positive anaerobes: *C. perfringens, Peptostreptococcus, Peptococcus, Propionibacterium acnes)*

Mechanism

Bactericidal—inhibits cell wall synthesis

Dosage with Qualifiers

Bacterial infection—1-2g IM/IV q8h
Gonorrhea—1g IM ×1
Surgical prophylaxis—1g IV/IM 30-90min preoperatively

NOTE: renal dosing.

- **Contraindications**—hypersensitivity to drug or class
- **Caution**—penicillin allergy, renal dysfunction, antibiotic-associated colitis, seizure disorder, concomitant use of nephrotoxic drugs

Maternal Considerations

Cefotaxime is used to treat lower respiratory tract infections, GU tract infections, skin infections, and septicemia and for surgical prophylaxis because of its antimicrobial spectrum. **Cefotaxime** appears effective and safe during pregnancy for the treatment of acute infections. High AF concentrations suggest it may be advantageous for the treatment of chorioamnionitis. Third- and 4th-generation cephalosporins (e.g., **cefotaxime, cefoperazone, ceftriaxone, ceftazidime, ceftizoxime**) are generally not recommended for surgical prophylaxis. Despite these recommendations, they have been accepted by the medical community for prophylaxis and are today commonly misused. ***Side effects*** include anaphylaxis, serum sickness, pseudomembranous colitis, diarrhea, N/V, constipation, headache, fever, neutropenia, thrombocytopenia, rash, and urticaria.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. **Cefotaxime** crosses the human placenta. Though the kinetics remain to be elucidated, it achieves amniotic fluid concentrations that exceed the 90% MIC for most strains of *E. coli.* Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically.

Breastfeeding Safety

Scant quantities of **cefotaxime** are excreted into human breast milk, and it is generally considered compatible with breastfeeding.

Drug Interactions

Nephrotoxicity has been reported following co-administration of other cephalosporins and aminoglycosides.
Probenecid may decrease renal tubular secretion of cephalosporins, resulting in increased and more prolonged cephalosporin blood levels.

References

Geroulanos S, Marathias K, Kriaras J, Kadas B. J Chemother 2001; 13(1):23-6.
Kafetzis DA, Lazarides CV, Siafas CA, et al. J Antimicrob Chemother 1980; 6(Suppl A):135-41.
Kafetzis DA, Siafas CA, Georgakopoulos PA, Papadatos CJ. Acta Paediatr Scand 1981; 70:285-8.
Ninomiya K, Hasegawa Y, Kanamoto T, et al. Jpn J Antibiot 1982; 35:1882-92.
Yasuda J, Yamamoto T, Ito M, et al. Jpn J Antibiot 1982; 35:1877-81.

Summary

Pregnancy Category: B
Lactation Category: S

- **Cefotaxime** appears effective and safe during pregnancy for the treatment of acute obstetric infection and surgical prophylaxis.
- Third- and 4th-generation cephalosporins are generally not recommended for surgical prophylaxis.

Cefotetan—(Apatef; Cefotan)

International Brand Name—Apacef (Belgium, France); Apatef (Italy, Portugal, Switzerland); Cefotan (Canada); Ceftenon (Austria); Cepan (Italy); Yamatetam (Japan, Korea)

Drug Class

Antibiotics; Cephalosporins, 2nd-generation

Indications

Bacterial infections (gram-positive aerobes: *S. aureus, S. epidermidis, S. pneumoniae, S. pyogenes, Enterococcus;* gram-negative aerobes: *E. coli, Klebsiella, Enterobacter, Citrobacter, P. mirabilis, Pseudomonas aeruginosa, N. gonorrhoeae;* gram-positive anaerobes: *C. perfringens, Peptostreptococcus, Peptococcus, Propionibacterium acnes*)

Mechanism

Bactericidal—inhibits cell wall synthesis

Dosage with Qualifiers

Bacterial infection—1-3g IM/IV q12h
Preoperative prophylaxis—1-2g IV 30-60 min prior to surgery
Cesarean section surgical prophylaxis—1-2g IV after umbilical cord clamping

NOTE: renal dosing.

- **Contraindications**—hypersensitivity to drug or class
- **Caution**—penicillin allergy, renal dysfunction, antibiotic-associated colitis, seizure disorder, concomitant use of nephrotoxic drugs

Maternal Considerations

Because of its antimicrobial spectrum, **cefotetan** is used to treat lower respiratory tract infections, GU tract infections, skin infections, septicemia, and surgical prophylaxis. **Cefotetan** appears effective and safe during pregnancy for the treatment of acute infections. However, it has no activity against *Chlamydia trachomatis.* When used for the treatment of PID, appropriate antichlamydial coverage should be added. Single-dose **cefotetan** can replace the multidose **cefoxitin** regimen for post–cesarean section prophylaxis with considerable cost savings. Case reports

describe maternal hemolysis associated with **cefotetan** for post–cesarean section prophylaxis.
Side effects include anaphylaxis, agranulocytosis, prolonged INR, pseudomembranous colitis, neutropenia, thrombocytopenia, rash, urticaria, hemolysis, and hemolytic anemia.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. **Cefotetan** crosses both rodent and human placentas, though the kinetics remain to be elucidated. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically.

Breastfeeding Safety

While there are no adequate reports or well-controlled studies in nursing women, **cefotetan** is excreted in scant quantities into human breast milk and is generally considered compatible with breastfeeding.

Drug Interactions

Increases in serum creatinine have been reported after solo administration. Renal function should be carefully monitored if **cefotetan** and an aminoglycoside are used together.
Probenecid may decrease renal tubular secretion of cephalosporins, resulting in increased and more prolonged cephalosporin blood levels.

References

Martin C, Thomachot L, Albanese J. Clin Pharmacokinet 1994; 26:248-58.
Naylor CS, Steele L, Hsi R, et al. Am J Obstet Gynecol 2000; 182:1427-8.
Noyes N, Berkeley AS, Freedman K, Ledger W. Infect Dis Obstet Gynecol 1998; 6:220-3.
Shariatmadar S, Storry JR, Sausais L, Reid ME. Immunohematol 2004; 20:63-6.
Spinnato JA, Youkilis B, Cook VD, et al. J Matern Fetal Med 2000; 9:348-50.
Suzuki H, Imamura K, Yoshida T, et al. J Antimicrob Chemother 1983; 11:179-83.
Todd MW, Benrubi G. Hosp Formul 1990; 25:446-50.

Summary

Pregnancy Category: B
Lactation Category: S

- **Cefotetan** appears effective and safe during pregnancy for the treatment of acute obstetric infection and for surgical prophylaxis.

Cefoxitin—(Cefxitin; Mefoxin)

International Brand Name—Cefmore (Taiwan); Cefoxin (Thailand); Cefoxona (Argentina); Cefxitin (Thailand); Gamacef (Brazil); Mefoxil (Greece); Mefoxin (Belgium, Brazil, Bulgaria, Canada, China, Czech Republic, Finland, Hungary, Ireland, Italy, Netherlands, Philippines, Poland, Portugal, Taiwan); Mefoxitin (Austria, Bulgaria, Denmark, Germany, Norway, Spain, Sweden, Switzerland, Venezuela); Monowel (Philippines); Panafox (Philippines); Sephros (Malaysia)

Drug Class

Antibiotics; Cephalosporins, 2nd-generation

Indications

Bacterial infections (gram-positive aerobes: *S. aureus, S. epidermidis, S. pneumoniae, S. pyogenes, Enterococcus;* gram-negative aerobes: *E. coli, Klebsiella, Enterobacter, Citrobacter, P. mirabilis, Pseudomonas aeruginosa, N. gonorrhoeae;* gram-positive anaerobes: *C. perfringens, Peptostreptococcus, Peptococcus, Propionibacterium acnes*)

Mechanism

Bactericidal—inhibits cell wall synthesis

Dosage with Qualifiers

Bacterial infection—1-2g IV q6-8h; alternatively for severe infection, 2g q4h or 3g q6h
Perioperative prophylaxis—2g IV, 30-60min preoperatively

NOTE: renal dosing.

- **Contraindications**—hypersensitivity to drug or class
- **Caution**—penicillin allergy, renal dysfunction, antibiotic-associated colitis, seizure disorder, concomitant use of nephrotoxic drugs

Maternal Considerations

Cefoxitin is used to treat lower respiratory tract infections, GU tract infections, skin infections, and septicemia and for surgical prophylaxis because of its antimicrobial spectrum. It is a preferred agent for the treatment of PID where inpatient and outpatient therapy (combined with **doxycycline**) yield similar results. **Cefoxitin** appears effective and safe during pregnancy for the treatment of acute infection, though there are more cost-effective regimens for post–cesarean section prophylaxis. It is not beneficial for elective cesarean delivery.
Side effects include anaphylaxis, agranulocytosis, serum sickness, pseudomembranous colitis, neutropenia, thrombocytopenia, acute renal failure, and hemolytic anemia.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. **Cefoxitin** crosses the human placenta, achieving an F:M ratio approximating 0.6 at 45min after maternal injection. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically.

Breastfeeding Safety

Most cephalosporins are excreted into breast milk. There is little detectable **cefoxitin** in human breast milk after post–cesarean section prophylaxis. It is generally considered compatible with breastfeeding.

Drug Interactions

Nephrotoxicity has been reported following co-administration of other cephalosporins and aminoglycosides.
Probenecid may decrease renal tubular secretion of cephalosporins, resulting in increased and more prolonged cephalosporin blood levels.

References

Amstey MS, Casian-Colon AE. Obstet Gynecol 1997; 90:667-8.
Bagratee JS, Moodley J, Kleinschmidt I, Zawilski W. BJOG 2001; 108:143-8.
Dubois M, Delapierre D, Chanteux L, et al. J Clin Pharmacol 1981; 21:477-83.
Ness RB, Soper DE, Holley RL, et al. Am J Obstet Gynecol 2002; 186:929-37.
Noyes N, Berkeley AS, Freedman K, Ledger W. Infect Dis Obstet Gynecol 1998; 6:220-3.
Roex AJ, van Loenen AC, Puyenbroek JI, Arts NF. Eur J Obstet Gynecol Reprod Biol 1987; 25:299-302.
Todd MW, Benrubi G. Hosp Formul 1990; 25:446-50.

Summary

Pregnancy Category: B
Lactation Category: S

- **Cefoxitin** appears effective and safe during pregnancy for the treatment of acute obstetric infection.
- There are more cost-effective regimens for post–cesarean section prophylaxis.

Cefpodoxime—(Banan; Cepodem; Vantin)

International Brand Name—Banan (China, Hong Kong, Indonesia, Japan, Korea, Philippines, Taiwan, Thailand); Banan Dry Syrup (Korea); Biocef (Austria); Cefodox (Israel, Italy); Cepodem (India); Orelox (Costa Rica, Czech Republic, Denmark, Dominican Republic, El Salvador, England, France, Germany, Guatemala, Honduras, Hungary, Ireland, Italy, Netherlands, Nicaragua, Panama, Poland, Portugal, South Africa, Spain, Sweden, Switzerland); Otreon (Austria, Italy); Podomexef (Germany, Switzerland); Podox (Korea)

Drug Class ..... Antibiotics; Cephalosporins, 3rd-generation

Indications ..... Bacterial infections (gram-positive aerobes: *S. aureus, S. epidermidis, S. pneumoniae, S. pyogenes, Enterococcus;* gram-negative aerobes: *E. coli, Klebsiella, Enterobacter, Citrobacter, P. mirabilis, Pseudomonas aeruginosa, N. gonorrhoeae;* gram-positive anaerobes: *C. perfringens, Peptostreptococcus, Peptococcus, Propionibacterium acnes*)

Mechanism ..... Bactericidal—inhibits cell wall synthesis

Dosage with Qualifiers ..... Bacterial infection—100-400mg PO bid, max 800mg qd
Surgical prophylaxis—100mg PO bid ×3d

- **Contraindications**—hypersensitivity to drug or class
- **Caution**—penicillin allergy, renal dysfunction, antibiotic-associated colitis, seizure disorder, concomitant use of nephrotoxic drugs

Maternal Considerations ..... There is little published experience with **cefpodoxime** during pregnancy. Third- and 4th-generation cephalosporins are generally not recommended for surgical prophylaxis. Despite these recommendations, they have been accepted by the medical community for prophylaxis and are commonly misused. Cephalosporins are usually considered safe during pregnancy. ***Side effects*** include anaphylaxis, seizure, diarrhea, pseudomembranous colitis, leukopenia, anemia, thrombocytopenia, Stevens-Johnson syndrome, nausea, dyspepsia, rash, and pruritus.

Fetal Considerations ..... There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **cefpodoxime** crosses the human placenta. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically.

Breastfeeding Safety ..... Most cephalosporins are excreted into breast milk. While there is no published experience in nursing women, **cefpodoxime** reportedly is excreted in breast milk at modest levels. The kinetics remain to be detailed.

Drug Interactions ..... High doses of antacids (sodium bicarbonate and aluminum hydroxide) or H_2 blockers reduce peak plasma levels by 24-42% and absorption by 27-32%, respectively.
Oral anticholinergics (e.g., **propantheline**) delay peak plasma levels (47% increase in Tmax), but do not affect the AUC.
Renal excretion of **cefpodoxime** is inhibited by **probenecid,** increasing the **cefpodoxime** AUC by 31% and the peak plasma level by 20%.
Although nephrotoxicity has not been reported after **cefpodoxime** alone, close monitoring of renal function is advised if given with known nephrotoxic agents.

References ..... Escande F, Borde M, Pateyron F. Arch Pediatr 1997; 4:1116-8.

Hayashi H, Yaginuma Y, Yamashita T, et al. Chemotherapy 2000; 46:213-8.
Mikamo H, Izumi K, Ito K, et al. Jpn J Antibiot 1993; 46:269-73.

Summary

Pregnancy Category: B
Lactation Category: U

- **Cefpodoxime** appears effective and safe during pregnancy for the treatment of acute obstetric infection.
- There are alternative agents for which there is more experience during pregnancy and lactation.
- Third- and 4th-generation cephalosporins are generally not recommended for surgical prophylaxis.

Cefprozil—(Cefzil; Procef)

International Brand Name—Arzimol (Spain); Cefzil (Brazil, Bulgaria, Canada, Egypt, England, Indonesia, Ireland, Korea, Poland); Procef (Austria, Chile, Colombia, Costa Rica, Ecuador, El Salvador, Guatemala, Honduras, Hong Kong, Italy, Malaysia, Mexico, Nicaragua, Panama, Philippines, Thailand, Venezuela); Prozef (South Africa); Refzil-O (India)

Drug Class

Antibiotics; Cephalosporins, 2nd-generation

Indications

Bacterial infections (gram-positive aerobes: *S. aureus, S. epidermidis, S. pneumoniae, S. pyogenes, Enterococcus;* gram-negative aerobes: *E. coli, Klebsiella, Enterobacter, Citrobacter, P. mirabilis, Pseudomonas aeruginosa, N. gonorrhoeae;* gram-positive anaerobes: *C. perfringens, Peptostreptococcus, Peptococcus, Propionibacterium acnes*)

Mechanism

Bactericidal—inhibits cell wall synthesis

Dosage with Qualifiers

Bacterial infection—250-500mg PO qd or bid

NOTE: renal dosing.

- **Contraindications**—hypersensitivity to drug or class
- **Caution**—penicillin allergy, renal dysfunction, antibiotic-associated colitis, seizure disorder, concomitant use of nephrotoxic drugs

Maternal Considerations

There is no published experience with **cefprozil** during pregnancy. Cephalosporins are usually considered safe during pregnancy.
Side effects include anaphylaxis, seizures, pseudomembranous colitis, nephrotoxicity, leukopenia, thrombocytopenia, and erythema multiforme.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **cefprozil** crosses the human placenta. Small quantities cross the rodent placenta. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically.

Breastfeeding Safety

Cefprozil is excreted into human breast milk in very small quantities, but even if one assumes the concentration in milk remains constant at the highest observed, a neonate ingesting an average of 800ml of milk/d would ingest a maximum of about 3mg of **cefprozil**/d.

Drug Interactions

Nephrotoxicity has been reported following administration of aminoglycoside antibiotics and cephalosporin antibiotics. **Probenecid** doubles the AUC for **cefprozil.**

References

Nakanomyo H, Ishikawa K, Esumi Y, et al. Jpn J Antibiot 1990; 43:1325-34.
Shyu WC, Shah VR, Campbell DA, et al. Antimicrob Agents Chemother 1992; 36:938-41.

Summary

Pregnancy Category: B
Lactation Category: S

- There are alternative agents for which there is more experience during pregnancy and lactation.

Ceftazidime—(Ceptaz; Fortaz; Taricef; Tazidime)

International Brand Name—Biotum (Poland); Cefazime (Singapore); Cef-Dime (Thailand); Ceffotan (Colombia); Cefortam (Portugal); Cefpiran (Peru); Ceftazim (Mexico); Ceftidin (India); Ceftim (Italy, Portugal); Ceftum (Indonesia); Cetazine (Taiwan); Cetazum (Indonesia); Dimase (Thailand); Dimcef (Philippines); Extimon (Indonesia); Fortadim (Thailand); Fortam (Spain, Switzerland, Uruguay); Fortaz (Brazil); Fortum (Argentina, Austria, Bulgaria, Chile, China, Costa Rica, Czech Republic, Denmark, Dominican Republic, Ecuador, El Salvador, England, France, Germany, Guatemala, Honduras, Hong Kong, Hungary, India, Indonesia, Ireland, Korea, Malaysia, Mexico, Netherlands, Nicaragua, Norway, Panama, Paraguay, Peru, Philippines, Puerto Rico, Sweden, Taiwan, Thailand, Venezuela); Fortum Pro (Hungary); Fortumset (France); Forzid (Indonesia, Thailand); Fournox (Thailand); Ftazidime (Greece); Glazidim (Belgium, Finland, Italy); Izadima (Colombia, Ecuador, Mexico); Kefadim (Belgium, Brazil, China, Czech Republic, South Africa, Taiwan); Kefamin (Spain); Kefazim (Austria); Kefzim (Chile, South Africa); Lacedim (Indonesia); Modacin (Japan); Negacef (Indonesia); Panzid (Italy); Pharodime 19 (Indonesia); Potendal (Spain); Solvetan (Greece); Spectrum (Italy); Starcef (Italy); Tagal (Mexico); Tazidan (Philippines); Tazidem (Philippines); Tazidime (Canada); Tazime (China, Korea); Thidim (Indonesia); Tinacef (Argentina); Waytrax (Mexico); Zadim (Philippines); Zadolina (Mexico); Zeptrigen (Philippines); Zibac (Indonesia); Zydime (Philippines); Zytaz (India)

Drug Class

Antibiotics; Cephalosporins, 3rd-generation

Indications

Bacterial infections (gram-positive aerobes: *S. aureus, S. epidermidis, S. pneumoniae, S. pyogenes, Enterococcus;* gram-negative aerobes: *E. coli, Klebsiella, Enterobacter, Citrobacter, P. mirabilis, Pseudomonas aeruginosa, N. gonorrhoeae;* gram-positive anaerobes: *C. perfringens, Peptostreptococcus, Peptococcus, Propionibacterium acnes*)

Mechanism

Bactericidal—inhibits cell wall synthesis

Dosage with Qualifiers

Bacterial infection—1g IV/IM q8-12h (2g IV/IM q8h for meningitis)

NOTE: renal dosing.

- **Contraindications**—hypersensitivity to drug or class
- **Caution**—penicillin allergy, impaired renal function, antibiotic-associated colitis, seizure disorder, concomitant use of nephrotoxic drugs

Maternal Considerations

Ceftazidime is a 3rd-generation cephalosporin that retains a broad spectrum of *in vitro* antimicrobial activity and clinical utility in serious infections, particularly those due to major nosocomial pathogens, and respiratory infections in patients with cystic fibrosis. **Ceftazidime**-containing regimens are important for febrile episodes in neutropenic patients. There are no adequate reports or well-controlled studies of **ceftazidime** in pregnant women. Maternal renal elimination is increased during pregnancy, and the dose may need adjustment to achieve

therapeutic levels. Third- and 4th-generation cephalosporins are not generally recommended for surgical prophylaxis. Despite these recommendations, they have been accepted by the medical community for prophylaxis and are today commonly misused. ***Side effects*** include seizures, agranulocytosis, thrombocytopenia, and anaphylaxis.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. **Ceftazidime** crosses the human placenta, achieving an F:M ratio in the 2nd trimester approximating 0.15, and a M:AF ratio of 0.19. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically.

Breastfeeding Safety

Ceftazidime is excreted into human breast milk in very small quantities, but even if one assumes the concentration in milk remains constant at the highest observed, a neonate ingesting an average of 800ml of milk/d would ingest a maximum of about 4mg of **ceftazidime**/d.

Drug Interactions

Nephrotoxicity has been reported following administration of aminoglycoside antibiotics and cephalosporin antibiotics. **Chloramphenicol** is antagonistic to β-lactam antibiotics, including **ceftazidime,** based on *in vitro* studies and time kill curves with enteric gram-negative bacilli. This drug combination should be avoided.

References

Blanco JD, Jorgensen JH, Castaneda YS, Crawford SA. Antimicrob Agents Chemother 1983; 23:479-80.
Geroulanos S, Marathias K, Kriaras J, Kadas B. J Chemother 2001; 13(1):23-6.
Jorgensen NP, Walstad RA, Molne K. Acta Obstet Gynecol Scand 1987; 66:29-33.
Kulakov VI, Voropaeva SD, Kasabulatov NM. Akush Ginekol (Mosk) 1995; 2:17-9.
Kuzemko J, Crawford C. Lancet 1989; 2:385.
Nathorst-Boos J, Philipson A, Hedman A, Arvisson A. Am J Obstet Gynecol 1995; 172:163-6.
Rains CP, Bryson HM, Peters DH. Drugs 1995; 49:577-617.
Tassi PG, Tarantini M, Cadenelli GP, et al. Int J Clin Pharmacol Ther Toxicol 1987; 25:582-8.

Summary

Pregnancy Category: B
Lactation Category: S

- Third- and 4th-generation cephalosporins are generally not recommended for surgical prophylaxis.
- There are alternative agents for which there is more experience during pregnancy and lactation.

Ceftibuten—(Cedax)

International Brand Name—Cedax (Bulgaria, China, Costa Rica, Czech Republic, Dominican Republic, Ecuador, El Salvador, Guatemala, Honduras, Hong Kong, Hungary, Indonesia, Ireland, Israel, Italy, Malaysia, Mexico, Netherlands, Nicaragua, Panama, Philippines, Poland, South Africa, Thailand, Venezuela); Ceftem (Korea); Ceten (Korea); Keimax (Germany); Seftem (Japan, Korea, Taiwan)

Drug Class

Antibiotics; Cephalosporins, 3rd-generation

Indications

Bacterial infections (gram-positive aerobes: *S. aureus, S. epidermidis, S. pneumoniae, S. pyogenes, Enterococcus;* gram-negative aerobes: *E. coli, Klebsiella, Enterobacter, Citrobacter, P. mirabilis, Pseudomonas aeruginosa, N. gonorrhoeae;* gram-positive anaerobes: *C. perfringens, Peptostreptococcus, Peptococcus, Propionibacterium acnes*)

Mechanism

Bactericidal—inhibits cell wall synthesis

Dosage with Qualifiers

Bacterial infection—400mg PO qd 1-2h pc

NOTE: renal dosing.

- **Contraindications**—hypersensitivity to drug or class
- **Caution**—penicillin allergy, renal dysfunction, antibiotic-associated colitis, seizure disorder, concomitant use of nephrotoxic drugs

Maternal Considerations

Ceftibuten is effective treatment for acute UTI during pregnancy. There is little experience during pregnancy with other indications. Third- and 4th-generation cephalosporins are not generally recommended for surgical prophylaxis. Despite these recommendations, they have been accepted by the medical community for prophylaxis and are today commonly misused. Cephalosporins are usually considered safe during pregnancy. ***Side effects*** include seizures, agranulocytosis, thrombocytopenia, and anaphylaxis.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **ceftibuten** crosses the human placenta. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically.

Breastfeeding Safety

Most cephalosporins are excreted into breast milk. However, the concentration of **ceftibuten** in breast milk is minimal and considered compatible with breastfeeding.

Drug Interactions

Nephrotoxicity has been reported following co-administration of other cephalosporins and aminoglycosides.
Probenecid may decrease renal tubular secretion of cephalosporins, resulting in increased and more prolonged cephalosporin blood levels.
A single dose of liquid antacid did not affect the Cmax or AUC of **ceftibuten;** however, 150mg of **ranitidine** q12h for 3d increased the **ceftibuten** Cmax by 23% and AUC by 16%.

References

Barr WH, Lin CC, Radwanski E, et al. Diagn Microbiol Infect Dis 1991; 14:93-100.
Krcmery S, Hromec J, Demesova D. Int J Antimicrob Agents 2001; 17:279-82.

Summary

Pregnancy Category: B
Lactation Category: S

- Third- and 4th-generation cephalosporins are generally not recommended for surgical prophylaxis.
- There are alternative agents for which there is more experience during pregnancy and lactation.

Ceftizoxime—(Cefizox)

International Brand Name—Acantex (Argentina, Chile); Cefigrand (Argentina); Cefizox (Austria, Canada, Czech Republic, England, India, Indonesia, Ireland, Portugal, Spain); Ceftix (Germany); Ceftizon (Argentina); Epocelin (Finland, Hungary, Japan, Poland, Spain, Taiwan); Eposerin (Italy); Tefizox (Israel); Tergecin (Philippines); Ultracef (Mexico)

Drug Class

Antibiotics; Cephalosporins, 3rd-generation

Indications

Bacterial infections (gram-positive aerobes: *S. aureus, S. epidermidis, S. pneumoniae, S. pyogenes, Enterococcus;* gram-negative aerobes: *E. coli, Klebsiella, Enterobacter, Citrobacter, P. mirabilis, Pseudomonas aeruginosa, N. gonorrhoeae;* gram-positive anaerobes: *C. perfringens, Peptostreptococcus, Peptococcus, Propionibacterium acnes*)

Mechanism

Bactericidal—inhibits cell wall synthesis

Dosage with Qualifiers

Bacterial infection—1-2g IV/IM q8-12h; alternatively for severe infection, 3-4g IV/IM q8h
Gonorrhea—1g IM

NOTE: renal dosing.

- **Contraindications**—hypersensitivity to drug or class
- **Caution**—penicillin allergy, renal dysfunction, antibiotic-associated colitis, seizure disorder, concomitant use of nephrotoxic drugs

Maternal Considerations

Ceftizoxime appears effective and safe for the treatment of acute infections during pregnancy. It has no effect on the interval to delivery, or the duration of pregnancy in women treated for preterm labor with intact membranes. Third- and 4th-generation cephalosporins are not generally recommended for surgical prophylaxis. Despite these recommendations, they have been accepted by the medical community for prophylaxis and are today commonly misused. Cephalosporins are usually considered safe during pregnancy.
Side effects include rash, anaphylaxis, pruritus, eosinophilia, and hepatic enzyme elevation.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. **Ceftizoxime** concentrations are higher in cord blood and AF than in maternal blood, perhaps because of more avid binding to fetal serum proteins. It is the only antibiotic known to have such high transfer. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically.

Breastfeeding Safety

Most cephalosporins are excreted into breast milk, but the amount of **ceftizoxime** excreted is minimal and generally considered compatible with breastfeeding.

Drug Interactions

Nephrotoxicity has been reported following co-administration of other cephalosporins and aminoglycosides.
Probenecid may decrease renal tubular secretion of cephalosporins, resulting in increased and more prolonged cephalosporin blood levels.

References

Cho N, Fukunaga K, Kunii K, et al. Jpn J Antibiot 1988; 41:1142-54.
Fortunato SJ, Welt SI, Eggleston M, et al. J Perinatol 1990; 10:252-6.

Fortunato SJ, Welt SI, Stewart JT. Am J Obstet Gynecol 1993; 168:914-5.
Gordon M, Samuels P, Shubert P, et al. Am J Obstet Gynecol 1995; 172:1546-52.
Mercer BM, Arheart KL. Lancet 1995; 346:1271-9.
Yamamoto T, Yasuda J, Kanao M, Okada H. Jpn J Antibiot 1988; 41:1164-71.

Summary

Pregnancy Category: B
Lactation Category: S

- Third- and 4th-generation cephalosporins are generally not recommended for surgical prophylaxis.
- There are alternative agents for which there is more experience during pregnancy and lactation.
- The high placental transfer makes **ceftizoxime** potentially an attractive agent for the treatment of fetal sepsis.

Ceftriaxone—(Cef-3; Rocephin; Rowecef)

International Brand Name—Acantex (Argentina, Chile, Paraguay); Axone (Israel); Benaxona (Mexico); Biotriax (Indonesia); Bioxon (Indonesia); Broadced (Indonesia); Brospec (Indonesia); Cef-3 (Philippines); Cefaflox (Indonesia); Cefalogen (Peru); Cefaxona (Colombia, Mexico); Cefaxone (Korea, Malaysia, Singapore); Cefin (China, Singapore); Cefotal (Peru); Cefriex (Indonesia); Ceftrex (Mexico, Thailand); Ceftrian (Ecuador); Ceftrilem (Mexico); Cefxon (Indonesia); Cephin (Thailand); Cerixon (Korea); Chef (Taiwan); Cikedrix (Philippines); Ecotrixon (Indonesia); Elpicef (Indonesia); Eurocef (Philippines); Exempla (Argentina); Ferfacef (Indonesia); Forgram (Philippines); Glicocef (Brazil); Gomcephin (Korea); Grifotriaxona (Peru); Incephin (Indonesia); Keftriaxon (Israel); Keptrix (Philippines); Longacef (Israel); Lyceft (India); Medoxonum (Hong Kong); Megion (Mexico, Philippines); Mesporin (Malaysia); Mesporin IM (Hong Kong); Mesporin IV (Hong Kong); Monocef (India); Nakaxone (Taiwan); Novosef (Israel); Oframax (India, Singapore, South Africa, Thailand); Pantrixon (Philippines); Retrokor (Philippines); Rinxofay (Thailand); Rocefalin Roche (Spain); Rocefin (Brazil, Colombia, Italy); Rocephalin (Denmark, Finland); Rocephin (Mexico); Rocephin ''Biochemie'' (Austria); Rocephine (Belgium, France); Rocephine ''Roche'' (Bulgaria); Rocephin ''Roche'' (Austria, Czech Republic); Rocidar (Israel); Rowecef (Costa Rica, Dominican Republic, El Salvador, Guatemala, Honduras, Nicaragua, Panama); Roxcef (South Africa); Roxon (Philippines); Samixon (Israel); Sintrex (Taiwan); Socef (Indonesia); Sunflow (Taiwan); Tacex (Mexico); Torocef-1 (Republic of Yemen); Trexofin (Singapore); Triaken (Mexico); Triax (Israel); Triaxone (Indonesia); Tricef (Taiwan); Tricefin (Singapore); Tricephin (Thailand); Trijec (Indonesia); Xtenda (Philippines); Zefaxone (Thailand); Zefone 250 (South Africa)

Drug Class

Antibiotics; Cephalosporins, 3rd-generation

Indications

Bacterial infections (gram-positive aerobes: *S. aureus, S. epidermidis, S. pneumoniae, S. pyogenes, Enterococcus;* gram-negative aerobes: *E. coli, Klebsiella, Enterobacter, Citrobacter, P. mirabilis, Pseudomonas aeruginosa, N. gonorrhoeae;* gram-positive anaerobes: *C. perfringens, Peptostreptococcus, Peptococcus, Propionibacterium acnes*)

Mechanism

Bactericidal—inhibits cell wall synthesis

Dosage with Qualifiers

Gonorrhea—250mg IM ×1 (see CDC STD guidelines)
Bacterial infection—1-2g IV qd
Preoperative prophylaxis—1g IV

- **Contraindications**—hypersensitivity to drug or class
- **Caution**—penicillin allergy, renal dysfunction, antibiotic-associated colitis, seizure disorder, concomitant use of nephrotoxic drugs

Maternal Considerations

Ceftriaxone appears effective and safe during pregnancy for the treatment of acute infections. **Ceftriaxone** (single dose given IM) is a drug of choice for the treatment of gonorrhea in pregnancy.

A single dose is as effective for post–cesarean prophylaxis as 3 doses of **ampicillin/cloxacillin.** However, 3rd- and 4th-generation cephalosporins are not generally recommended for surgical prophylaxis. Despite these recommendations, they have been accepted by the medical community for prophylaxis and are today commonly misused. Cephalosporins are usually considered safe during pregnancy.
Side effects include thrombocytopenia, anaphylaxis, diarrhea, pseudomembranous colitis, eosinophilia, and vomiting.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. **Ceftriaxone** rapidly crosses the human placenta, reaching therapeutic concentrations in the fetal compartments. Some studies suggest that intrapartum prophylaxis with **ceftriaxone** decreases the rates of bacterial colonization and early-onset infection in newborns. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically. However, **ceftriaxone** weakly impairs *in vitro* rat nephrogenesis at all doses studied except 1000mcg/ml, which blocked kidney development completely.

Breastfeeding Safety

Most cephalosporins are excreted into breast milk, but the amount of **ceftriaxone** excreted is <5% of a 2g maternal dose. It is generally considered compatible with breastfeeding.

Drug Interactions

Nephrotoxicity has been reported following co-administration of other cephalosporins and aminoglycosides.
Probenecid may decrease renal tubular secretion of cephalosporins, resulting in increased and more prolonged cephalosporin blood levels.

References

Ahmed ET, Mirghani OA, Gerais AS, Adam I. East Mediterr Health J 2004; 10:277-88.
Bourget P, Quinquis-Desmaris V, Fernandez H. Ann Pharmacother 1993; 27:294-7.
Hercogova J, Brzonova I. Curr Opin Infect Dis 2001; 14:133-7.
Nathanson S, Moreau E, Merlet-Benichou C, Gilbert T. J Am Soc Nephrol 2000; 11:874-84.
Ramus RM, Sheffield JS, Mayfield JA, Wendel GD Jr. Am J Obstet Gynecol 2001; 185:629-32.
Roberts JA. Urol Clin North Am 1999; 26:753-63.
Saez-Llorens X, Ah-Chu MS, Castano E, et al. Clin Infect Dis 1995; 21:876-80.
Shaffer EA. Curr Gastroenterol Rep 2001; 3:166-73.
Temmerman M, Njagi E, Nagelkerke N, et al. J Reprod Med 1995; 40:176-80.
Wing DA, Hendershott CM, Debuque L, Millar LK. Obstet Gynecol 1999; 94:683-8.

Summary

Pregnancy Category: B
Lactation Category: S

- **Ceftriaxone** appears effective and safe during pregnancy for the treatment of acute obstetric infections.
- Third- and 4th-generation cephalosporins are generally not recommended for surgical prophylaxis.

Cefuroxime—(Ceftin; Kefurox; Zinacef)

International Brand Name—Axetine (Hong Kong); Axurocef (Thailand); Bearcef (Korea); Cefogen (Thailand); Ceftil (Korea); Ceftin (Canada); Cefudura (Germany); Cefuhexal (Germany); Cefuracet (Mexico); Cefurax (Germany); Cefuril (India); Cefuro-Puren (Germany); Cefurox-wolff (Germany); Cefutil (Israel); Celocid (Indonesia); Cepazine (France); Cervin (Philippines); Cethixim (Indonesia); Cetoxil (Mexico); Curocef (Austria, Chile); Curoxima (Spain); Curoxime (Portugal); Deltrox (Argentina); Elobact (Germany); Eroxmit (Philippines); Froxal (Mexico); Froxime (Israel); Furoxime (Thailand); Kalcef (Indonesia); Kefurox (Canada); Laxinat (Philippines); Magnaspor (Thailand); Oracef (Japan); Oraxim (Israel); Sharox-500 (Indonesia); Vekfazolin (Greece); Zinacef (Canada, Colombia, New Zealand, Philippines); Zinat (Switzerland); Zinate (Taiwan); Zinnat (Austria, Belgium, Brazil, Bulgaria, Chile, China, Colombia, Costa Rica, Czech Republic, Denmark, Dominican Republic, Ecuador, El Salvador, England, Finland, France, Germany, Guatemala, Honduras, Hong Kong, Hungary, Indonesia, Ireland, Israel, Italy, Korea, Malaysia, Mexico, Netherlands, Nicaragua, Panama, Paraguay, Peru, Philippines, Poland, South Africa, Spain, Switzerland, Taiwan, Thailand, Uruguay, Venezuela); Zonef (Thailand); Zoref (Portugal)

Drug Class	Antibiotics; Cephalosporins, 2nd-generation
Indications	Bacterial infections (gram-positive aerobes: *S. aureus, S. epidermidis, S. pneumoniae, S. pyogenes, Enterococcus;* gram-negative aerobes: *E. coli, Klebsiella, Enterobacter, Citrobacter, P. mirabilis, Pseudomonas aeruginosa, N. gonorrhoeae;* gram-positive anaerobes: *C. perfringens, Peptostreptococcus, Peptococcus, Propionibacterium acnes*)
Mechanism	Bactericidal—inhibits cell wall synthesis
Dosage with Qualifiers	Bacterial infection—0.75-1.5g IM/IV q6-8h; max 3.0g q8h for bacterial meningitis Surgical prophylaxis—1.5g IV ×1 *NOTE: renal dosing.* • **Contraindications**—hypersensitivity to drug or class • **Caution**—penicillin allergy, renal dysfunction, antibiotic-associated colitis, seizure disorder, concomitant use of nephrotoxic drugs
Maternal Considerations	There are no adequate reports or well-controlled studies of **cefuroxime** in pregnant women. It appears to be safe and effective during pregnancy for the treatment of acute infections, especially pyelonephritis. One investigator suggested it was a first-choice option for the treatment of acute pyelonephritis during pregnancy due to its tolerance, microbiologic activity, and superior clinical effect compared to **cephradine.** Cephalosporins are usually considered safe during pregnancy. ***Side effects*** include thrombocytopenia, anaphylaxis, pseudomembranous colitis, eosinophilia, diarrhea, vomiting, interstitial nephritis, neutropenia, and elevated hepatic enzymes.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. **Cefuroxime** crosses the human placenta at a rate unaffected by gestational age and anemia, but requires a dose of at least 1500mg to achieve the typical MIC in the fetus. Bactericidal concentrations can be demonstrated in maternal plasma and in AF leaking from the vagina. A concentration-time curve in AF occurs, with peak concentrations 3-4h after infusion. Therapeutically active levels are present in the newborns. The resorption of **cefuroxime** by the fetal membranes is high. There is no evidence of teratogenicity after 1st trimester exposure, and children of women treated with **cefuroxime** are normal at 18mo. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically.

Breastfeeding Safety

Most cephalosporins are excreted into breast milk. While there are no adequate reports or well-controlled studies in nursing women, **cefuroxime** is generally considered compatible with breastfeeding.

Drug Interactions

Probenecid increases the **cefuroxime** serum AUC by 50%. The peak serum **cefuroxime** concentration after a 1.5g single dose is greater when taken with 1g of probenecid (mean = 14.8mcg/ml) than without probenecid (mean = 12.2mcg/ml).
Drugs that reduce gastric acidity may result in a lower bioavailability of **cefuroxime** compared with that of fasting state and tend to cancel the effect of postprandial absorption.

References

Berkovitch M, Segal-Socher I, Greenberg R, et al. Br J Clin Pharmacol 2000; 50:161-5.
De Leeuw JW, Roumen FJ, Bouckaert PX, et al. Obstet Gynecol 1993; 81:255-60.
Holt DE, Fisk NM, Spencer JA, et al. Arch Dis Child 1993; 68:54-7.
Kristensen GB, Beiter EC, Mather O. Acta Obstet Gynecol Scand 1990; 69:497-500.
Manka W, Solowiow R, Okrzeja D. Drug Saf 2000; 22:83-8.
Ovalle A, Martinez MA, Wolff M, et al. Rev Med Chil 2000; 128:749-57.

Summary

Pregnancy Category: B
Lactation Category: S

- **Cefuroxime** is a reasonable candidate for the noted indications.
- The high degree of placental transfer renders **cefuroxime** a potentially attractive agent for fetal treatment.

Celecoxib—(Celebrex)

International Brand Name—Artroxil (Colombia); Caditar (Peru); Celcox (Israel); Celebra (Brazil, Chile, Costa Rica, El Salvador, Guatemala, Honduras, Israel, Nicaragua, Panama, Uruguay); Celebrex (Canada, Colombia, England, France, Germany, Hong Kong, Indonesia, Israel, Korea, Mexico, Philippines, Singapore, Taiwan, Thailand); Celib (India); Coxel (Argentina); Coxid (Philippines); Dilox (Colombia); Eliflam (Paraguay); Lexfin (Colombia)

Drug Class

COX-2 inhibitors; NSAIDs

Indications

Osteoarthritis, rheumatoid arthritis, familial adenomatous polyposis, acute pain

Mechanism

COX-2 inhibitor

Dosage with Qualifiers

Osteoarthritis—200mg PO qd
Rheumatoid arthritis—100-200mg PO bid
Familial adenomatous polyposis—200mg PO bid; begin with 100mg PO qd
Pain, acute—200mg PO bid

- **Contraindications**—hypersensitivity to drug or class, nonsteroidal drug–induced asthma, nonsteroidal drug–induced urticaria, aspirin triad, hepatic and renal failure
- **Caution**—nasal polyps, GI bleeding, renal or hepatic dysfunction, CHF, hypertension, dehydration, fluid retention, asthma

Maternal Considerations

Celecoxib is the prototype COX-2 inhibitor. There are no adequate reports or well-controlled studies in pregnant women.

In vitro studies reveal inhibition of uterine contractions by COX-2 inhibition. In two small trials, **celecoxib** was employed as a tocolytic agent with modest effect. **Celecoxib** (80 and 160mg/kg/d) significantly reduces fertility, prolongs pregnancy, and inhibits normal cervical ripening in rats. The authors concluded it was similar to **indomethacin** but with a lower frequency of adverse fetal effects. However, in a series of recent studies, COX-2 inhibition was associated with a dose-related increase in death from CV causes, MI, stroke, or heart failure. In light of these reports, **celecoxib** use should be avoided for most indications in favor of other agents especially in women with CV and GI risks. ***Side effects*** include GI bleeding, GI ulceration, esophagitis, hypersensitivity reaction, bronchospasm, heart failure, hepatic toxicity, renal papillary necrosis, diarrhea, abdominal pain, flatulence, dizziness, and pharyngitis.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. **Celecoxib** crosses the human placenta, as do other NSAIDs, and can cause ductus arteriosus constriction late in pregnancy. Fetal levels are dependent on the maternal concentrations because NSAID agents are not metabolized by the fetal kidney. It reduces renal blood and urine flows in the ovine fetus. **Celecoxib** increases the incidence of VSD and other fetal alterations such as fused ribs and misshapen sternum in rabbits treated during organogenesis. There is a dose-dependent increase in the frequency of diaphragmatic hernia in rats.

Breastfeeding Safety

There are no adequate reports or well-controlled studies of **celecoxib** in nursing women. A single case report found a concentration of 133ng/ml approximately 5h after a 100mg dose and an elimination t/2 of 4.0-6.5h. If this level were sustained, the amount ingested by a 3.5kg newborn in 24h should be subclinical.

Drug Interactions

Celecoxib is metabolized by hepatic CYP2C9. Drugs known to inhibit 2C9 should be given cautiously.
C**elecoxib** inhibits *in vitro* CYP2D6 activity. Thus, there is a potential for an *in vivo* drug interaction with drugs that are metabolized by CYP2D6.
NSAIDs may diminish the antihypertensive effect of ACEIs.
Administration of **aspirin** with **celecoxib** increases the rate of GI ulceration and other complications compared to **celecoxib** alone.
Celecoxib is not a substitute for **aspirin** for CV prophylaxis.
Fluconazole increases **celecoxib** plasma concentrations by 2-fold. This increase is due to the inhibition of **celecoxib** metabolism by CYP2C9.
NSAIDs can reduce the natriuretic effect of **furosemide** and thiazides in some patients.
Lithium levels are increased approximately 17%. Patients on **lithium** should be closely monitored when **celecoxib** is introduced or withdrawn.
Bleeding events have been reported post-marketing in patients receiving **celecoxib** and **warfarin,** predominantly in the elderly.

References

Borna S, Saeidi FM. J Obstet Gynaecol Res 2007; 33:631-4.
Bukowski R, Mackay L, Fittkow C, et al. Am J Obstet Gynecol 2001; 184:1374-8.
Davies NM, McLachlan AJ, Day RO, Williams KM. Clin Pharmacokinet 2000; 38:225-42.
Kajino H, Roman C, Clyman RI. Biol Neonate 2002; 82:257-62.
Knoppert DC, Stempak D, Baruchel S, Koren G. Pharmacotherapy 2003; 23:97-100.

Slattery MM, Friel AM, Healy DG, Morrison JJ. Obstet Gynecol 2001; 98:563-9.
Solomon SD, McMurray JJ, Pfeffer MA, et al; Adenoma Prevention with Celecoxib (APC) Study Investigators. N Engl J Med 2005; 352:1071-80.
Solomon SD, Pfeffer MA, McMurray JJ, et al; APC and PreSAP Trial Investigators. Circulation 2006; 114:1028-35.
Sookvanichsilp N, Pulbutr P. Contraception 2002; 65:373-8.
Stika CS, Gross GA, Leguizamon G, et al. Am J Obstet Gynecol 2002; 187:653-60.

Summary

Pregnancy Category: C
Lactation Category: U

- **Celecoxib** and other COX-2 inhibitors may be associated with an excess of CV mortality, and their use should probably be confined to secondary or tertiary treatment.
- **Celecoxib** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Cephalexin—(Alsporin; Biocef; Carnosporin; Cefaseptin; Cephin; Ceporexin-E; Check; Ed A-Ceph; Keflet; Keflex; Lopilexin; Mamlexin; Synecl; Winlex)

International Brand Name—Airex (Philippines); Alexin (India); Anxer (Hong Kong); Bandax (Philippines); Bloflex (Philippines); Cefablan (Colombia); Cefacin-M (Hong Kong); Cefadin (Ecuador); Cefadina (Spain); Cefalin (Indonesia, Israel, Philippines); Cefaporin (Ecuador); Cefax (Colombia); Ceforal (Israel); Cefovit (Israel); Cefrin (Peru); Celexil (Philippines); Celexin (Thailand); Cepastar (Philippines); Cepexin (Austria); Cephalen (Singapore); Cephalexyl (Thailand); Cephanmycin (Singapore); Cephia (Thailand); Cepol (Japan); Ceporex (Belgium, Bulgaria, Czech Republic, Ecuador, England, Hong Kong, Ireland, Italy, Malaysia, Mexico, Netherlands, Philippines, Portugal, South Africa, Spain, Switzerland, Thailand); Ceporex Forte (Portugal); Ceporexin (Argentina, Germany); Ceporexine (France); Ceprax (Colombia); Cerexin (South Africa); Cromlex (Philippines); Difagen (Philippines); Durantel DS (Japan); Erocetin (Argentina, Paraguay, Uruguay); Falexin (Korea); Farmalex (Thailand); Felexin (Hong Kong, Malaysia); Fexin (South Africa); Ialex (Australia); Ibilex (Taiwan, Thailand); Inphalex (Indonesia); Kefacin (Korea); Kefalex (Finland); Kefalospes (Greece); Kefaxin (Greece, Ireland); Kefexin (Czech Republic, Finland, Germany, Ireland); Keflex (Austria, Bulgaria, Colombia, Denmark, England, Greece, Ireland, Israel, Japan, Malaysia, Mexico, Norway, Peru, Philippines, Poland, Portugal, Sweden, Switzerland, Taiwan, Thailand); Kefloridina (Spain); Keforal (Argentina, Belgium, France, Italy, Netherlands); Kemolexin (Indonesia); LC-Lexin (Philippines); Lenocef (South Africa); Lexin (Peru); Lonaxel (Philippines); Lonflex (Taiwan); Madlexin (Indonesia); Mamalexin (Japan); Medolexin (Malaysia); Montralex (Philippines); Neokef (Malaysia); Novolexin (Canada); Nufex (India); Oracef (Bulgaria, Czech Republic, Germany); Oriphex (South Africa); Ospexin (Austria, Bulgaria, Costa Rica, Czech Republic, Dominican Republic, El Salvador, Guatemala, Honduras, Hong Kong, Indonesia, Malaysia, Nicaragua, Panama); Ospexina (Colombia); Paferxin (Mexico); Palitrex (Ecuador, Indonesia, Peru); Pectril (Philippines); Pharmexin (Israel); Pondnacef (Thailand); Pyassan (Hungary); Refosporen (Argentina); Relaxin (Philippines); Respinal (Philippines); Rofex (India); Sanaxin (Austria); Sefasin (Thailand); Sepexin (India); Septilisin (Argentina); Servicef (Mexico); Servispor (Malaysia); Sialexin (Thailand); Sinlex (Taiwan); Sinthecillin (Greece); Sofilex (Hong Kong, Singapore); Sorlex (Philippines); Sporahexal (Australia); Sporicef (Thailand); Sporidex (India, Philippines, Thailand); Syncle (Japan); Tepaxin (Indonesia); Tokiolexin (Japan); Uphalexin (Malaysia); Velexin (Thailand); Voxxim (Philippines); Zeplex (Thailand); Zucoflaxin (Philippines)

Drug Class — Antibiotics; Cephalosporins, 1st-generation

Indications — Bacterial infections (gram-positive aerobes: *S. aureus*, β_1-hemolytic streptococci; gram-negative aerobes: *E. coli*, *P. mirabilis*, *Klebsiella* species, *Moraxella catarrhalis*)

Mechanism — Bactericidal—inhibits cell wall synthesis

Dosage with Qualifiers

Bacterial infection—250mg-1g PO q6h

- **Contraindications**—hypersensitivity to drug or class

- **Caution**—penicillin allergy, renal dysfunction, antibiotic-associated colitis

Maternal Considerations

Cephalexin is used for the treatment of UTIs, acute obstetric infections, and pharyngitis because of its antimicrobial spectrum. **Cephalexin** appears effective and safe during pregnancy for the treatment of acute bacterial infection. It is extensively used for the oral phase of treatment for pyelonephritis.
Side effects include neutropenia, thrombocytopenia, anaphylaxis, pseudomembranous colitis, diarrhea, nausea, and elevated hepatic enzymes.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. **Cephalexin** crosses the human placenta in a carrier-mediated fashion. The magnitude of transfer is greater than **cephapirin,** and produces a fetal concentration above the MIC for most sensitive pathogens. There is no evidence of teratogenicity. Rodent studies are also reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically.

Breastfeeding Safety

Most cephalosporins are excreted into breast milk, but the amount of **cephalexin** excreted is small and generally considered compatible with breastfeeding.

Drug Interactions

Nephrotoxicity has been reported following co-administration of other cephalosporins and aminoglycosides.
Probenecid may decrease renal tubular secretion of cephalosporins, resulting in increased and more prolonged cephalosporin blood levels.

References

Campbell-Brown M, McFadyen IR. Br J Obstet Gynaecol 1983; 90:1054-9.
Creatsas G, Pavlatos M, Lolis D, Kaskarelis D. Curr Med Res Opin 1980; 7:43-6.
Czeizel AE, Rockenbauer M, Sorensen HT, Olsen J. Am J Obstet Gynecol 2001; 184:1289-96.
Griffith RS. Postgrad Med J 1983; 59(Suppl 5):16-27.
Kafetzis DA, Siafas CA, Georgakopoulos PA, Papadatos CJ. Acta Paediatr Scand 1981; 70:285-8.
Kudo Y, Urabe T, Fujiwara A, et al. Biochim Biophys Acta 1989; 978:313-8.
Pfau A, Sacks TG. Clin Infect Dis 1992; 14:810-4.
Stage AH, Glover DD, Vaughan JE. J Reprod Med 1982; 27:113-9.
Wing DA, Hendershott CM, Debuque L, Millar LK. Obstet Gynecol 1998; 92:249-53.

Summary

Pregnancy Category: B
Lactation Category: S

- **Cephalexin** is a popular cephalosporin for which there is a broad and reassuring experience during pregnancy.

Cephalothin—(Note: This drug has been withdrawn from the US market.)

International Brand Name—Arecamin (Argentina, Paraguay); Baccef (Brazil); Cefadin (Malaysia, Singapore, Thailand); Ceftina (Mexico); Ceporacin (Bulgaria, Canada, Netherlands); Cepovenin (Germany); Falot (Mexico); Jnflin (Taiwan); Keflin (Argentina, Australia, Colombia, Denmark, Ecuador, Finland, Israel, Korea, Mexico, Netherlands, Norway, Sweden, Switzerland, Venezuela); Keflin-N (Taiwan); Keflin Neutral (Austria); Keflin Neutro (Italy); Practogen (Greece)

Drug Class

Antibiotics; Cephalosporins, 1st-generation

Indications

Bacterial infections (gram-positive aerobes: *S. aureus,* β_1-hemolytic streptococci; gram-negative aerobes: *E. coli, P. mirabilis, Klebsiella* species, *Moraxella catarrhalis*)

Mechanism

Bactericidal—inhibits cell wall synthesis

Dosage with Qualifiers

Bacterial infection—500mg-2gm IM/IV q4-6h
Surgical prophylaxis—1-2g IV 30-60min preoperatively

- **Contraindications**—hypersensitivity to drug or class
- **Caution**—penicillin allergy, renal dysfunction, antibiotic-associated colitis, seizure disorder, concomitant use of nephrotoxic drugs

Maternal Considerations

The elimination t/2 of this 1st-generation cephalosporin is reduced by ⅓ during pregnancy. Primary treatment of UTIs with a 1st-generation cephalosporin during pregnancy may no longer be appropriate in some geographic locales as a significant number of isolates (11%) are resistant to **cephalothin.** Prophylactic **cephalothin** decreases the incidence of endometritis in women undergoing midtrimester abortion and cesarean section as well as do other cephalosporins.
Side effects include anemia, thrombocytopenia, anaphylaxis, pseudomembranous colitis, diarrhea, nausea, and elevated hepatic enzymes.

Fetal Considerations

There are no adequate reports or well-controlled studies of **cephalothin** in human fetuses. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically.

Breastfeeding Safety

Most cephalosporins are excreted into breast milk, but the amount of **cephalothin** excreted is small and generally considered compatible with breastfeeding.

Drug Interactions

Nephrotoxicity has been reported following co-administration of other cephalosporins and aminoglycosides.
Probenecid may decrease renal tubular secretion of cephalosporins, resulting in increased and more prolonged cephalosporin blood levels.

References

Angel JL, O'Brien WF, Finan MA, et al. Obstet Gynecol 1990; 76:28-32.
Fan YD, Pastorek JG 2nd, Miller JM Jr, Mulvey J. Am J Perinatol 1987; 4:324-6.
Kafetzis DA, Siafas CA, Georgakopoulos PA, Papadatos CJ. Acta Paediatr Scand 1981; 70:285-8.
Noschel H, Peiker G, Voigt R, et al. Arch Toxicol Suppl 1980; 4:380-4.

Philipson A, Stiernstedt G, Ehrnebo M. Clin Pharmacokinet 1987; 12:136-44.
Rudge MV, Atallah AN, Peracoli JC, et al. Acta Obstet Gynecol Scand 2006; 85:945-8.
Spence MR, King TM, Burkman RT, Atienza MF. Obstet Gynecol 1982; 60:502-5.

Summary

Pregnancy Category: B
Lactation Category: S
- **Cephalothin** is a popular cephalosporin for which there is a broad and reassuring experience with use during pregnancy.

Cephapirin—(Cefadyl)

International Brand Name—Brisfirina (Portugal, Spain); Brisporin (Ecuador); Cefaloject (France); Cefatrex (Greece, Korea); Cefatrexyl (Bulgaria, Czech Republic, Poland); Lopitrex (Taiwan); Unipirin (Taiwan)

Drug Class

Antibiotics; Cephalosporins, 1st-generation

Indications

Bacterial infections (gram-positive aerobes: *S. aureus,* β_1-hemolytic streptococci; gram-negative aerobes: *E. coli, P. mirabilis, Klebsiella* species, *Moraxella catarrhalis*)

Mechanism

Bactericidal—inhibits cell wall synthesis

Dosage with Qualifiers

Bacterial infection—1-2g IV/IM q4-6h; max 12g qd

- **Contraindications**—hypersensitivity to drug or class
- **Caution**—penicillin allergy, renal dysfunction, antibiotic-associated colitis, seizure disorder, concomitant use of nephrotoxic drugs

Maternal Considerations

Cephapirin appears effective and safe for the treatment of acute infection during pregnancy.
Side effects include anemia, thrombocytopenia, anaphylaxis, pseudomembranous colitis, diarrhea, nausea, and elevated hepatic enzymes.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. **Cephapirin** crosses the human placenta, and though the magnitude of transfer is less than **cephalexin,** it does produce a fetal concentration above the MIC for most sensitive pathogens. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically.

Breastfeeding Safety

Most cephalosporins are excreted into breast milk, but the amount of **cephapirin** excreted is small and generally considered compatible with breastfeeding.

Drug Interactions

Nephrotoxicity has been reported following co-administration of other cephalosporins and aminoglycosides.
Probenecid may decrease renal tubular secretion of cephalosporins, resulting in increased and more prolonged cephalosporin blood levels.

References

Creatsas G, Pavlatos M, Lolis D, Kaskarelis D. Curr Med Res Opin 1980; 7:43-6.
Dashow EE, Read JA, Coleman FH. Obstet Gynecol 1986; 68:473-8.

Kafetzis DA, Siafas CA, Georgakopoulos PA, Papadatos CJ. Acta Paediatr Scand 1981; 70:285-8.
Levin DK, Gorchels C, Andersen R. Am J Obstet Gynecol 1983; 147:273-7.
Prades M, Brown MP, Gronwall R, Miles NS. Am J Vet Res 1988; 49:1888-90.

Summary

Pregnancy Category: B
Lactation Category: S

- A fairly large clinical experience with **cephapirin** during pregnancy is reassuring.

Cephradine—(Anspor; Cefamid; Cefradina; Eskefrin; Nobitina; Velosef)

International Brand Name—Bactocef (South Africa); Broadcef (Korea); Cefadin (Taiwan); Cefirex (France); Cefra (Guatemala); Cefradine (China); Cefradur (Dominican Republic, El Salvador, Guatemala, Honduras, Panama); Cefrasol (Israel); Cefril (South Africa); Cefro (Japan); Celex (Italy); Daicefalin (Japan); Duphratex (Philippines); Dynacef (Indonesia); Eskacef (South Africa); Folzep (Philippines); Gramcep (Philippines); Lisacef (Taiwan); Lovecef (Indonesia); Maxisporin (Belgium, Netherlands, Portugal); Nakacef-A (Taiwan); Opebrin (Greece); Qualisef (Hong Kong); Racep (Philippines); S-60 (Taiwan); Safdin (Korea); Sefril (Austria, Germany, Poland, Switzerland, Uruguay); Sephros (Taiwan); Solphride (Philippines); Taicefran (Japan); Tricef (Korea); U-Save (Taiwan); Vamocef (Philippines); V-Cefra (Taiwan); Velocef (Argentina, Peru, Spain); Velodyne (Philippines); Velosef (Belgium, Chile, China, England, Ethiopia, Greece, Hong Kong, Indonesia, Kenya, Korea, Netherlands, New Zealand, Nigeria, Portugal, Taiwan, Tanzania, Uganda); Velosef Viol (Greece); Veracef (Colombia, Costa Rica, Ecuador, El Salvador, Guatemala, Honduras, Mexico, Nicaragua, Panama, Venezuela); Zeefra (Hong Kong); Zolicef (Philippines)

Drug Class

Antibiotics; Cephalosporins, 1st-generation

Indications

Bacterial infections (gram-positive aerobes: *S. aureus*, β_1-hemolytic streptococci; gram-negative aerobes: *E. coli*, *P. mirabilis*, *Klebsiella* species, *Moraxella catarrhalis*)

Mechanism

Bactericidal—inhibits cell wall synthesis

Dosage with Qualifiers

Bacterial infection—250-500mg PO q6h
UTI—up to 1g PO q6h

- **Contraindications**—hypersensitivity to drug or class
- **Caution**—penicillin allergy, renal dysfunction, antibiotic-associated colitis, seizure disorder, concomitant use of nephrotoxic drugs

Maternal Considerations

Cephradine has been used for the treatment of UTI and pharyngitis because of its antimicrobial spectrum. However, its elimination t/2 is decreased by 25% during pregnancy, which might in part explain why **cefuroxime** proved superior in one randomized trial for the treatment of UTI.
Side effects include anemia, thrombocytopenia, anaphylaxis, pseudomembranous colitis, diarrhea, nausea, and elevated hepatic enzymes.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. **Cephradine** rapidly crosses the human placenta and is found in the AF within hours of maternal administration. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically.

Breastfeeding Safety

Cephradine is excreted into human breast milk. Its M:P ratio approximates 0.2, suggesting **cephradine** should be compatible with breastfeeding.

Drug Interactions

Bacteriostatic agents may interfere with the bactericidal action of cephalosporins in acute infection; other agents (e.g., aminoglycosides, **colistin,** polymyxins, **vancomycin**) may increase the possibility of nephrotoxicity.
Potent "loop diuretics" (e.g., **furosemide, ethacrynic acid**) may enhance the possibility for renal toxicity.
Probenecid may decrease renal tubular secretion of cephalosporins, resulting in increased and more prolonged cephalosporin blood levels.

References

Lange IR, Rodeck C, Cosgrove R. Br J Obstet Gynaecol 1984; 91:551-4.
Mischler TW, Corson SL, Larranaga A, et al. J Reprod Med 1978; 21:130-6.
Ovalle A, Martinez MA, Wolff M, et al. Rev Med Chil 2000; 128:749-57.
Philipson A, Stiernstedt G, Ehrnebo M. Clin Pharmacokinet 1987; 12:136-44.

Summary

Pregnancy Category: B
Lactation Category: S

- A fairly large experience with **cephradine** during pregnancy is reassuring, though there are alternative agents that may be superior for use during pregnancy.

Cetirizine—(Alltec; Zyrtec)

International Brand Name—Acidrine (Colombia); Adezio (Hong Kong, Singapore); Agelmin (Singapore); Alercet (Colombia, Ecuador, Peru); Alerid (China, Israel); Alertop (Chile, Paraguay); Alerviden (Colombia); Aletir (Brazil); Alled (Indonesia); Allertec (Singapore); Alltec (Taiwan); Alzytec (Singapore); Betarhin (Indonesia); Cabal (Argentina); Cerazine (Korea); Cerini (Indonesia); Cerotec (Korea); Cesta (Korea); Cetalerg (Germany); Cethis (Hong Kong, Thailand); Cetimin (Philippines); Cetin (Taiwan); Cetirax (Colombia); Cetirin (Hong Kong); Cetizin (Korea); Cetrimed (Thailand); Cetrine (China, Singapore, Thailand); Cetrizet (Thailand); Cetrizin (Thailand); Cety (Taiwan); Cetymin (Indonesia); Ceza (Thailand); Cistamine (Thailand); Deallergy (Taiwan); Falergi (Indonesia); Finallerg (Israel); Histazine (Hong Kong, Israel); Histica (Thailand); Incidal-OD (Indonesia, Thailand); Lergium (Peru); Nosemin (Korea); Nosmin (Korea); Ozen (Indonesia); Prixlae (Philippines); Razene (New Zealand); Reactine (Canada, France, Germany); Rhizin (Singapore); Risima (Indonesia); Ryvel (Indonesia); Ryzen (Indonesia); Sancotec (Korea); Selitex (Korea); Setin (Thailand); Setizin (Taiwan); Simtec (Malaysia); Sutac (Thailand); Symitec (Taiwan); Terizin (Singapore); Terzine (Thailand); Triz (India); Vick-Zyrt (Hong Kong); Virlix (France, Italy, Mexico, Philippines, Portugal, Spain); Zenriz (Indonesia); Zensil (Thailand); Zeran (South Africa); Zertine (Hong Kong, Thailand); Zetir (Germany); Zicet (Hong Kong); Zinex (Philippines); Zirtek (England, Ireland); Zirtin (India); Zyllergy (Israel); Zymed (Thailand); Zyrac (Thailand); Zyrazine (Thailand); Zyrcon (Thailand); Zyrlex (Sweden); Zyrtec (Argentina, Brazil, Chile, China, Colombia, Costa Rica, Dominican Republic, Ecuador, El Salvador, Guatemala, Honduras, Hong Kong, India, Korea, Malaysia, Mexico, Nicaragua, Panama, Peru, Philippines, South Africa, Taiwan, Thailand, Uruguay, Venezuela)

Drug Class

Allergy; Antihistamines

Indications

Allergic rhinitis, urticaria

Mechanism

Inhibition of peripheral H_1 receptors

Dosage with Qualifiers

Allergic rhinitis—5-10mg PO qd; max 10mg qd
Urticaria—5-10mg PO qd; max 10mg qd

NOTE: may be combined with ***pseudoephedrine.***

- **Contraindications**—hypersensitivity to drug or class
- **Caution**—hepatic or renal dysfunction, CNS depressant use

Maternal Considerations

There are no adequate reports or well-controlled studies of **cetirizine** in pregnant women. The product labels state medications for allergic rhinitis should be avoided during pregnancy owing to lack of fetal safety, though the majority of agents have human data that refute this position. In general, treatment of allergic rhinitis during pregnancy should begin with the 1st-generation antihistamines, **chlorpheniramine** and **tripelennamine.** Pregnant women who cannot tolerate 1st-generation antihistamines may be offered a 2nd-generation agent, either **loratadine** or **cetirizine.**
Side effects include bronchospasm, hepatitis, hypersensitivity, somnolence, fatigue, dry mouth, pharyngitis, dizziness, abdominal pain, and diarrhea.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **cetirizine** crosses the human placenta. Neither 1st- (e.g., **chlorpheniramine**) nor 2nd-generation (e.g., **cetirizine**) antihistamines are incriminated as human teratogens. Though 1st trimester exposure studies are reassuring, 1st-generation antihistamines are preferred as there is more conclusive evidence of safety. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically.

Breastfeeding Safety

There are no adequate reports or well-controlled studies in nursing women. **Cetirizine** enters human breast milk, though the kinetics remain to be elucidated.

Drug Interactions

There is a small decrease in the clearance of **cetirizine** after 400mg of **theophylline;** it is possible a larger **theophylline** dose could have a greater effect.

References

Blaiss MS; Food and Drug Administration (U.S.); ACAAI-ACOG (American College of Allergy, Asthma, and Immunology and American College of Obstetricians and Gynecologists). Ann Allergy Asthma Immunol 2003; 90(6 Suppl 3):16-22.
Einarson A, Bailey B, Jung G, et al. Ann Allergy Asthma Immunol 1997; 78:183-6.
Mazzotta P, Loebstein R, Koren G. Drug Saf 1999; 20:361-75.
Paris-Kohler A, Megret-Gabeaud ML, Fabre C, et al. Allerg Immunol (Paris) 2001; 33:399-403.
Weber-Schoendorfer C, Schaefer C. Reprod Toxicol 2008; 26:19-23.

Summary

Pregnancy Category: B
Lactation Category: U

- **Cetirizine** is a reasonable selection for the listed indications, though there are alternative agents for which there is more experience during pregnancy and lactation.

Chenodiol—(Chebil; Chelobil; Chendal; Chenix; Chenocol; Chenodex; Chino; Soluston)

International Brand Name—Aylehning (Taiwan); Chebil (Portugal); Chendol (England, Malaysia, Portugal); Cheno (Taiwan); Chenodex (France); Chenofalk (Austria, Belgium, Czech Republic, England, Germany, Hong Kong, Hungary, Indonesia, Italy, Malaysia, Netherlands, Philippines, Poland, Switzerland); Chenossil (Italy); Quenobilan (Spain); Quenocol (Spain); Soluston (Israel); Theramatic (Greece)

Drug Class	Gallstone solubilizers
Indications	Gallstones (cholesterol)
Mechanism	Reduces hepatic synthesis of cholesterol
Dosage with Qualifiers	Gallstones—250mg PO bid ×2w, increase by 250mg/w until the max tolerated or recommended dose is reached (13-16mg/kg/d) in 2 divided doses • **Contraindications**—hypersensitivity to drug or class, acute cholecystitis, cholangitis, gallstone pancreatitis, intrahepatic cholestasis, and primary biliary cirrhosis or sclerosing cholangitis • **Caution**—gallstones
Maternal Considerations	Because of potential hepatotoxicity, poor response rates in some subgroups of **chenodiol**-treated patients, and an increased cholecystectomy rate in other treated subgroups, **chenodiol** is not appropriate treatment for many patients with gallstones. There are no adequate reports or well-controlled studies of **chenodiol** in pregnant women. Maternal pregnancy outcome may be improved in pregnancies complicated by intrahepatic cholestasis by treatment with ursodeoxicholic acid. ***Side effects*** include diarrhea, dyspepsia, N/V, constipation, and dizziness.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. It is unknown if **chenodiol** crosses the placenta. Bile acid levels are lower in both AF and umbilical blood samples from pregnancies treated for intrahepatic cholestasis with ursodeoxicholic acid, suggesting placental transfer. Serious hepatic, renal, and adrenal lesions occurred in rhesus fetuses given 60-90mg/kg/d (4-6× the MRHD) from day 21 to day 45 of pregnancy. Hepatic lesions occurred in neonatal baboons whose mothers received 18-38mg/kg (1-2× the MRHD) throughout pregnancy. Fetal malformations were not observed. Neither fetal liver damage nor fetal abnormalities occurred in reproduction studies in rats and hamsters.
Breastfeeding Safety	There are no adequate reports or well-controlled studies in nursing women. It is unknown whether **chenodiol** enters human breast milk.
Drug Interactions	No clinically significant interactions noted.
References	Carey WD, Tangedahl TN. Postgrad Med 1982; 71:163-72. Mazzela G, Nicola R, Francesco A, et al. Hepatology 2001; 33:504-8. Palmer AK, Heywood R. Toxicology 1974; 2:239-46.
Summary	**Pregnancy Category: X** **Lactation Category: U**

- **Chenodiol** is generally considered contraindicated in women who are or may become pregnant.
- **Chenodiol** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Chloral Hydrate—(Aquachloral; Chloralhydrat; Chloralix; Dormel; Kloral; Noctec)

International Brand Name—Ansopal (Portugal); Chloraldurat (Austria, Germany, Netherlands, Switzerland); Chloralhydrat 500 (Indonesia); Chloralum Hydratum (Poland); Medianox (Switzerland); Novochlorhydrate (Canada); Pocral (Korea); Somnox (Belgium); Welldorm (England, Ireland)

Drug Class	Hypnotics; Sedatives
Indications	Insomnia, anxiety, alcohol withdrawal
Mechanism	Unknown
Dosage with Qualifiers	Insomnia, anxiety—500mg-1g PO prn qhs Alcohol withdrawal—500mg-1g PO q6h *NOTE: also available in suppository form.* • **Contraindications**—hypersensitivity to drug or class, cardiac disease, hepatic failure • **Caution**—depression, drug abuse, porphyria
Maternal Considerations	**Chloral hydrate** is an anxiolytic hypnotic. There are no adequate reports or well-controlled studies in pregnant women. There is a case report of successful hemodialysis during pregnancy for the treatment of a **chloral hydrate** overdose. ***Side effects*** include hypersensitivity, leukopenia, dependence, respiratory depression, hyperbilirubinemia, and angioedema.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. Chronic use during pregnancy may result in neonatal withdrawal, suggesting placental transfer. Rodent teratogenicity studies have apparently not been performed. Equine studies suggest a higher frequency of miscarriage after **chloral hydrate.**
Breastfeeding Safety	There are no adequate reports or well-controlled studies in nursing women. **Chloral hydrate** is excreted into human breast milk and may cause neonatal sedation.
Drug Interactions	May worsen hypoprothrombinemia in patients taking oral anticoagulants. When followed by IV **furosemide,** may result in sweating, hot flashes, and variable BP, including hypertension due to a hypermetabolic state caused by displacement of thyroid hormone from its bound state. Administration should be delayed in patients who have ingested significant amounts of alcohol in the preceding 12-24h. CNS depressants are additive in effect, and the dosage should be reduced when such combinations are given concurrently.
References	Akpokodje JU, Akusu MO, Osuagwu AI. Vet Rec 1986; 118:306. Vaziri ND, Kumar KP, Mirahmadi K, Rosen SM. South Med J 1977; 70:377-8.

Summary

Pregnancy Category: C
Lactation Category: NS (possibly)
- **Chloral hydrate** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Chlorambucil—(Leukeran; Linfolysin)

International Brand Name—Chloraminophene (France); Leuceran (Bulgaria); Leukeran (Argentina, Brazil, Canada, Chile, Ecuador, Mexico, Peru, Uruguay)

Drug Class

Antineoplastics, alkylating agents

Indications

Palliative therapy for a variety of cancers, including leukemia, lymphomas, trophoblastic disease

Mechanism

Alkylating agent—cross-links DNA and RNA and inhibits protein synthesis

Dosage with Qualifiers

Cancer—varies based on the type of neoplasm. Most regimens recommend 0.1-0.2mg/kg/d ×3-6w

- **Contraindications**—hypersensitivity to drug or class, resistance to drug
- **Caution**—neutropenia, thrombocytopenia, seizures, fever, hepatotoxicity, epilepsy

Maternal Considerations

Chlorambucil is an alkylating agent used in chemotherapy protocols for many malignant diseases, including gestational trophoblastic disease and ovarian cancer. There are no adequate reports or well-controlled studies in pregnant women. There are many case reports of a successful outcome in women treated with **chlorambucil** throughout pregnancy.
Side effects include bone marrow suppression, N/V, confusion, anxiety, seizures, skin hypersensitivity, and pulmonary fibrosis.

Fetal Considerations

There are no adequate reports or well-controlled studies in animal and human fetuses. It is unknown whether **chlorambucil** crosses the human placenta. The sole report of a **chlorambucil**-associated birth defect is unilateral renal agenesis in 1 fetus of a set of twins. The lack of reports suggests **chlorambucil** is not a major human teratogen, and fetal tolerance later in gestation is quite high. **Chlorambucil** is a teratogen in rodents, causing postclosure exencephaly and axial skeletal abnormalities.

Breastfeeding Safety

There are no adequate reports or well-controlled studies in nursing women. It is unknown whether **chlorambucil** enters human breast milk.

Drug Interactions

A number of drugs may increase myelosuppression, including **allopurinol, azathioprine, dasatinib, flucytosine, ganciclovir, hydroxyurea, ibritumomab, primaquine, pyrimethamine, trimetrexate,** and **zidovudine.**
Alefacept may enhance immunosuppression.
Natalizumab may increase the risk of infection.
Palifermin may increase the risk and severity of mucositis.

References

Curry SL, Blessing JA, DiSaia PJ, et al. Obstet Gynecol 1989; 73:357-62.
Evans AC Jr, Soper JT, Clarke-Pearson DL, et al. Gynecol Oncol 1995; 59:226-30.

Padmanabhan R, Samad PA. Reprod Toxicol 1999; 13:189-201.

Summary

Pregnancy Category: D
Lactation Category: U

- **Chlorambucil** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Chloramphenicol—(Amphicol; Archifen; Aromycetin; Bekamycetin; Biomycetin; Chlomin; Chloradrops; Chlornitromycin; Chlorocort; Chlorofair; Chloromycetin; Chloromyxin; Chloronitrin; Chloroptic; Cloramfeni; Cloramplast; Cloromicetin; Danmycetin; Denicol; Econochlor; Heminevrin; I-Chlor; Infa-Chlor; Isopto; Kemicetina; Leukomycin; Mychel; Newlolly; Ocu-Chlor; Ophthochlor; Optomycin; Spectro-Chlor; Sunchlormycin; Troymycetin; Vernacetin)

International Brand Name—Abefen (Colombia); Alchlor (Indonesia); Alphagram (Philippines); Anpechlor (Philippines); Aphrenil (Philippines); Aquamycetin (Germany); Archifen Eye (Thailand); Aristophen (Hong Kong); Aurachlor (Philippines); Beaphenicol (Malaysia); Biophenicol (Austria); Cadimycetin (South Africa); Cebenicol (France); Cetina (Mexico); Chemicetina (Italy); Chloment (Hong Kong); Chlomy (Japan); Chloracil (Thailand); Chloramex (South Africa); Chloramno (Thailand); Chloramphenicol (Czech Republic, Germany, Israel, South Africa); Chloramphenicol ''Agepha'' Augensalbe (Austria); Chloramphenicol ''Agepha'' Ohrentropfen (Austria); Chloramphenicol Faure, Ophthadoses (Switzerland); Chloramphenicol Ophthalmic (Czech Republic); Chloramphenicol POS (Germany); Chloramphenicol PW Ohrentropfen (Germany); Chloramphenicol RIT (Belgium); Chloramsaar N (Germany); Chlorcol (South Africa); Chlornicol (South Africa); Chlornitromycin (Bulgaria); Chloromycetin (Argentina, Canada, Chile, England, Finland, India, Ireland, Italy, Japan, Mexico, Philippines, Portugal, South Africa, Spain, Sweden, Switzerland, Taiwan, Venezuela); Chloromycetine (Belgium); Chloromycetin Eye Drops (New Zealand); Chloromycetin Eye Ointment (New Zealand); Chloromycetin Eye Preparations (Australia); Chlor-Oph (Hong Kong); Chloroptic (Greece, Ireland, Philippines, South Africa); Chlorphen (South Africa); Chlorsig (New Zealand, Philippines); Chlorsig Eye Preparations (Australia); Cloftal (Venezuela); Clorafen (Mexico); Cloramfeni Ofteno (Mexico); Cloramfeni Ungena (Mexico); Cloramicina (Costa Rica, Guatemala, Nicaragua, Panama); Cloranfenicol N.T. (Ecuador); Cloromisan (Mexico, Peru); Cloroptic (Colombia, Ecuador, Peru); Cogetine (Thailand); Colain (Indonesia); Colircusi Cloramfenicol (Spain); Colsancetine (Indonesia); Detreomycyna (Poland); Diochloram (Canada); Enclor (Malaysia); Enkacetyn (Indonesia); Epiphenicol (Israel); Esnicol (Philippines); Fen-Alcon (Philippines); Fenicol (Indonesia); Fenicol oft (Peru); Gemitin oftalmico (Chile); Genercin (Thailand); Gerafen (Philippines); Globenicol (Netherlands); Halomycetin Augensalbe (Austria); Helocetin (Korea); Hinicol (Taiwan); Ikamicetin (Indonesia); Iprobiot (Argentina); Isopto Fenicol (Argentina, Israel, New Zealand, Paraguay, Singapore, South Africa, Spain, Sweden, Uruguay); Isotic Salmicol (Indonesia); Kemicetin Augensalbe (Austria); Kemicetine (Greece, Hong Kong, India, Indonesia, Israel, Portugal, Thailand); Kemicetine Otologic (Philippines); Keromycin (Taiwan); Kloramfenicol (Denmark, Norway, Sweden); Kloramfenikol (Sweden); Kloramphenicol (Norway); Klorita (Finland); Lacroemol (Philippines); Levomycetin (Thailand); Minims Chloramphenicol (Israel); Minims Eye Drops (New Zealand); Miroptic (Colombia); New-Lylo (Taiwan); Ocuchloram (Korea); Ofenicol (Paraguay); Oftacin (Colombia); Oftan-Akvakol (Finland); Oleomycetin (Germany); Oliphenicol (Philippines); Ophtho-Chloram (Canada); Opticle (Korea); Optomycin (Philippines); Paraxin (Germany, India, Mexico, South Africa); Pentamycetin (Canada); Pharmacetin Otic (Thailand); Phenicol (Israel); Poenfenicol (Australia); Quemicitina (Argentina, Brazil, Colombia, Mexico); Reclor (India); Reco (Indonesia); Scanicol (Philippines); Silmycetin (Thailand); Spersanicol (Hong Kong, Korea, Malaysia, Philippines); Suismycetin (Puerto Rico); Sustachlor (Philippines); Unifenicol (Brazil); Vanafen Otologic (Thailand); Vanafen S (Singapore, Thailand); Vanmycetin (India); Vioclor (Uruguay); Vitamycetin (India); Xepanicol (Hong Kong, Malaysia); Ximex Avicol (Indonesia)

Drug Class

Antibiotics; Ophthalmics; Otics

Indications

Bacterial infections (gram-positive and -negative bacteria: *Rickettsia*, lymphogranuloma psittacosis, *V. cholerae, Salmonella typhi, H. influenzae*)

Mechanism

Bacteriostatic—interferes with protein synthesis

Dosage with Qualifiers

Bacterial infections—50-100mg/kg IV qd; max 100mg/kg/d
Rickettsial infections—50-100mg/kg IV qd; max 100mg/kg/d
Ophthalmic—1-2 gtts/eye q4-6×/d ×72h, then adjust to response

NOTE: ***chloramphenicol*** *is not considered a first-line therapy.*

- **Contraindications**—hypersensitivity to drug or class, pregnancy, infancy, mild infectious process
- **Caution**—hepatic failure, G6PD deficiency, bone marrow suppression

Maternal Considerations

There are no adequate reports or well-controlled studies of **chloramphenicol** in pregnant women. It has been used for the treatment of rickettsial disease, also known as scrub typhus. ***Side effects*** include bone marrow suppression, N/V, fever, rash, urticaria, pruritus, neuropathy, optic neuritis, blurred vision, confusion, headache, mental confusion, gray baby syndrome, thrombocytopenia, aplastic anemia, agranulocytosis, and pseudomembranous colitis.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **chloramphenicol** crosses the human placenta. Thiamphenicol does cross the rodent placenta. **Chloramphenicol** is not teratogenic in either humans or rodents. It does cause neonatal gray baby syndrome. Case reports document successful treatment of meningoencephalitis in neonates caused by maternal *Mycoplasma hominis.*

Breastfeeding Safety

There are no adequate reports or well-controlled studies in nursing women. **Chloramphenicol** enters human breast milk, but the levels achieved appear low, ranging from 0.54 to 2.84mg/L in women taking 250mg PO qid, and 1.75-6.10mg/L in women taking 500mg PO qid. The M:P ratio range is between 0.53 and 0.84. Yet, caution is advised in nursing mothers treated systemically due to the danger of gray baby syndrome in neonates.

Drug Interactions

May increase the INR of women on **warfarin.**
May potentiate hypoglycemic effects of sulfonylureas.
May increase the levels of **bosentan, entacapone, phenytoin, tacrolimus,** and **variconazole.**
May decrease levels of mycophenolate mofetil.

References

Amstey MS. Clin Infect Dis 2000; 30:237.
Czeizel AE, Rockenbauer M, Sorensen HT, Olsen J. Eur J Epidemiol 2000; 16:323-7.
Havelka J, Hejzlar M, Popov V, et al. Chemotherapy 1968; 13:204-11.
Knausz M, Niederland T, Dosa E, Rozgonyi F. J Med Microbiol 2002; 51:187-8.
Matsuda S. Biol Res Pregnancy Perinatol 1984; 5:57-60.
Phupong V, Srettakraikul K. Southeast Asian J Trop Med Public Health 2004; 35:358-60.
Stallings SP. Obstet Gynecol Surv 2001; 56:37-42.

Summary

Pregnancy Category: C
Lactation Category: U

- The risk of neonatal gray baby syndrome is a major negative factor for the systemic use of **chloramphenicol.**
- **Chloramphenicol** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Chlordiazepoxide—(Benzodiapin; Chlordiazachel; Chuichin; Kalbrium; Karmoplex; Libnum; Libritabs; Librium; Medilium; Poxi; Reposans; Restocalm; Ripolin; Vapine; Zenecin)

International Brand Name—Apo-Chlordiazepoxide (Canada); Balance (Japan); Benpine (Malaysia, Thailand); Cetabrium (Indonesia); Chlordiazepoxidum (Netherlands); Contol (Japan); Cozep (Thailand); Diazebrum (Argentina); Diazepina (Argentina); Disarim (Portugal); Elenium (Bulgaria, Czech Republic, Hungary, Poland); Eposal (Venezuela); Epoxide (Thailand); Equilibrium (India); Huberplex (Spain); Klopoxid (Denmark); Klorpo (Philippines); Lentotran (Portugal); Liberth (Korea); Librium (Denmark, England, Finland, Ghana, Hong Kong, Hungary, India, Ireland, Italy, Kenya, Malaysia, South Africa, Taiwan, Tanzania, Uganda, Zambia); Multum (Germany); Neo-Gnostorid (Greece); Normide (Spain); Nova-Pam (New Zealand); Novopoxide (Canada); Oasil (Greece); O.C.M. (Argentina); Omnalio (Spain); Paxium (Portugal); Psicofar (Italy); Psicosedin (Brazil); Radepur (Israel, Germany); Raysedan (Argentina); Reliberan (Italy); Retcol (Japan); Risachief (Japan); Risolid (Denmark, Finland); Seren (Italy); Sintesedan (Argentina); Tensinyl (Indonesia); Tropium (England)

Drug Class	Anxiolytics; Benzodiazepines
Indications	Anxiety, severe alcohol dependence
Mechanism	Enhances GABA effects and acts through benzodiazepine receptors
Dosage with Qualifiers	Anxiety—5-10mg PO tid or qid Severe anxiety—20-25mg PO tid or qid Alcohol withdrawal—50-100mg PO/IM/IV; max 300mg qd • **Contraindications**—hypersensitivity to drug or class • **Caution**—alcohol, hepatic or renal failure
Maternal Considerations	There are no adequate reports or well-controlled studies of **chlordiazepoxide** during pregnancy. The available information is insufficient to determine whether the potential benefits of benzodiazepines to the mother outweigh the risks to the fetus. High peak concentrations are avoided by dividing the daily dosage into 2 or 3 doses. ***Side effects*** include agranulocytosis, drowsiness, ataxia, confusion, rash, edema, menstrual irregularities, decreased libido, and extrapyramidal effects.
Fetal Considerations	Benzodiazepines are rapidly transferred across the placenta during early and late pregnancy, and 1st trimester exposure to this class of drugs has been linked to an increased risk of anomalies. While there are no well-controlled studies of **chlordiazepoxide** in human fetuses, the overall experience has been reassuring. In some 550 children followed up to 4y, there was no increase in either malformations or adverse effects on neurobehavioral development and IQ. Some infants exposed in the 3rd trimester exhibit either the floppy infant syndrome or marked neonatal withdrawal symptoms. Symptoms vary from mild sedation, hypotonia, and reluctance to suck to apneic spells, cyanosis, and impaired metabolic responses to cold stress, and may persist for hours to months after birth. This correlates with the pharmacokinetic and placental transfer of the benzodiazepines and their disposition in the neonate. **Chlordiazepoxide** retards motor development and physical maturation in mice. Rodent studies reveal no increased risk of congenital anomalies, IUGR, or adverse effects on lactation.
Breastfeeding Safety	There are no adequate reports or well-controlled studies of **chlordiazepoxide** in nursing women. The drug enters human

	breast milk in low concentrations such that only high clinical doses might be expected to exert an effect on the nursing newborn.
Drug Interactions	No clinically relevant interactions identified.
References	Czeizel AE, Rockenbauer M, Sorensen HT, Olsen J. Neurotoxicol Teratol 2004; 26:593-8. Gidal J, Acs N, Banhidy F, Czeizel A. Toxicol Ind Health 2008; 24:41-51. Iqbal MM, Sobhan T, Ryals T. Psychiatr Serv 2002; 53:39-49. Kanto JH. Drugs 1982; 23:354-80. McElhatton PR. Reprod Toxicol 1994; 8:461-75.
Summary	**Pregnancy Category: D** **Lactation Category: S** (likely) • **Chlordiazepoxide** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk. • Benzodiazepines should be used as monotherapy at the lowest effective dose for the shortest possible duration. • High peak concentrations are avoided by dividing the daily dosage into 2 or 3 doses.

Chlorhexidine—(Peridex; PerioGard; Plakicide; Savacol)

International Brand Name—AB Antiseptico (Paraguay); Alcloxidine (Israel); Bactoscrub (Israel); Bactosept Concentrate (Israel); Blend-A-Med (Germany); Bucoglobin (Uruguay); Chlorhex (Thailand); Chlorhexamed (Belgium, Germany, Switzerland); Chlorhexidine Mouthwash (Australia); Chlorhexidine Obstetric Lotion (Australia); Chlorhexidinium (Poland); Chlorohex gel (Australia); Chlorohex gel Forte (Australia); Chlorohex Mouth Rinse (Australia); Cleardent (Israel); Corsodyl (Italy, Portugal, Switzerland); Dosiseptine (France); Exitane (South Africa); Exoseptoplix (France); Fectin (Indonesia); Hexadent (Korea); Hexol (Thailand); Hibiclens Solution (New Zealand); Hibident (Austria, Belgium, Netherlands); Hibidil (South Africa); Hibigel (Netherlands); Hibiguard (Belgium); Hibiscrub (Belgium, France, Hong Kong, Indonesia, Netherlands, Spain, Taiwan, Thailand); Hibisol (Hong Kong, Indonesia, Israel, Malaysia, South Africa); Hibitan (Korea); Hibitane (Belgium, Denmark, Finland, France, Hong Kong, Indonesia, Israel, South Africa, Sweden); Hibitane Concentrate (Malaysia, Taiwan, Thailand); Hibitane Cream (Greece); Hibitane Dental (Norway, Sweden); Hibitane Pastillas (Spain); Hibitane Solution (Greece, New Zealand, Spain); Hidine (Thailand); Improved Phisohex (Philippines); Klorheksidos (Finland); Klorhexidin (Norway); Klorhexol (Finland); Lemocin CX (Germany); Peridex (Canada); Perio Chip (Israel); Periodentix (Israel); Perioxidin (Mexico); Savlon (Spain); Septalone (Israel); Septol (Israel); Trachisan (Germany)

Drug Class	Anti-infectives, topical
Indications	Gingivitis, cleansing of the birth canal to prevent infection
Mechanism	Antibacterial
Dosage with Qualifiers	Gingivitis, infection prevention—15ml PO, swish/spit bid • **Contraindications**—hypersensitivity to drug or class • **Caution**—unknown
Maternal Considerations	While there are no adequate reports or well-controlled studies in pregnant women, **chlorhexidine** is considered safe for cleansing of the birth canal, and may be as effective as **ampicillin** for the prevention of neonatal group B streptococcus. Some studies suggest its use during labor may also decrease HIV transmission. It does not, however, reduce the incidence of postpartum endometritis. ***Side effects*** include staining of teeth, taste change, and salivary gland inflammation.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **chlorhexidine** crosses the

human placenta. Exposure to **chlorhexidine** during birth is not associated with any increase in neonatal mortality rate due to sepsis, fever, poor feeding, apnea, or dyspnea in newborns.

Breastfeeding Safety — It is not known whether **chlorhexidine** enters human milk. While there are no adequate reports or well-controlled studies in nursing women, the quantity of drug absorbed systemically during a brief encounter is likely minimal.

Drug Interactions — No clinically significant interactions identified.

References

Facchinetti F, Piccinini F, Mordini B, Volpe A. J Matern Fetal Neonatal Med 2002; 11:84-8.
Gaillard P, Mwanyumba F, Verhofstede C, et al. AIDS 2001; 15:389-96.
Goldenberg RL, McClure EM, Saleem S, et al. Obstet Gynecol 2006; 107:1139-46.
Kaihura CT, Ricci L, Bedocchi L, et al. Acta Biomed Ateneo Parmense 2000; 71(Suppl 1):567-71.
Saleem S, Reza T, McClure EM, et al. Obstet Gynecol 2007; 110:977-85.
Stade B, Shah V, Ohlsson A. Cochrane Database Syst Rev 2004; (3):CD003520.
Stray-Pedersen B, Bergan T, Hafstad A, et al. Int J Antimicrob Agents 1999; 12:245-51.
Sweeten KM, Eriksen NL, Blanco JD. Am J Obstet Gynecol 1997; 176:426-30.

Summary

Pregnancy Category: B
Lactation Category: S (likely)

- **Chlorhexidine** is safe to use for cleansing of the birth canal; its use during labor may decrease group B streptococcus and HIV transmission.

Chloroquine—(Aralen; Aralen Injection; Chlorofoz; Dichinalex; Lariago; Quinalan)

International Brand Name—Anoclor (South Africa); Aralen Phosphate (Canada, Ecuador, Mexico, Peru, Philippines, Portugal); Arechin (Poland); Avloclor (England, Indonesia, Ireland, Israel, South Africa); Cadiquin (South Africa); Chlorofoz (Philippines); Chloroquini Diphosphas (Netherlands); Chlorquin (Australia); Cidanchin (Spain); Clo-Kit Junior (India); Delagil (Czech Republic, Hungary, Puerto Rico); Diclokin (Brazil); Diroquine (Thailand); Emquin (India); Genocin (Thailand); Heliopar (Finland); Klorokinfosfat (Denmark); Lagaquin (Puerto Rico, South Africa, Switzerland); Malaquin (Israel); Malarex (Denmark, Indonesia, Israel, Malaysia, Philippines); Malarivon (Israel, Puerto Rico); Malaviron (South Africa); Maliaquine (Thailand); Maquine (Israel); Melubrin (India); Mexaquin (Indonesia); Mirquin (South Africa); Nivaquine (Indonesia); Nivaquine DP (Indonesia); P Roquine (Thailand); Repal (Colombia); Resochin (Austria, Germany, India, Indonesia, Israel, Netherlands, South Africa, Spain, Switzerland); Resochina (Portugal)

Drug Class — Antiprotozoals

Indications — Malaria prophylaxis and treatment, amebiasis

Mechanism — Unknown

Dosage with Qualifiers

Malaria prophylaxis—500mg PO qw; begin 2w before travel and continue until 8w postexposure (500mg phosphate = 300mg base)
Malaria treatment—begin 1g PO ×1, then 500mg PO 6-8h later, then 500mg PO qd ×2
Amebiasis—begin 1g qd ×2, then 500mg PO qd ×2-3w

- **Contraindications**—hypersensitivity to drug or class, porphyria, retinal field changes
- **Caution**—GI disorder, neurologic disease, hepatic failure

Maternal Considerations

Chloroquine is closely related to **hydroxychloroquine** and has similar uses. A body of clinical experience suggests **chloroquine** is safe during pregnancy and improves outcome in women with active disease. In one study of 96 women with active malaria, **chloroquine** (10mg/kg) was given at time 0 and 24h and again at 48h (5mg/kg). The T_{max} after the first dose was 3.5h, whereas plasma concentrations (CP_{max}) at 2, 28, and 52h were 204.36, 343.51, and 257.04ng/ml respectively. There was total parasitemia clearance before the end of 96h in all the subjects. In another study, the conversion of **chloroquine** to its major metabolite, desethylchloroquine, was increased in the 3rd trimester, suggesting the need for caution when considering the use of higher doses. Current study suggests there are more effective treatment options. **Chloroquine** is also used as an adjunct for the treatment of SLE in women who have failed to respond to first-line agents. Recent studies suggest it may have a role in the treatment of HIV, and thus may have a role in HIV-infected breastfeeding women. While prolonged treatment with quinine-type drugs is associated with pigmentary retinopathy, the risk is not increased during pregnancy. ***Side effects*** include agranulocytosis, thrombocytopenia, aplastic anemia, dermatitis, ototoxicity, vomiting, dizziness, diarrhea, and pruritus.

Fetal Considerations

Chloroquine crosses the placenta, achieving an F:M ratio approximating 0.7-0.8. Fetal retinopathy was noted in some animal studies, but more recent investigation casts doubt on the association and suggests it is safe during the 1st trimester. No increase in spontaneous abortion or major birth defects is reported in humans.

Breastfeeding Safety

Chloroquine enters human breast milk, achieving an M:P ratio ranging from 0.268 to 0.462. Some studies suggest it may actually be concentrated. However, it is generally considered compatible with breastfeeding.

Drug Interactions

Antacids and kaolin may reduce absorption; an interval of at least 4h between intake of these agents should be observed.
Cimetidine inhibits **chloroquine** metabolism, increasing its plasma level.
In a study of healthy volunteers, **chloroquine** reduced **ampicillin** bioavailability. Wait at least 2h between drugs.
Chloroquine may increase **cyclosporine** levels. Monitor closely.

References

Akintonwa A, Gbajumo SA, Mabadeje AF. Ther Drug Monit 1988; 10:147-9.
Boelaert JR, Piette J, Sperber K. J Clin Virol 2001; 20:137-40.
Chukwuani MC, Bolaji OO, Onyeji CO, et al. Trop Med Int Health 2004; 9:601-5.
Fakeye TO, Fehintola FA, Ademowo OG, Walker O. West Afr J Med 2002; 21:286-7.
Garner P, Gulmezoglu AM. Cochrane Database Syst Rev 2006; (4):CD000169.
Klinger G, Morad Y, Westall CA, et al. Lancet 2001; 358:813-4.
Koren G. Can Fam Physician 1999; 45:2869-70.
McGready R, Thwai KL, Cho T, et al. Trans R Soc Trop Med Hyg 2002; 96:180-4.
Motta M, Tincani A, Faden D, et al. Lancet 2002; 359:524-5.
Orton LC, Dmari AA. Cochrane Database Syst Rev 2008 Oct 8; (4):CD004912.

Summary	**Pregnancy Category: C** **Lactation Category: S** • **Chloroquine** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Chlorothiazide—(Azide; Chlothin; Diurazide; Diuret; Diuril; Saluretil)

International Brand Name—Chlotride (Denmark, Japan, Netherlands, Taiwan); Saluric (England)

Drug Class	Diuretics; Thiazides
Indications	Hypertension, peripheral edema
Mechanism	Inhibits resorption of sodium and chloride
Dosage with Qualifiers	Edema—500-1000mg PO qd or bid Hypertension—250-500mg PO qd or bid *NOTE: may be combined with* ***methyldopa*** *or* ***reserpine.*** • **Contraindications**—hypersensitivity to drug or class, electrolyte imbalances • **Caution**—unknown
Maternal Considerations	Though popular among obstetricians for the treatment of edema and weight gain in the 1970s, there are no adequate reports or well-controlled studies of **chlorothiazide** in pregnant women. Physiologic edema should not be treated. Thiazide diuretics may be diabetogenic. Severe electrolyte imbalances in both mother and newborn are reported. Hemorrhagic pancreatitis is also reported after thiazide exposure. ***Side effects*** include renal failure, hyponatremia, hypochloremia, hypomagnesemia, glucose intolerance, hyperlipidemia, and photosensitivity.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. Thiazide diuretics readily cross the placenta. There is no clear evidence **chlorothiazide** increases the risk of malformation. However, older studies suggest thiazide diuretics may decrease placental perfusion by preventing normal plasma expansion and increase the risk of IUGR. Thrombocytopenia and hypoglycemia are major risks. The mechanism for the thrombocytopenia is unknown. Fetal bradycardia following exposure is the result of electrolyte imbalance (hypokalemia).
Breastfeeding Safety	Thiazide diuretics enter human breast milk in low concentrations. While there are no adequate reports or well-controlled studies in nursing women, they are generally considered compatible with breastfeeding.
Drug Interactions	Alcohol, barbiturates, and narcotics may potentiate orthostatic hypotension. May increase the hypoglycemia associated with oral hypoglycemic agents and **insulin.** Both **cholestyramine** and **colestipol** may bind thiazide diuretics and reduce their absorption. Corticosteroids and ACTH may increase electrolyte depletion.

May increase responsiveness to skeletal muscle relaxants and nondepolarizing neuromuscular blockers (e.g., **tubocurarine**).
Diuretic agents reduce the renal clearance of **lithium** and create a high risk of **lithium** toxicity.
NSAIDs may reduce the diuretic, natriuretic, and antihypertensive effects of loop, potassium-sparing, and thiazide diuretics.

References

Beermann B, Fahraeus L, Groschisky-Grind M, Lindstrom B. Gynecol Obstet Invest 1980; 11:45-8.
Finnerty FA, Buchholz JH, Tuckman J. JAMA 1958; 166:1414.
George JD, Price CJ, Tyl RW, et al. Fundam Appl Toxicol 1995; 26:174-80.
Goldman JA, Neri A, Ovadia J, et al. Am J Obstet Gynecol 1969; 105:556-60.
Hall DR, Odendaal HJ. Int J Gynaecol Obstet 1998; 60:63-4.
Pritchard JA, Waley PJ. Am J Obstet Gynecol 1961; 81:1241-4.
Rodriguez SU, Leikin SL, Hiller MC. N Engl J Med 1964; 270:881-4.
Sibai BM, Grossman RA, Grossman HG. Am J Obstet Gynecol 1984; 150:831-5.

Summary

Pregnancy Category: D
Lactation Category: S

- **Chlorothiazide,** like other thiazides, poses a risk to the perinate and is generally contraindicated during pregnancy except for the treatment of CHF.

Chlorotrianisene—(Estregur; Tace)

International Brand Name—None identified.

Drug Class

Antineoplastics, hormone modifying; Estrogens

Indications

Severe vasomotor symptoms, atrophic vaginitis

Mechanism

Estrogen receptor agonist

Dosage with Qualifiers

Severe vasomotor symptoms—12-25mg PO qd; treat for 30d
Atrophic vaginitis—12-25mg PO qd; treat for 30d

- **Contraindications**—hypersensitivity to drug or class, pregnancy, breast carcinoma, hepatic carcinoma, thromboembolic disorder, smoker over 35y old
- **Caution**—hypertension, diabetes mellitus, hepatic dysfunction, hyperlipidemia, depression

Maternal Considerations

Chlorotrianisene is an estrogen analog that was and may still be used in some countries for the suppression of lactation. It is ineffective. **Chlorotrianisene** increases the risk of thromboembolism during pregnancy and postpartum. It is generally considered contraindicated during pregnancy.
Side effects include DVT.

Fetal Considerations

There are no adequate reports or well-controlled studies in pregnant women. It is unknown whether **chlorotrianisene** crosses the human placenta. There are suboptimal data linking oral contraceptive use with the VACTERL syndrome.

Breastfeeding Safety

There is no published experience in nursing women. It is unknown whether **chlorotrianisene** enters human breast milk.

	The use of estrogen analogs for lactation suppression has been discontinued due to poor efficacy and the risk of thrombosis.
Drug Interactions	No clinically significant interactions identified.
References	Niebyl JR, Bell WR, Schaaf ME, et al. Am J Obstet Gynecol 1979; 134:518-22. Phillips WP. J Ark Med Soc 1975; 72:163-7.
Summary	**Pregnancy Category: D** **Lactation Category: NS** • **Chlorotrianisene** is generally considered contraindicated during pregnancy and lactation. • Treated nonpregnant women with an intact uterus should be monitored closely for signs of endometrial, ovarian, and breast cancers, and appropriate diagnostic measures taken to rule out malignancy.

Chlorpheniramine—(Allerkyn; Chlor-Trimeton; Cloroetano; Clorten; Comin; Cophene-B; Corometon; Evenin; Histacort; Histex; Kelargine; Methyrit; Polaramine; Polaronil; Reston)

International Brand Name—Ahiston (Israel); Alerfin (Paraguay); Alergical (Peru); Alergidryl (Argentina); Alergitrat (Argentina); Aller (Malaysia); Allerfin (South Africa); Allergex (South Africa); Allergin (Japan, Thailand); Allermin (Taiwan); Allerphen (Singapore); Analerg (Uruguay); Anaphyl (Israel); Antamin (Philippines); Anti-Hist (Ireland); Antihistamin (Peru); Apomin (Hong Kong); Baromonic (Philippines); Cadistin (India, South Africa); Chlometon (Japan); Chloramine (Malaysia); Chlorleate (Thailand); Chlorpheniramine DHA (Hong Kong); Chlorpheno (Thailand); Chlorphenon (Indonesia); Chlorpyrimine (Hong Kong, Malaysia, Thailand); Chlortrimeton (South Africa); Chlor-Tripolon (Canada); Cloroalergan (Peru); Clorotrimeton (Colombia, Peru, Venezuela); Cloro Trimeton (Argentina); Cloro-Trimeton (Costa Rica, Dominican Republic, El Salvador, Guatemala, Honduras, Mexico, Nicaragua, Panama); Cohistan (Indonesia, Thailand); Com-Trimeton (Taiwan); Fenaler (Dominican Republic, El Salvador, Guatemala, Honduras, Nicaragua, Panama); Histafen (New Zealand); Histal (Puerto Rico); Histar (Japan); Histat (Israel); Histatapp (Thailand); Histaton (Peru); Histavil (Israel); Histin (Israel); Istamex (Greece); Istaminol (Greece); Kobis (Japan); Losmanin (Greece); Orphen (Indonesia); Pehachlor (Indonesia); Phenamine (Korea); Pirafene (Bulgaria); Piriton (Ireland, Israel, Malaysia, Puerto Rico, Thailand); Prof-N-4 (Argentina); Reston M (Japan); Sprinsol (Hong Kong); Trimeton (Italy); Trimeton Repetabs (Mexico); Valemine (Philippines)

Drug Class	Allergy; Antihistamine, 1st-generation
Indications	Allergic rhinitis, anaphylaxis
Mechanism	Antagonizes cholinergic (H_1) receptors
Dosage with Qualifiers	Allergic rhinitis—4mg PO q4-6h Anaphylaxis—5-20mg SC/IM q6-12h prn *NOTE: often combined with* ***hydrocodone, phenylephrine, phenylpropanolamine,*** *or* ***pseudoephedrine.*** • **Contraindications**—hypersensitivity to drug or class • **Caution**—GI obstruction, sedative
Maternal Considerations	There are no adequate reports or well-controlled studies of **chlorpheniramine** in pregnant women, and its safety during pregnancy is not established. However, it is widely available in OTC preparations and has not to date been implicated in adverse effects during pregnancy. In general, 1st-generation antihistamines are preferred to later generations because of the longer use experience. ***Side effects*** include hypotension, dry mouth, N/V, and constipation.

Fetal Considerations

Though there are no adequate reports or well-controlled studies in human fetuses, epidemiologic study suggests **chlorpheniramine** is not a human teratogen. It is unknown whether **chlorpheniramine** crosses the human placenta. However, H_1 receptors are specifically expressed in syncytiotrophoblast cells of human placenta. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically. In rodents, **chlorpheniramine** stimulates glycosaminoglycan alterations leading to palatal mesenchyme and cleft palate malformation.

Breastfeeding Safety

There is no published experience with **chlorpheniramine** in nursing women. Because preterm and term neonates can have adverse reactions to antihistamines, it should probably be avoided in the 3rd trimester.

Drug Interactions

Azelastine and **dexmedetomidine** may increase the risk of CNS depression when taken with **chlorpheniramine**.
Pramlintide may delay gastric emptying if combined with **chlorpheniramine.**

References

Brinkley LL, Morris-Wiman J. Am J Anat 1986; 176:379-89.
Matsuyama K, Ichikawa T, Nitta Y, et al. J Pharmacol Sci 2006; 102:331-7.
Mazzotta P, Loebstein R, Koren G. Drug Saf 1999; 20:361-75.
The American College of Obstetricians and Gynecologists (ACOG) and The American College of Allergy, Asthma and Immunology (ACAAI). Ann Allergy Asthma Immunol 2000; 84:475-80.
Wilk AL, King CT, Pratt RM. Teratology 1978; 18:199-209.
Young GL, Jewell D. Cochrane Database Syst Rev 2000; (2):CD000027.

Summary

Pregnancy Category: B
Lactation Category: NS (possibly)

- **Chlorpheniramine** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Chlorpromazine—(Artomin; Fenactil; Klorazin; Megaphen; Promacid; Protran; Romazine; Sonazine; Thorazine)

International Brand Name—Ampliactil (Argentina); Aspersinal (Argentina); Bellacina (Paraguay); Cepezet (Indonesia); Chlomazine (Japan); Chloractil (England); Chlorazin (Bulgaria, Switzerland); Chlormazine (Thailand); Chlorpromanyl (Canada); Chlorpromed (Thailand); Clonazine (Ireland); Clorpromaz (Brazil); Clozine (India); Contomin (Japan); Duncan (Thailand); Esmino (Japan); Fenactil (Poland); Hibernal (Hungary, Sweden); Klorproman (Czech Republic, Finland); Klorpromazin (Finland); Laractyl (Philippines); Largactil (Austria, Belgium, Canada, Chile, Costa Rica, Czech Republic, Denmark, Dominican Republic, Ecuador, El Salvador, England, Finland, France, Greece, Guatemala, Honduras, Hong Kong, Indonesia, Iran, Israel, Italy, Jordan, Mexico, Netherlands, Norway, Panama, Peru, Portugal, Puerto Rico, Spain, Switzerland, Uruguay, Venezuela); Largactil Forte (New Zealand); Matcine (China, Malaysia, Thailand); Megatil (India); Neomazine (Korea); Plegomazine (Iraq, Puerto Rico, Syria); Promactil (Indonesia); Promexin (Japan); Propaphenin (Germany); Prozil (Denmark); Prozin (Italy); Psynor (Philippines); Taroctyl (Israel); Thorazine (Philippines); Winsumin (Taiwan); Wintermin (Japan, Taiwan)

Drug Class

Antiemetics/antivertigo agents; Antipsychotics; Phenothiazines; Tranquilizers

Indications

Psychosis, N/V, hiccups, tetanus, porphyria (acute)

Mechanism

Unknown; believed to antagonize the D_2 dopamine receptors

Dosage with Qualifiers

Psychosis—200-800mg IM qd; divide dose tid or qid
Nausea—10-25mg PO q4-6h
Hiccups—25-50mg PO tid or qid; if no response PO, may be given IM/IV
Tetanus—25-50mg IM/IV q6-8h
Porphyria (acute)—25-50mg IM tid or qid

- **Contraindications**—hypersensitivity to drug or class, sedation, bone marrow depression, Parkinson's disease
- **Caution**—hepatic failure, hypotension, glaucoma

Maternal Considerations

There are no adequate reports or well-controlled studies in pregnant women. **Chlorpromazine** seems safe and effective when used for the preceding indications during pregnancy.
Side effects include seizure, thrombocytopenia, agranulocytosis, and neuroleptic malignant syndrome.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. **Chlorpromazine** rapidly crosses the placenta, and an extrapyramidal syndrome can occur in newborns of women given **chlorpromazine** during labor. There is no evidence **chlorpromazine** is a human teratogen. Rodent studies are also reassuring, though learning and behavioral abnormalities are reported in some studies. The injection of **chlorpromazine** into each rat uterine horn significantly reduces the number of implantation sites.

Breastfeeding Safety

There are no adequate reports or well-controlled studies in nursing women. **Chlorpromazine** is excreted into human breast milk, though the kinetics remain to be elucidated. The occasional dose of **chlorpromazine** is probably compatible with breastfeeding.

Drug Interactions

Chlorpromazine interacts with many drugs, and the list here is not inclusive. Each individual drug should be checked before administering with **chlorpromazine.**
May cause QT prolongation and arrythmias when combined with multiple agents, including **abarelix, amiodarone, apomorphine, azithromycin, cinacalcet, ciprofloxacin, cisapride, clarithromycin, dofetilide, dolasetron, duloxetine, erythromycin, fluconazole, ibutilide, imatinib, lopinavir, methadone,** palonosetron, **pimozide, pindolol, posaconazole, ritonavir, sotalol, tacrolimus, tamoxifen,** and class IA antiarrythmics.
May antagonize **dopamine** and **epinephrine** agonists.
Lithium may increase the risk of extrapyramidal symptoms.
May diminish the effect of oral anticoagulants.
May lower the seizure threshold; dosage adjustments of anticonvulsants may be necessary.
Use with **propranolol** may increase the plasma levels of both drugs.
Thiazide diuretics may accentuate the orthostatic hypotension that may occur with phenothiazines.
Drugs that lower the seizure threshold, including phenothiazine derivatives, should not be used with metrizamide.
Should be discontinued at least 48h before myelography, should not be resumed for at least 24h, and should not be used for the control of N/V occurring either before or after myelography with **metrizamide**.

References

Finnerty M, Levin Z, Miller LJ. Am J Psychiatry 1996; 153:261-3.
Hammond JE, Toseland PA. Arch Dis Child 1970; 45:139-40.
Hill RM, Desmond MM, Kay JL. J Pediatr 1966; 69:589-95.
Yang RZ, Xie XY, Sun HY, et al. Contraception 1998; 58:315-20.
Yoshida K, Smith B, Craggs M, Kumar R. Psychol Med 1998; 28:81-91.

Summary

Pregnancy Category: B
Lactation Category: NS (possibly)
- **Chlorpromazine** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Chlorpropamide—(Arodoc; Chlordiabet; Chlorprosil; Diabenil; Diabinese; Diamide; Diatanpin; Dibetes; Gliconorm; Glycermin; Glymese; Insilange; Meldian; Mellitos; Milligon; Norgluc; Normoglic; Orodiabin; Promide; Tanpinin)

International Brand Name—Abemide (Japan, Taiwan); Anti-D (Malaysia); Apo-Chlorpropamide (Canada); Arodoc C (Japan); Chlomide (Singapore); Chlormide (Japan); Chlorpropamide Medochemie (Malaysia); Copamide (India); Dabinese (Venezuela); Deavynfar (Mexico); Diabeedol (Thailand); Diabemide (Italy, South Africa); Diabenese (Argentina, Belgium, Canada, Colombia, Costa Rica, Cyprus, Ecuador, Egypt, El Salvador, England, Finland, Greece, Guatemala, Honduras, Iran, Ireland, Israel, Italy, Mexico, Nicaragua, Norway, Panama, Peru, Portugal, Puerto Rico, Spain, Sudan, Switzerland); Diabexan (Italy); Diabiclor (Mexico); Diabines (Sweden); Diabinese (Brazil, Chile, Hong Kong, Indonesia, Israel, Korea, Peru, Philippines, Poland, Thailand, Uruguay); Diabitex (South Africa); Dibecon (Thailand); Glicoben (Brazil); Glycemin (Thailand); Hypomide (South Africa); Insilange C (Japan); Insogen (Mexico); Mellitos C (Japan); Melormin (Finland); Neo-Toltinon (Taiwan); Propamide (Malaysia, Thailand); Tesmel (Indonesia); Trane (Argentina)

Drug Class

Antidiabetic agents; Sulfonylureas

Indications

Diabetes mellitus type II, diabetes insipidus

Mechanism

Stimulates release of insulin from pancreatic islet beta cell

Dosage with Qualifiers

Diabetes mellitus type II—100-500mg PO qd
Diabetes insipidus—200-500mg PO qd

- **Contraindications**—hypersensitivity to drug or class, diabetic ketoacidosis, sulfonamides allergy
- **Caution**—hepatic or renal dysfunction

Maternal Considerations

There are no adequate reports or well-controlled studies of **chlorpropamide** in pregnant women. Current study suggests that some modern oral hypoglycemic drugs are safe and useful, not only later in pregnancy but also in the 1st trimester, providing excellent control of blood glucose. The treatment of women with gestational diabetes after delivery does not appear to alter the timing or reduce the ultimate frequency of type II diabetes. **Chlorpropamide** and other sulfonylureas may provoke an **antabuse**-like reaction if the patient consumes alcohol. There are alternative agents with minimal placental transport that are better candidates for maternal therapy. Older reports note its use for diabetes insipidus. Presently, **DDAVP** is preferred for this indication.
Side effects include hypoglycemia, agranulocytosis, anemia, thrombocytopenia, cholestatic jaundice, hepatic dysfunction, blurred vision, N/V, weight gain, pruritus, and photosensitivity.

Fetal Considerations

Chlorpropamide crosses the placenta and has a long t/2. It significantly reduces birth weight and perinatal mortality in the offspring of diabetic women without increasing the incidence of birth defects. More recent studies suggest that some oral hypoglycemic agents are relatively safe during pregnancy with no increased risk of macrosomia, hypoglycemia, and lung

immaturity, though there are alternative agents with less placental transfer. Rodent teratogenicity studies have not been conducted.

Breastfeeding Safety

While there are no adequate studies in nursing mothers, **chlorpropamide** enters the breast milk, achieving an M:P ratio of 0.2, and neonatal hypoglycemia has been reported.

Drug Interactions

Hypoglycemia may be potentiated by NSAIDs and other drugs that are highly protein bound, such as salicylates, sulfonamides, **chloramphenicol, probenecid,** coumarins, MAOIs, and β-adrenergic antagonists.
Thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, **phenytoin,** nicotinic acid, sympathomimetics, calcium channel blocking drugs, and **isoniazid** may decrease the hypoglycemic effect. Observe closely for hypoglycemia when such drugs are withdrawn from a patient receiving **chlorpropamide.**
Barbiturates may be prolonged by therapy with **chlorpropamide.**
A potential interaction between oral **miconazole** and oral hypoglycemic agents leading to severe hypoglycemia has been reported. Whether this interaction also occurs with the IV, topical, or vaginal preparations of **miconazole** is not known.

References

Coetzee EJ, Jackson WP. S Afr Med J 1984; 65:635-7.
Elliott BD, Schenker S, Langer O, et al. Am J Obstet Gynecol 1994; 171:653-60.
Langer O, Conway DL, Berkus MD, et al. N Engl J Med 2000; 343:1134-8.
Onegova RF. Probl Endokrinol (Mosk) 1978; 24:67-70.
Robinson AG, Verbalis JG. Curr Ther Endocrinol Metab 1994; 5:1-6.
Stowers JM, Sutherland HW, Kerridge DF. Diabetes 1985; 34(Suppl 2):106-10.

Summary

Pregnancy Category: C
Lactation Category: NS

- **Chlorpropamide** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.
- There are alternative agents with less placental transport that are better candidates for maternal therapy.

Chlorthalidone—(Hydro; Hygroton; Servidone; Thalidone; Thalitone; Urolin)

International Brand Name—Apo-Chlorthalidone (Canada); Clortalil (Brazil); Higroton (Brazil, Ecuador, Mexico, Venezuela); Higrotona (Spain); Hydro-Long (Germany); Hygroton (Argentina, Indonesia, Japan, Malaysia); Hygroton 50 (South Africa); Hypertol (Finland); Hythalton (India); Igroton (Italy); Urandil (Czech Republic)

Drug Class

Diuretics; Thiazides

Indications

Hypertension, peripheral edema

Mechanism

Inhibits sodium and chloride reabsorption in the distal convoluted tubules

Dosage with Qualifiers

Hypertension—25-100mg PO qd
Edema—begin 30-60mg PO qd; max 120mg/d

*NOTE: may also be combined with **clonidine** or **reserpine.***

- **Contraindications**—hypersensitivity to drug or class, anuria, sensitivity to sulfonamides
- **Caution**—hepatic or renal dysfunction, and bronchial asthma

Maternal Considerations

Chlorthalidone is an oral diuretic with a prolonged action (48-72h). There are no adequate reports or well-controlled studies in pregnant women. Physiologic edema should not be treated. Thiazide diuretics may be diabetogenic. Severe electrolyte imbalances are reported in both mother and newborn. Hemorrhagic pancreatitis is also reported after thiazide exposure. ***Side effects*** include aplastic anemia, agranulocytosis, thrombocytopenia, exfoliative dermatitis, anorexia, N/V, hypokalemia, constipation, vertigo, dizziness, purpura, photosensitivity, leukopenia, rash, hyperglycemia, pancreatitis, and orthostatic hypotension.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. **Chlorthalidone** crosses the placenta, achieving an F:M ratio approximating 0.15. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically.

Breastfeeding Safety

While **chlorthalidone** is excreted into human breast milk, the pharmacokinetics remain to be clarified. It is generally considered compatible with breastfeeding.

Drug Interactions

May add to or potentiate the action of other antihypertensive drugs.
Insulin requirements may be variably altered in diabetic patients. The dose of oral hypoglycemic agents may need to be increased.
May increase the responsiveness to **tubocurarine.**
May decrease arterial responsiveness to NE.
Lithium renal clearance is reduced, increasing the risk of **lithium** toxicity.

References

Mulley BA, Parr GD, Pau WK, et al. Eur J Clin Pharmacol 1978; 13:129-31.

Summary

Pregnancy Category: B
Lactation Category: S (likely)
- Thiazide diuretics are rarely indicated during pregnancy and lactation.
- **Chlorthalidone** should be given during pregnancy and lactation only if the potential benefit outweighs the potential risks to the perinate.

Chlorzoxazone—(Biomioran; Eze D.S.; Myoforte; Paraflex; Parafon Forte DSC; Relaxazone; Relax-ds; Remular; Strifon Forte DSC)

International Brand Name—Escoflex (Switzerland); Klorzoxazon (Denmark); Matalmin (Taiwan); Muscol (Taiwan); Myoflexin (Hungary); Paraflex (South Africa); Parafon DSC (India); Parafon Forte (Thailand); Prolax (Taiwan); Salalin (Taiwan); Solaxin (Hong Kong, Indonesia, Malaysia)

Drug Class

Muscle relaxants

Indications

Muscle spasms

Mechanism	Depresses CNS activity
Dosage with Qualifiers	Muscle spasm—250-750mg PO tid or qid *NOTE: should be prescribed in conjunction with other treatment modalities, such as physical therapy.* • **Contraindications**—hypersensitivity to drug or class, alcohol consumption • **Caution**—hepatic or renal failure
Maternal Considerations	There are no adequate reports or well-controlled studies in pregnant women. **Chlorzoxazone** should not be taken if there is an allergy to any skeletal muscle relaxant. ***Side effects*** include N/V, diarrhea, loss of appetite, headache, severe weakness, unusual increase in sweating, fainting, breathing difficulties, irritability, convulsions, feeling of paralysis, and loss of consciousness.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **chlorzoxazone** crosses the human placenta. Rodent teratogenicity studies have not been performed.
Breastfeeding Safety	There is no published experience in nursing women. It is unknown whether **chlorzoxazone** enters human breast milk.
Drug Interactions	No clinically significant interactions identified.
References	There is no published experience in pregnancy or during lactation.
Summary	**Pregnancy Category: C** **Lactation Category: U** • **Chlorzoxazone** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk. • It should be combined with other measures to relieve discomfort.

Cholera vaccine

Drug Class	Vaccines
Indications	Travel to a cholera-endemic area
Mechanism	Active immunity
Dosage with Qualifiers	Cholera susceptibility—0.5ml intradermal q1w ×2 doses, then q1mo ×2 doses; boosters 0.3-0.5ml after 5y • **Contraindications**—hypersensitivity to drug or class, any acute illness • **Caution**—avoid IV injection
Maternal Considerations	**Cholera vaccine** is a sterile suspension of killed *V. cholerae.* There are no adequate reports or well-controlled studies of **cholera vaccine** in pregnant women. ***Side effects*** include erythema, induration, pain, and tenderness at the site of injection; malaise, headache, and mild to moderate temperature elevations that may persist for 1-2d.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. It is likely **cholera vaccine**–induced IgG crosses

the human placenta. There is no evidence of fetal harm. Rodent studies have not been performed.

Breastfeeding Safety — There are no adequate reports or well-controlled studies in nursing women. **Cholera vaccine**–induced antibodies enter human breast milk.

Drug Interactions — Some data suggest that giving **cholera vaccine** and **yellow fever vaccine** within 3w of each other may decrease antibody levels for both. However, there is no evidence that protection from either disease is diminished.When feasible, **cholera vaccine** and **yellow fever vaccine** should be administered at least 3w apart.

References — Hahn-Zoric M, Carlsson B, Jalil F, et al. Scand J Infect Dis 1989; 21:421-6.

Summary —
Pregnancy Category: C
Lactation Category: S
- **Cholera vaccine** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Cholestyramine—(Choles; Cholybar; Cuemid; Questran; Questran Light)

International Brand Name—Choles (Taiwan); Cholesthexal (Germany); Chol-Less (Israel); Colestepril (Colombia); Colestiramina (Chile, Colombia); Colestrol (Italy); Lipocol-Merz (Germany); Lismol (Spain); Quantalan (Germany, Portugal, Switzerland); Quantalan Zuckerfrei (Austria); Questran (Belgium, Bulgaria, Canada, Denmark, Ecuador, Egypt, England, Finland, France, Greece, Hong Kong, Hungary, Indonesia, Ireland, Italy, Korea, Malaysia, Mexico, Netherlands, New Zealand, Norway, Poland, South Africa, Sweden, Taiwan); Questran Light (Argentina, Brazil, Canada, Czech Republic, Malaysia); Questran Lite (Australia, Philippines); Questran Loc (Denmark, Sweden); Resincolestiramina (Singapore, Uruguay); Resincoles-Tiramina (Costa Rica, Dominican Republic, El Salvador, Guatemala, Panama); Vasosan P-Granulat (Germany); Vasosan S-Granulat (Germany)

Drug Class — Antihyperlipidemics; Bile acid sequestrants

Indications — Hypercholesterolemia

Mechanism — Binds intestinal bile acids in a nonabsorbable complex

Dosage with Qualifiers — Hypercholesterolemia—begin 4g PO 1-6×/d; maintenance 4-8g in 2 divided doses

NOTE: it is recommended patients take other medications at least 1h before or 4-6h after ***cholestyramine.***

- **Contraindications**—hypersensitivity to drug or class, biliary obstruction
- **Caution**—constipation

Maternal Considerations — **Cholestyramine** is the chloride salt of a basic anion exchange resin that is not systemically absorbed, but could interfere with the uptake of fat-soluble vitamins. **Cholestyramine** is used by some for the treatment of cholestasis of pregnancy, but its efficacy has long been questioned. The only randomized trial compared it to **ursodeoxycholic acid**. The results demonstrated **cholestyramine** was inferior for the relief of prutitus and was associated with worse pregnancy outcomes.
Side effects include severe constipation, flatulence, gastric pain, anorexia, dyspepsia, headache, rash, fatigue, and weight loss.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. **Cholestyramine** is not systemically absorbed, but could interfere with the uptake of fat-soluble vitamins. Rodent studies are reassuring, revealing no evidence of infertility, increased pregnancy loss, teratogenicity, or IUGR despite the use of doses higher than those used clinically.

Breastfeeding Safety

There is no published experience with **cholestyramine** in nursing women. The resin is not absorbed from the maternal gut and thus is not secreted into breast milk.

Drug Interactions

May delay or reduce the absorption of concomitant oral agents such as **phenylbutazone, warfarin,** thiazide diuretics (acidic), **propranolol** (basic), **tetracycline, penicillin G, phenobarbital,** thyroid and thyroxine preparations, estrogens and progestins, and **digitalis.**

May interfere with the pharmacokinetics of drugs that undergo enterohepatic circulation. The discontinuance of **cholestyramine** could pose a hazard if a potentially toxic drug such as **digitalis** has been titrated to a maintenance level while the patient was taking **cholestyramine.**

May interfere with normal fat digestion and absorption and thus may prevent absorption of fat-soluble vitamins such as A, D, E, and K.

References

Haave NC, Innis SM. J Dev Physiol 1989; 12:11-4.

Hassan AS, Hackley JJ, Johnson LL. Atherosclerosis 1985; 57:139-48.

Innis SM. Am J Obstet Gynecol 1983; 146:13-6.

Kondrackiene J, Beuers U, Kupcinskas L. Gastroenterology 2005; 129:894-901.

Lammert F, Marschall HU, Matern S. Curr Treat Options Gastroenterol 2003; 6:123-132.

Olsson R, Tysk C, Aldenborg F, Holm B. Gastroenterology 1993; 105:267-71.

Palinski W, D'Armiento FP, Witztum JL, et al. Circ Res 2001; 89:991-6.

Summary

Pregnancy Category: C
Lactation Category: S

- **Cholestyramine** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.
- There are superior agents for the treatment of cholestasis of pregnancy.

Ciclopirox—(Batrafen; Brumixol; Loprox Laca)

International Brand Name—Batrafen (Bulgaria, Czech Republic, Ecuador, Germany, Greece, Hungary, Ireland, Italy, Korea, Malaysia, New Zealand, Pakistan, Peru, Philippines, Puerto Rico, Spain, Switzerland, Taiwan, Thailand); Batrafen Gel (Germany); Batrafen Nail Lacquer (Israel); Brumixol (Italy, Taiwan); Ciclochem (Spain); Cicloderm (Thailand); Dafnegin Supp (Korea); Fungopirox (Peru); Fungowas (Spain); Loprox (Argentina, Brazil, Canada, Costa Rica, Dominican Republic, Ecuador, El Salvador, Guatemala, Honduras, Korea, Mexico, Netherlands, Nicaragua, Panama, Thailand); Loprox Laca (Mexico); Miclast (Italy); Micopirox (Argentina); Micoxolamina (Italy); Mycofen (Denmark); Mycoster (France); Nail Batrafen (New Zealand); Primax (Colombia); Stieprox (Malaysia, Philippines, Singapore, Taiwan, Thailand); Stiprox (Mexico)

Drug Class

Antifungals

Indications

Yeast infection

Mechanism	Chelates polyvalent cations (Fe^{3+} or Al^{3+}), inhibiting metal-dependent enzymes responsible for degradation of peroxides within fungal cell
Dosage with Qualifiers	Yeast infection—apply cream (1%) or lotion (1%) onto the affected and surrounding skin bid • **Contraindications**—hypersensitivity to drug or class • **Caution**—hepatic or renal failure
Maternal Considerations	There are no adequate reports or well-controlled studies of **ciclopirox** in pregnant women. Treatment of mycotic cervical inflammation during pregnancy is followed by a significant reduction in symptoms and the number of active colonies. ***Side effects*** include itching at the site of application, worsening of the condition being treated, and mild to severe burning.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **ciclopirox** crosses the human placenta. Though well absorbed by the pregnant rodent, placental transfer is low, and the fetal tissue concentration is always lower than in maternal blood. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically.
Breastfeeding Safety	There is no published experience in nursing women. It is unknown whether **ciclopirox** enters human breast milk.
Drug Interactions	No clinically significant interactions identified.
References	Kellner HM, Arnold C, Christ OE, et al. Arzneimittelforschung 1981; 31:1337-53. Novachkov V, Damianov L, Tsankova M, Ivanov S. Akush Ginekol 1999; 38:54-5.
Summary	**Pregnancy Category: B** **Lactation Category: U** • **Ciclopirox** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk. • There are alternative agents for which there is more experience during pregnancy and lactation.

Cidofovir—(Visticide)

International Brand Name—None identified.

Drug Class	Antivirals; Dermatologics
Indications	CMV retinitis in AIDS patients
Mechanism	Inhibits viral DNA synthesis
Dosage with Qualifiers	CMV retinitis—5mg/kg IV qw administered over 1h; drink copious amounts of water to avoid renal failure *NOTE: administer with* ***probenecid;*** *renal dosing.* • **Contraindications**—hypersensitivity to drug or class, direct intraocular injection • **Caution**—renal failure

Maternal Considerations

The published experience with **cidofovir** during pregnancy is limited to a single case report. Its use was associated with breast adenocarcinoma in female rats.
Side effects include neutropenia, renal failure, uveitis, N/V, anorexia, and anemia.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **cidofovir** crosses the human placenta. However, it was used successfully in a guinea pig model to prevent congenital CMV. Rodent studies conducted at doses below the MRHD revealed maternal toxicity and embryotoxicity associated with skeletal malformations.

Breastfeeding Safety

There is no published experience in nursing women. It is unknown whether **cidofovir** enters human breast milk. Breastfeeding is contraindicated in HIV-infected nursing women where formula is available to reduce the risk of neonatal transmission.

Drug Interactions

The pharmacokinetics of **zidovudine** were evaluated in 10 patients receiving **zidovudine** alone or with IV **cidofovir** (without **probenecid**). There was no evidence of an effect of **cidofovir** on the pharmacokinetics of **zidovudine.**
Probenecid is known to interact with the metabolism or renal tubular excretion of many drugs (e.g., ACEIs, **acetaminophen, acyclovir,** aminosalicylic acid, barbiturates, benzodiazepines, **bumetanide, clofibrate, famotidine, furosemide, methotrexate,** NSAIDs, **theophylline, zidovudine**). Concomitant medications should be carefully assessed.
Concomitant administration of **cidofovir** and agents with nephrotoxic potential (e.g., **amphotericin B,** aminoglycosides, **foscarnet,** and IV **pentamidine**) should be avoided.

References

Awan AR, Field HJ. Antimicrob Agents Chemother 1993; 37:2478-82.
McNicholl IR, Palmer SM, Ziska DS, Cleary JD. Ann Pharmacother 1999; 33:607-14.
Midtvedt K, Bjorang O, Letting AS. Clin Transplant 2007; 2:571-3.
Schleiss MR, Anderson JL, McGregor A. Virol J 2006; 3:9.

Summary

Pregnancy Category: C
Lactation Category: U

- **Cidofovir** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.
- Physicians are encouraged to register pregnant women under the Antiretroviral Pregnancy Registry (1-800-258-4263) for a better follow-up of the outcome while under treatment with **cidofovir.**

Cimetidine—(Beamat; Cimebec; Cimetegal; Cimetidine in Sodium Chloride; Cimewet; Ciwidine; Edalene; Gerucim; Paoweian; Procimeti; Proctospre; Tagagel; Tagamed; Tagamet; Tagamin; Tratol; Ulcinfan; Ulpax; Valmagen; Wergen)

International Brand Name—Acibilin (Argentina); Acidnor (Israel); Aciloc (Denmark, Sweden); Aci-Med (South Africa); Acinil (Denmark, Sweden); Aidar (Thailand); Antag (Philippines); Apo-Cimetidine (Canada, New Zealand); Asaurex (Mexico); Azucimet (Germany); Biomag (Italy); Brumetidina (Italy); Campanex (Greece); Cemedin 200 (Israel); Cemedin 400 (Israel); Cemedin 800 (Israel); Cementin (Singapore); Ciclem (Philippines); Cidine (Thailand); Cigamet (Thailand); Cignatin (Korea); Ciket M (Philippines); Cimal (Norway); Cimehexal (Australia, Germany); Cimeldine (Ireland); Cimet (Indonesia, Thailand); Cimetag (Austria, Israel); Cimetalgin (Austria); Cimetase (Mexico); Cimetid (Norway); Cimetidin (Bulgaria, Denmark, Germany, Switzerland); Cimetidina (Chile, Paraguay, Spain); Cimetigal (Mexico); Cimetin (Czech Republic, Ecuador, India); Cimetum (Argentina); Cimewell (Taiwan); Cimex (Finland); Cimlok (South Africa); Cimulcer (Malaysia, Thailand); Cinadine (South Africa); Cinulcus (Spain); Cismetin (Korea); Citidine (Hong Kong, Singapore); Corsamet (Indonesia); Cytine (New Zealand); Defense (Taiwan); Duomet (South Africa); Dyspamet (England); Erlmetin (Singapore); Eureceptor (Italy); Fremet (Spain); Gadol (Venezuela); Gastab (Hong Kong); Gastidine (Hong Kong); Gastrobitan (Norway); Gastrodin (Taiwan); Gastroprotect (Germany); Gawei (Taiwan); Getidin (Philippines); H-2 (Korea); Hexamet (South Africa); Himetin (Korea); Histodil (Hungary, Poland); Inesfay (Mexico); Lenamet (South Africa); Lenamet OTC (South Africa); Lock 2 (India); Manomet (Thailand); Maritidine (Hong Kong); Med-Gastramet (Thailand); Meticon (Korea); Neutronorm (Austria); Novocimetine (Canada); Nulcer (Indonesia); Piovalen (Greece); Pondarmett (Thailand); Powegon (Taiwan); Promet (Thailand); Sanmetidin (Indonesia); Secapine (South Africa); Sertidine (Thailand); Shintamet (Malaysia, Philippines); Siamidine (Thailand); Sigmetadine (Australia); Simaglen (Hong Kong); Stogamet (Taiwan); Stomakon (Brazil); Stomedine (France); Stomet (Italy); Tagamet (Argentina, Australia, Belgium, Brazil, China, Costa Rica, Denmark, Dominican Republic, El Salvador, England, France, Germany, Greece, Guatemala, Honduras, Hong Kong, Indonesia, Ireland, Italy, Korea, Mexico, Netherlands, Nicaragua, Norway, Panama, Philippines, Poland, Portugal, Spain, Sweden, Switzerland, Taiwan, Thailand); Tagma (Korea); Tametin (Italy); Tobymet (Indonesia); Ulcedin (Italy); Ulcedine (Thailand); Ulcemet (Ecuador); Ulcenon (Philippines); Ulcerfen (Argentina); Ulcidine (Malaysia); Ulcim (South Africa); Ulcimet (Argentina, Ecuador, Indonesia, Peru, Uruguay); Ulcodina (Italy); Ulcolind H2 (Germany); Ulcomedina (Italy); Ulcomet (Hong Kong); Ulcumet (Indonesia); Ulsikur (Indonesia); Umamett (Thailand); Weisdin (Taiwan); Xepamet (Malaysia); Zymerol (Mexico)

Drug Class	Antihistamines, H_2; Antiulcer agents
Indications	Peptic ulcer disease, GERD, Zollinger-Ellison syndrome
Mechanism	Antagonizes histamine H_2 receptors
Dosage with Qualifiers	Gastric ulcer—300mg PO/IM/IV qid; max 2.5g/d GERD—400mg PO qac or qhs or 800mg PO bid ×12w Zollinger-Ellison syndrome—300-600mg PO/IM/IV qid *NOTE: renal dosing.* • **Contraindications**—hypersensitivity to drug or class • **Caution**—unknown
Maternal Considerations	There are no adequate reports or well-controlled studies of **cimetidine** in pregnant women, and evidence documenting the safety of acid-suppressing drugs during pregnancy is very limited. Antacids and antacid/alginic acid combinations or **sucralfate** constitute first-line medical therapy. If the symptoms are not adequately relieved or if complications develop, treatment with **cimetidine** or **ranitidine** may be considered. The treatment of "heartburn" with **cimetidine** is not followed by significant maternal adverse reactions. Drugs that inhibit hepatic microsomal enzymes, such as **cimetidine,** may promote the accumulation of unexpectedly high (possibly toxic) blood concentrations of **lidocaine. Cimetidine** has some antiandrogenic effect. ***Side effects*** include neutropenia, thrombocytopenia, agranulocytosis, headache, diarrhea, vomiting, rash, and hepatic failure.

Fetal Considerations

There are no adequate reports or well-controlled studies of **cimetidine** in human fetuses. Studies conducted in pregnant subjects found no relation between drug exposure and birth defects. However, one large epidemiologic investigation noted a possible association between preterm birth and 1st trimester exposure to H_2 antagonists. Further study seems warranted. Rodent studies reveal inhibition of both testicular descent and genital differentiation and postnatal cryptorchidism. These events might occur in human fetuses when high doses of **cimetidine** are administered to pregnant women around the end of the 1st trimester.

Breastfeeding Safety

There are no adequate reports or well-controlled studies in nursing women. **Cimetidine** enters human breast milk and is actively transported by BCRP (breast cancer resistance protein). The percentage of the maternal dose ingested based on neonatal body weight is <10%, which should be safe under normal conditions. However, the excretion of alternative agents such as **famotidine** and **nizatidine** is even lower.

Drug Interactions

May reduce the hepatic metabolism of **warfarin, phenytoin, propranolol, nifedipine, chlordiazepoxide, diazepam,** certain TCAs, **lidocaine, theophylline,** and **metronidazole.** The dose of these drugs and other similarly metabolized drugs, particularly those of low therapeutic ratio or in patients with renal and/or hepatic impairment, may require adjustment when starting or stopping **cimetidine.**
An altered pH may affect absorption of certain drugs (e.g., **ketoconazole**). They should be given at least 2h before **cimetidine.**

References

Broussard CN, Richter JE. Drug Saf 1998; 19:325-37.
Garbis H, Elefant E, Diav-Citrin O, et al. Reprod Toxicol 2005; 19:453-8.
Katz PO, Castell DO. Gastroenterol Clin North Am 1998; 27:153-67.
Oo CY, Kuhn RJ, Desai N, McNamara PJ. Clin Pharmacol Ther 1995; 58:548-55.
Ruigomez A, Garcia Rodriguez LA, Cattaruzzi C, et al. Am J Epidemiol 1999; 150:476-81.
Staud F, Vackova Z, Pospechova K, et al. J Pharmacol Exp Ther 2006; 319:53-62.
Takeshi S, Kai H, Suita S. Surgery 2002; 131(1 Suppl):S301-5.

Summary

Pregnancy Category: B
Lactation Category: S

- Antacids and antacid/alginic acid combinations or sucralfate constitute first-line medical therapy.
- If symptoms are not adequately relieved or if complications develop, treatment with **cimetidine** or **ranitidine** may be considered.

Cinoxacin—(Cinobac)

International Brand Name—None identified.

Drug Class

Antibiotics; Quinolones

Indications

UTI from *E. coli, P. mirabilis, P. vulgaris, Klebsiella,* and *Enterobacter* species

Mechanism

Bactericidal—inhibits DNA synthesis (activity of DNA gyrase and topoisomerase)

Dosage with Qualifiers

UTI (prophylaxis)—250mg PO qhs ×5mo
UTI (treatment)—250mg PO q6h or 500mg PO q12h ×7-12d

NOTE: renal dosing.

- **Contraindications**—hypersensitivity to drug or class
- **Caution**—not known

Maternal Considerations

There is no published experience with **cinoxacin** during pregnancy.
Side effects include skin rash, urticaria, pruritus, edema, angioedema, eosinophilia, itching, redness, swelling, dizziness, headache, increased sensitivity of skin to sunlight, and thrombocytopenia.

Fetal Considerations

There are no adequate reports or well-controlled studies of **cinoxacin** in human fetuses. The use of the new quinolones during the 1st trimester of pregnancy is not associated with an increased prevalence of malformations or musculoskeletal problems; however, longer follow-up and MRI of the joints may be warranted to exclude subtle cartilage and bone damage. While rodent studies did not reveal evidence of teratogenicity, **cinoxacin** was associated with bone development abnormalities in young animals.

Breastfeeding Safety

There is no published experience in nursing women. It is unknown whether **cinoxacin** enters human breast milk.

Drug Interactions

There is little specific information on **cinoxacin.** Other quinolones may prolong the elimination t/2 of **theophylline** and increase serum levels.
Some quinolones reduce the clearance of **caffeine** and prolong its serum t/2.
Multivalent cation–containing products such as magnesium/aluminum antacids, **sucralfate, didanosine** chewable/buffered tablets or pediatric powder, other highly buffered drugs, or products containing calcium, iron, or zinc may substantially decrease quinolone absorption.
Some quinolones variably alter **phenytoin** levels.
Some quinolones are associated with transient elevations in serum creatinine when given with **cyclosporine.**
Quinolones may enhance the effects of **warfarin.**
Probenecid interferes with renal tubular secretion of quinolones.
Some quinolones may inhibit renal tubular transport of **methotrexate,** leading to increased levels of **methotrexate.**
NSAIDs (but not **aspirin**), in combination with very high doses of quinolones, have been shown to provoke convulsions in preclinical studies.

References

Bardi M, Manzoni A. Clin Ter 1988; 127:185-8.
Cristiano P, Morelli G, Simioli F, et al. Minerva Med 1989; 80:393-5.
Peters HJ. Z Arztl Fortbild 1995; 89:279-86.

Summary

Pregnancy Category: C
Lactation Category: U

- **Cinoxacin** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.
- There are alternative agents for which there is more experience during pregnancy and lactation.

Ciprofloxacin—(Ciloxan; Cipro; Cyprobay)

International Brand Name—Acire (Korea); Alcon Cilox (Colombia, Indonesia); Bacquinor (Indonesia); Bactiflox (Singapore); Baflox (Colombia); Baycip (Chile, Spain); Bernoflox (Indonesia); Cefaxin (Korea); Cetraxal (Guatemala, Honduras, Panama, Spain); C-Flox (Australia, Uruguay); C-Floxacin (Thailand); Ciclodin (Philippines); Cidroxal (Philippines); Ciflo (Thailand); Ciflox (France, Taiwan); Cifloxin (Hong Kong, Thailand); Cifran (India, Malaysia, South Africa); Cilab (Thailand); Ciloquin (Australia); Ciloxan (Argentina, Austria, Belgium, Brazil, Canada, Chile, Czech Republic, Ecuador, England, France, Germany, Greece, Hong Kong, Hungary, Ireland, Israel, Malaysia, Mexico, Netherlands, Paraguay, Philippines, Sweden, Switzerland, Taiwan, Thailand, Uruguay, Venezuela); Cimogal (Mexico); Cinaflox (Peru); Cipflox (New Zealand); Cipide (Hong Kong); Cipio (Korea); Ciplox (Hong Kong, India, Israel); Ciplus (Korea); Cipocin (Taiwan); Ciprecu (Ecuador); Ciprinol (Bulgaria, Hungary); Cipro (Argentina, Brazil, Canada, Colombia, Paraguay); Ciprobac (Mexico); Ciprobay (Bulgaria, China, Czech Republic, Germany, Hungary, Korea, Malaysia, Philippines, Poland, South Africa, Thailand); Ciprobay Uro (Germany); Ciprobid (India, South Africa, Thailand); Ciprobiotic (Dominican Republic); Ciprocan (Korea); Ciprocep (Thailand); Ciprocin (Israel); Ciprocinol (Bulgaria); Ciprodex (Israel); Ciproflox (Bulgaria, Mexico, Peru); Ciprogis (Israel); Ciproglen (Thailand); Ciprok (Spain); Ciprolet (Singapore); Ciprolin (Peru); Cipromycin (Greece); Cipropharm (Israel); Ciproquin (Israel); Ciproquinol (Portugal); Ciproval (Chile); Ciprox (Israel); Ciproxacol (Peru); Ciproxan (Japan, Thailand); Ciproxin (Austria, Denmark, England, Finland, Greece, Hong Kong, Indonesia, Ireland, Israel, Italy, Netherlands, New Zealand, Norway, Sweden, Switzerland, Taiwan); Ciproxina (Costa Rica, Dominican Republic, Ecuador, El Salvador, Guatemala, Honduras, Mexico, Nicaragua, Panama, Portugal); Ciproxine (Belgium); Ciproxyl (Hong Kong, Thailand); Ciriax (Peru); Cirok (Philippines); Cirokan (Korea); Cirox (Singapore); Ciroxin (Singapore); Citopcin (Korea); Cixa (Taiwan); Cobay (Thailand); Corsacin (Indonesia); Cosflox (India); Cycin (Korea, Singapore); Cyfloxin (Hong Kong); Cypral (Venezuela); Cysfec (Korea); Eni (Mexico); Enoxin (Singapore); Eprocin (Korea); Fimoflox (Indonesia); Floroxin (Israel); Floxager (Mexico); Floxantina (Mexico); Floxbio (Indonesia); Gonning (Hong Kong); Grifociprox (Peru); H-Next (Colombia); Holdestin (Philippines); Inciflox (Indonesia); Iprolan (Philippines); Isotic (Indonesia); Jayacin (Indonesia); Kenzoflex (Mexico); Kinoves (Philippines); Kipocin (Korea); K-Sacin (Korea); Lofucin (Korea); Loxan (Colombia, Ecuador); Medociprin (Hong Kong, Thailand); Mitroken (Mexico); Neofloxin (Singapore); Nivoflox (Mexico); Opthaflox (Thailand); Otosec (Colombia); Probiox (Peru); Procin (Brazil); Proflaxin (Costa Rica, Nicaragua); Proflox (Thailand); Profloxin (Australia); Proksi 250 (El Salvador, Guatemala, Honduras); Proksi 500 (El Salvador, Guatemala, Honduras); Proquin (Australia); Qilaflox (Indonesia); Qinosyn (Philippines); Quilox (Philippines); Quinobiotic (Peru); Quinolide (El Salvador, Guatemala, Honduras); Quintor (Bahrain, India, Republic of Yemen); Qupron (Korea); Rofcin (Korea); Rosacin Eye Drop (Korea); SARF (Indonesia); Septicide (Peru); Sifloks (Israel); Siprogut (Korea); Sophixin Ofteno (Mexico); Spitacin (Korea); Superocin (Taiwan); Unex (Ecuador); Uniflox (France); Uroxin (Singapore); Zipra (Mexico); Zumaflox (Indonesia)

Drug Class ..... Antibiotics; Quinolones

Indications ..... Anthrax, cystitis (gram-negative infection), enteric fever

Mechanism ..... Bactericidal—inhibits DNA gyrase and topoisomerase

Dosage with Qualifiers .....

UTI, uncomplicated cystitis—250-750mg PO bid
UTI, severe—200-400mg IV bid
Anthrax—400mg IV bid (or 500mg PO bid) ×60d
Gonorrhea—500mg PO ×1

- **Contraindications**—hypersensitivity
- **Caution**—renal or hepatic failure, dehydration, diabetes, seizure disorder, sun exposure

Maternal Considerations .....

Fluoroquinolone therapy is widely used as a treatment for gonorrhea because it is a relatively inexpensive, oral, and single-dose therapy. However, fluoroquinolone-resistant disease is being identified more frequently. A test for cure is essential. There are no adequate reports or well-controlled studies in pregnant women. **Ciprofloxacin** is also usually selected when penicillin-class agents have no effect on gram-negative rods. **Ciprofloxacin** has the best safety profile of second-line drugs for drug-resistant tuberculosis. It is the drug of choice for prophylaxis among asymptomatic pregnant women exposed to *B. anthracis*. In instances where the strain is penicillin-sensitive, prophylaxis with **amoxicillin,** 500mg tid ×60d, may be considered. Isolates of *B. anthracis* implicated in the recent bioterrorist attacks are susceptible to **penicillin** in laboratory tests, but may contain penicillinase activity. Penicillins are not recommended for

treatment of anthrax. **Ciprofloxacin** has also been used to treat Q fever during pregnancy.
Side effects include seizures, pseudomembranous colitis, psychosis, hypersensitivity, N/V, dizziness, rash, increased CK levels, arthropathy (animal), photosensitivity, pruritus, agitation, confusion, tendonitis, arthralgia, and elevated hepatic enzymes.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. **Ciprofloxacin** crosses the human placenta, and can be found in AF in low quantities. The mean transplacental transfer percentage of **ciprofloxacin** across the isolated perfused human cotyledon approximates 3.2% and the transplacental transfer index (the ratio of transplacental transfer between **ciprofloxacin** and antipyrine) was 0.34. Short-duration treatment with **ciprofloxacin** appears free of adverse fetal responses. As a class, the new quinolones do not appear associated with an increased risk of malformation or musculoskeletal problems in humans. The effect of prolonged exposure such as that required for Crohn's disease or anthrax prophylaxis remains unknown. Longer follow-up and MRI of the joints may be warranted to exclude subtle cartilage and bone damage. There are no clinically significant musculoskeletal dysfunctions reported in children exposed to fluoroquinolones *in utero.* Treatment of fetal mice, dogs, and rabbits with other quinolones is associated with an acute arthropathy of the weight-bearing joints.

Breastfeeding Safety

There are no adequate reports or well-controlled studies in lactating human mothers. **Ciprofloxacin** enters human breast milk, and oral doses of this drug are concentrated in breast milk at levels higher than serum. *C. difficile* pseudomembranous colitis has been reported in a breastfed neonate whose mother was taking **ciprofloxacin.** In some animals, slow **ciprofloxacin** elimination results in blood levels out of proportion to that ingested. Though the American Academy of Pediatrics considers it safe for breastfeeding women, it is probably best to avoid **ciprofloxacin** when there are reasonable alternatives.

Drug Interactions

May prolong the elimination t/2 of **theophylline** and increase the risk of **theophylline**-related adverse reactions.
May reduce the clearance of **caffeine** and prolong its serum t/2.
Multivalent cation–containing products such as magnesium/aluminum antacids, **sucralfate, didanosine** chewable/buffered tablets or pediatric powder, other highly buffered drugs, or products containing calcium, iron, or zinc may substantially decrease **ciprofloxacin** absorption.
May variably alter **phenytoin** levels.
Use with **glyburide** has, on rare occasions, resulted in severe hypoglycemia.
Has been associated with transient elevations in serum creatinine in patients receiving **cyclosporine.**
May enhance the effects of **warfarin.**
Probenecid interferes with renal tubular secretion of **ciprofloxacin** and will increase the serum level.
May inhibit renal tubular transport of **methotrexate,** leading to increased levels of **methotrexate.**
Metoclopramide accelerates the absorption of oral **ciprofloxacin,** resulting in shorter time to peak maximum plasma concentrations.
NSAIDs (but not **aspirin**) may provoke convulsions when used with very high doses of quinolones.

References

American Academy of Pediatrics, Committee on Drugs. Pediatrics 2001; 108:776-89.
Berkovitch M, Pastuszak A, Gazarian M, et al. Obstet Gynecol 1994; 84:535-8.
Centers for Disease Control and Prevention. JAMA 2001; 286:2396-7.
Centers for Disease Control and Prevention. MMWR Morb Mortal Wkly Rep 2001; 50:960.
Connell W, Miller A. Drug Saf 1999; 21:311-23.
Gardner DK, Gabbe SG, Harter C. Clin Pharm 1992; 11:352-4.
Harmon T, Burkhart G, Applebaum H. J Pediatr Surg 1992; 7:744-6.
Koul PA, Wani JI, Wahid A. Lancet 1995; 346:307-8.
Loebstein R, Addis A, Ho E, et al. Antimicrob Agents Chemother 1998; 42:1336-9.
Polachek H, Holcberg G, Sapir G, et al. Eur J Obstet Gynecol Reprod Biol 2005; 122:61-5.
Siefert HM, Maruhn D, Maul W, et al. Arzneimittelforschung 1986; 36:1496-502.

Summary

Pregnancy Category: C
Lactation Category: S (possibly)

- **Ciprofloxacin** should be used during pregnancy only if the benefit justifies the potential perinatal risk.
- It should be avoided while breastfeeding.
- There are usually alternative agents for which there is more experience during pregnancy and lactation.

Cisapride—(Propulsid; Viprasen)

International Brand Name—Acenalin (Japan); Acpulsif (Indonesia); Alimix (England, Greece, Italy, Portugal); Alimix Forte (Czech Republic); Alipride (India); Cipr (Taiwan); Cipride (Thailand); Cisamod (Peru); Cisapron (Ecuador); Cisawal (India); Disflux (Indonesia); Dizmoprida (Colombia); Enteropride (Mexico); Eriken (Mexico); Esorid (India, Thailand); Ethiprid (Indonesia); Gastromet (Chile, Ecuador, Peru); Guarposid (Indonesia); Kineprid (Brazil); Kinestase (Mexico); Metison (Thailand); Motilar (Venezuela); Palcid (Thailand); Prepulsid (Bulgaria, China, Colombia, Costa Rica, Dominican Republic, Ecuador, Germany, Greece, Guatemala, Honduras, Hong Kong, Indonesia, Malaysia, Mexico, New Zealand, Nicaragua, Panama, Peru, Philippines, Poland, Slovenia, Taiwan, Thailand, Turkey); Presiston (Mexico); Prider (Taiwan); Pridesia (Indonesia); Prisic (Taiwan); Pulsar (Argentina); Refluxin (Israel); Risamol (Japan); Saprid (Colombia); Stimulit (Indonesia); Syspride (India); Tono-cis (Peru); Unamol (Mexico); Unipride (India); Viprasen (Costa Rica, Dominican Republic, El Salvador, Guatemala, Guyana, Nicaragua, Panama); Wepride (Taiwan)

Drug Class — Gastrointestinals, stimulant

Indications — GERD

Mechanism — Stimulates gastric motility by triggering the release of ACh by the myenteric plexus

Dosage with Qualifiers

GERD—10-20mg PO qac 15min before meals and hs; max 20mg PO qid

NOTE: check serum electrolytes and ECG before initiating.

- **Contraindications**—hypersensitivity, arrhythmia, sinus node dysfunction, AV block, CHF, ventricular arrhythmia, bradyarrhythmia
- **Caution**—electrolyte imbalances, prolongs QT interval on ECG

Maternal Considerations

There are no adequate reports or well-controlled studies of **cisapride** in pregnant women. Antacids and antacid/alginic acid combinations or sucralfate constitute first-line medical therapy.

Cisapride is reserved for patients with severe symptoms. Rodent studies suggest decreased fertility after exposure to **cisapride.** ***Side effects*** include severe arrhythmias (torsades de pointes), pancytopenia, thrombocytopenia, anemia, hepatic failure, headache, N/V, fatigue, and depression.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **cisapride** crosses the human placenta. There were no differences in maternal history, birth weight, gestational age at delivery, and rates of live births, spontaneous or therapeutic abortions, fetal distress, and major or minor malformations among the group of pregnant women exposed to **cisapride;** ¾ of exposures occurred during organogenesis. **Cisapride** rapidly crosses the ovine placenta, with an average F:M ratio of 0.71. Embryotoxicity was noted at doses that were multiples of the MRHD. However, a rat study noted the occurrence of a fetal arrhythmia associated with an increased prevalence of malformations.

Breastfeeding Safety

Cisapride enters human breast milk, but at low concentrations of 6ng/ml. Thus, the amount ingested by the neonate is likely without clinical effect.

Drug Interactions

Cisapride is metabolized mainly by CYP3A4. Ingestion with a 3A4 inhibitor can produce serious ventricular arrhythmias, QT prolongation, and torsades de pointes.
Clarithromycin, erythromycin, troleandomycin, nefazodone, indinavir, ritonavir fluconazole, itraconazole, and oral **ketoconazole** inhibit **cisapride** metabolism causing prolongation of the QT interval.
Anticholinergic compounds, such as **belladonna** and **dicyclomine,** would be expected to compromise the beneficial effects of **cisapride.**
Furosemide and the thiazides are associated with depletion of electrolytes, which may lead to **cisapride**-induced cardiac arrhythmias.
Cimetidine but not **ranitidine** increase the peak **cisapride** concentration and AUC.
Grapefruit juice increases the bioavailability of **cisapride** by an average of 50%.
Should not be used with drugs known to prolong the QT interval: certain antiarrhythmics, including those of class IA (e.g., **quinidine** and **procainamide**) and class III (e.g., **sotalol**); TCAs (e.g., **amitriptyline**); certain tetracyclic antidepressants (e.g., **maprotiline**); certain antipsychotic medications (e.g., **sertindole**); **bepridil,** and **sparfloxacin.**
The acceleration of gastric emptying by **cisapride** could affect the rate of absorption of other drugs. Patients receiving narrow therapeutic ratio drugs or other drugs that require careful titration should be followed closely.

References

Bailey B, Addis A, Lee A, et al. Dig Dis Sci 1997; 42:1848-52.
Broussard CN, Richter JE. Drug Saf 1998; 19:325-37.
Hofmeyr GJ, Sonnendecker EW. Eur J Clin Pharmacol 1986; 30:735-6.
Marshall JK, Thompson AB, Armstrong D. Can J Gastroenterol 1998; 12:225-7.
Skold AC, Danielsson C, Linder B, Danielsson BR. Reprod Toxicol 2002; 16:333-42.
Veereman-Wauters G, Monbaliu J, Meuldermans W, et al. Drug Metab Dispos 1991; 19:168-72.

Summary

Pregnancy Category: C
Lactation Category: S (likely)
- **Cisapride** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.
- There is considerably more experience with **metoclopramide** during pregnancy and lactation.
- **Cisapride** should be reserved for patients with severe symptoms unresponsive to other agents.

Cisatracurium—(Tracrium)

International Brand Name—Acrium (Korea); Aculex (Korea); Genso (Taiwan); Mycurium (Israel); Relatrac (Colombia, Peru); Tracrium (Argentina, Chile, Costa Rica, Dominican Republic, Ecuador, El Salvador, Guatemala, Honduras, Mexico, Nicaragua, Panama, Paraguay, Uruguay); Tracur (Brazil); Tracurix (Argentina)

Drug Class

Anesthesia, adjunct; Musculoskeletal agents; Neuromuscular blockers, nondepolarizing

Indications

Surgical paralysis

Mechanism

Antagonizes ACh motor end plate receptors; nondepolarizing

Dosage with Qualifiers

Surgical paralysis—0.4-0.5mg/kg IV; may supplement with 0.08-0.10mg/kg q15-25min

- **Contraindications**—hypersensitivity to drug or class
- **Caution**—hepatic or renal dysfunction, hypotension, CV disease, electrolyte abnormalities

Maternal Considerations

Atracurium is an intermediate-duration curare derivative producing effective surgical paralysis. There are no adequate reports or well-controlled studies of **cisatracurium** in pregnant women. The clearance and clinical duration of **atracurium** are unaltered during pregnancy. In contrast, the clearance of **pancuronium** is increased 27% during cesarean section, and the mean onset time and clinical duration of **cisatracurium** are significantly reduced.
Side effects include CV collapse, tachycardia, hypotension, rash, flushing, and urticaria, all due to histamine release and hypertension.

Fetal Considerations

There are no adequate reports or well-controlled studies of **cisatracurium** in human fetuses. **Atracurium** has been used in lieu of **pancuronium** to facilitate fetal procedures. While small amounts are shown to cross the human placenta, its use during cesarean section is not associated with neonatal sequelae. In theory, if used for long-term paralysis of a critically ill pregnant woman, fetal toxicity could be a risk. In cell culture, **cisatracurium** increases the rates of HUVEC apoptosis.

Breastfeeding Safety

There are no adequate reports or well-controlled studies in nursing women. It is unknown whether **cisatracurium** enters human breast milk. Considering its application, **cisatracurium** is unlikely to affect the breastfeeding newborn. While some rodent studies report an increase in malformations, they are confounded by the profound respiratory depression associated with the drug.

Drug Interactions

Isoflurane or **enflurane** administered with nitrous oxide/oxygen to achieve 1.25 MAC may prolong the clinically effective duration

of action of **cisatracurium.** The average infusion rate requirement may be decreased by as much as 30-40%.
Other drugs that may enhance the nondepolarizing neuromuscular blockade include certain antibiotics (e.g., aminoglycosides, tetracyclines, **bacitracin,** polymyxins, **lincomycin, clindamycin,** and **colistin**), magnesium salts, **lithium,** local anesthetics, **procainamide,** and **quinidine.**

References

Atherton DP, Hunter JM. Clin Pharmacokinet 1999; 36:169-89.
Guay J, Grenier Y, Varin F. Clin Pharmacokinet 1998; 34:483.
Mouw RJ, Klumper F, Hermans J, et al. Acta Obstet Gynecol Scand 1999; 78:763-7.
Pan PH, Moore C. J Clin Anesth 2001; 13:112-7.

Summary

Pregnancy Category: C
Lactation Category: S (likely)
- **Cisatracurium** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Cisplatin—(Asiplatin; Platinol)

International Brand Name—Abiplatin (Austria, Israel, Poland, South Africa, Taiwan); Blastolem (Mexico); Briplatin (Japan); Cisplatin-Ebewe (Malaysia); Cisplatino (Colombia, Peru); Cisplatinum (Malaysia, Thailand); Cisplatyl (Brazil, France, Peru); Citoplatino (Italy); Cytoplatin (Israel); Cytosplat (Philippines); Docistin (Philippines); Elvecis (Argentina); Kemoplat (India, Philippines); Lederplatin (Sweden); Neoplatin (Spain); Niyaplat (Mexico); Noveldexis (Mexico); Platamine (Bulgaria, Greece, Israel, Italy, Philippines, South Africa); Platamine RTU (Indonesia); Platiblastin (Austria, Germany, Switzerland); Platidiam (Bulgaria, Czech Republic, Hungary); Platinex (Germany, Italy); Platinil (Brazil); Platinol (Argentina, Belgium, Denmark, Ecuador, Finland, Greece, Norway, Philippines, Sweden, Switzerland, Taiwan, Thailand, Uruguay); Platinol-AQ (Canada); Platinoxan (Philippines); Platistil (Portugal, Spain); Platistin (Finland, Norway, Sweden); Platosin (England, Malaysia, Philippines, South Africa, Taiwan, Thailand); Sicatem (Paraguay); Tecnoplatin (Mexico)

Drug Class

Antineoplastics

Indications

Chemotherapy (cancer: ovary, bladder, lung, esophageal, cervical, breast, gastric, lymphoma, myeloma, sarcoma)

Mechanism

Binds and cross-links DNA

Dosage with Qualifiers

Cancer—Varies with the tumor. Most regimens recommend 100mg/m^2/cycle and require 3-4 cycles.

NOTE: prehydration and maintenance of an adequate urinary output are absolute requirements.

- **Contraindications**—hypersensitivity to drug or class, myelosuppression, pregnancy, lactation
- **Caution**—renal or hepatic failure, neuropathy, hearing impairment, myelosuppression

Maternal Considerations

There are no adequate reports or well-controlled studies in pregnant women. Patients should be advised to avoid pregnancy during treatment. The published literature consists mostly of case reports and small series. Good outcomes are possible. **Cisplatin** has been used during pregnancy for women discovered to have ovarian or other malignancies. Pregnancy and fetal age impact on **cisplatin** protein binding because of lower albumin levels. The resulting higher levels of free drug in the mother and fetus may increase the risk of toxicity in both. **Cisplatin** causes severe mitochondrial toxicity in the maternal rat kidney.

Side effects include nephrotoxity, ototoxicity, neuropathy, optic neuritis, papilledema, seizures, anemia, hypokalemia, hypoglycemia, blurred vision, paresthesia, ataxia, elevated hepatic enzymes, rash, urticaria, muscle weakness, and loss of taste.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. **Cisplatin** crosses the human placenta. Low fetal protein concentration increases the percentage of free drug. Malformations in offspring of women treated with **cisplatin** are rare. **Cisplatin** is embryotoxic and teratogenic in mice. Damage to the fetal renal and hepatic mitochondria as a result of transplacental drug exposure appears mild.

Breastfeeding Safety

Cisplatin enters human breast milk at concentrations at or below the level of detection, and is generally considered compatible with breastfeeding.

Drug Interactions

May be associated with decreased plasma levels of anticonvulsants.

References

Ben-Baruch G, Menczer J, Goshen R, et al. J Natl Cancer Inst 1992; 84:451-2.
da la Motte Rouge T, Pautier P, Duvillard P, et al. Ann Oncol 2008; 19:1435-41.
de Vries EG, van der Zee AG, Uges DR, Sleijfer DT. Lancet 1989; 1:497.
Gerschenson M, Paik CY, Gaukler EL, et al. Reprod Toxicol 2001; 15:525-31.
Kopf-Maier P, Erkenswick P, Merker HJ. Toxicology 1985; 34:321-31.
Marana HR, de Andrade JM, da Silva Mathes AC, et al. Gynecol Oncol 2001; 80:272-4.
Otton G, Higgins S, Phillips KA, Quinn M. Int J Gynecol Cancer 2001; 11:413-7.
Yoshinaka A, Fukasawa I, Sakamoto T, et al. Arch Gynecol Obstet 2000; 264:124-7.
Zemlickis D, Klein J, Moselhy G, Koren G. Med Pediatr Oncol 1994; 23:476-9.

Summary

Pregnancy Category: D
Lactation Category: S

- Patients should be advised to avoid pregnancy during treatment.
- However, should pregnancy occur or the neoplasm be discovered during pregnancy, there is increasing evidence for the relative safety of **cisplatin** during gestation.

Citalopram—(Celexa)

International Brand Name—Celexa (Canada); Cipram (China, Hong Kong, Indonesia, Israel, Korea, Malaysia, Singapore, Taiwan, Thailand); Cipramil (Belgium, Brazil, Chile, Costa Rica, Denmark, Dominican Republic, El Salvador, England, Finland, Germany, Guatemala, Honduras, Ireland, Israel, Netherlands, Nicaragua, Norway, Panama, Peru, Poland, South Africa, Sweden); Citopam (India); Futuril (Germany); Humorap (Paraguay); Kitapram (Taiwan); Lupram (Philippines); Psiconor (Uruguay); Recital (Israel); Sepram (Germany); Seralgan (Austria); Serital (Germany); Seropram (Austria, Bulgaria, Czech Republic, France, Hungary, Italy, Mexico, Spain, Switzerland, Venezuela); Talam (Australia); Zentius (Argentina, Chile, Colombia)

Drug Class

Antidepressants; SSRIs

Indications

Depression

Mechanism

Serotonin reuptake inhibition

Dosage with Qualifiers

Depression—20-60mg PO qd

- **Contraindications**—hypersensitivity to drug or class, MAOI use, abrupt withdrawal
- **Caution**—seizure disorder, mania, hepatic or renal dysfunction, suicidal ideation

Maternal Considerations

Depression is an important and often unrecognized problem during pregnancy and the puerperium. Pregnancy is not a reason to discontinue therapy. Pregnancy increases the metabolism of **citalopram** necessitating an increasing dose to maintain effect. ***Side effects*** include nephrotoxity, ototoxicity, neuropathy, optic neuritis, seizures, anemia, hypokalemia, and hypoglycemia.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. **Citalopram** crosses the human placenta, achieving an F:M ratio approximating 0.66, higher than either **sertraline** or **paroxetine.** Several recent epidemiologic studies note an association between 1st trimester SSRI use (most often **paroxetine**) and CV defects. The concern is great enough the ACOG has suggested caregivers avoid **paroxetine** in the 1st trimester. The use of antidepressants in early pregnancy does not seem to carry significant risk for the human infant during the newborn period. While the clinical reports are generally reassuring, neonatal withdrawal syndrome has been reported after 3rd trimester exposure. Rodent studies reveal CV and skeletal defects.

Breastfeeding Safety

Citalopram enters human breast milk, but the neonatal concentration is very low and likely poses no threat to breastfeeding neonates.

Drug Interactions

Serotonin release by platelets plays an important role in hemostasis. Epidemiologic studies reveal an association between SSRIs and the occurrence of upper GI bleeding that is potentiated by NSAID or **aspirin** use.
Cimetidine significantly increased both the **citalopram** AUC and Cmax. The clinical significance of these findings is unknown.
There are rare post-marketing reports describing patients with weakness, hyperreflexia, and incoordination following the use of an SSRI and **sumatriptan.**
Causes a 2-fold increase in plasma **metoprolol,** which may decrease cardioselectivity.

References

American College of Obstetricians and Gynecologists. Obstet Gynecol 2006; 108:1601-3.
Berard A, Ramos E, Rey E, et al. Birth Defects Res B Dev Reprod Toxicol 2007; 80:18-27.
Doehaerd S. Related Rev Med Brux 2001; 22:A264-6.
Ericson A, Kallen B, Wiholm B. Eur J Clin Pharmacol 1999; 55:503-8.
Heikkinen T, Ekblad U, Kero P, et al. Clin Pharmacol Ther 2002; 72:184-91.
Hendrick V, Stowe ZN, Altshuler LL, et al. Am J Psychiatry 2003; 160:993-6.
Kallen BA, Olausson PO. Birth Defects Res A Clin Mol Teratol 2007; 79:301-8.
[No authors]. Prescrire Int 2006; 15:222-3.
Nordeng H, Lindemann R, Perminov KV, Reikvam A. Acta Paediatr 2001; 90:288-91.
Sit DK, Perel JM, Helsel JC, Wisner KL. J Clin Psychiatry 2008; 69:652-8.

Summary

Pregnancy Category: C
Lactation Category: S (likely)

- **Citalopram** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.
- There are alternative agents for which there is more experience during pregnancy and lactation.

Clarithromycin—(Biaxin; Biaxin XL; Klacid XL)

International Brand Name—Abbotic (Indonesia); Abbotic XL (Indonesia); Adel (Mexico); Aeroxina (Argentina); Bactirel (Colombia); Biaxin (Canada); Biaxin HP (Germany); Biclar (Belgium); Bicrolid (Indonesia); Binoklar (Indonesia); Carimycin (Taiwan); C-Clarin (Korea); Clacin (Hong Kong); Clacine (Indonesia); Clambiotic (Indonesia); Clapharma (Indonesia); Clari (Korea); Claribid (India); Claridar (Israel); Clarimac (India); Claripen (Singapore); Clarith (Japan); Claritrol (Colombia); Claroma (Korea); Clormicin (Colombia); Crixan (Singapore); Dicupal (Peru); Gervaken (Mexico); Hecobac (Indonesia); Helitic (Indonesia); Klacid (Austria, China, Denmark, Germany, Hong Kong, Hungary, Ireland, Israel, Italy, Malaysia, Netherlands, New Zealand, Portugal, South Africa, Spain, Sweden, Switzerland, Thailand); Klacid XL (Israel); Klacina (Colombia); Klaribac (Israel); Klaricid (Colombia, Costa Rica, Dominican Republic, Ecuador, El Salvador, England, Greece, Guatemala, Honduras, Japan, Korea, Mexico, Nicaragua, Panama, Peru, Philippines, Puerto Rico, Taiwan); Klaricid H.P. (Mexico); Klaricid O.D. (Mexico); Klaricid Pediatric (Philippines); Klaricid XL (Korea); Klaridex (Israel); Klaridia (Colombia); Klarin (Israel); Klerimed (Israel); Lagur (Peru); Macladin (Italy); Macrobiol (Mexico); Macrobiol S.R. (Mexico); Mavid (Germany); Naxy (France); Veclam (Italy); Zeclar (France)

Drug Class

Antibiotics; Macrolides

Indications

Infections (gram-positive aerobes: MRSA, *S. pneumoniae, S. pyogenes*; gram-negative aerobes: *H. influenzae, Moraxella catarrhalis;* other microorganisms: *Mycoplasma pneumoniae, Chlamydia pneumoniae,* MAC, *Mycobacterium intracellulare, H. pylori*)

Mechanism

Inhibits bacterial protein synthesis by binding to the 50S ribosomal subunit

Dosage with Qualifiers

Bacterial infection—250-500mg PO bid
MAC infection—15mg/kg PO qd; dose divided q12h
Coxiella burnetii (Q fever) during pregnancy—250-500mg PO bid

- **Contraindications**—hypersensitivity to drug or class
- **Caution**—hepatic dysfunction or renal failure

Maternal Considerations

Clarithromycin is used for the treatment of lower respiratory tract infections, GU tract infections, skin infections, neutropenic patients, AIDS-related infections, acute maxillary sinusitis, and active duodenal ulcer. There are no adequate reports or well-controlled studies in pregnant women. It has been suggested that *H. pylori* infection might be a cause of persistent hyperemesis gravidarum. **Clarithromycin** has also been used successfully for the treatment of Q fever, Mediterranean spotted fever and MAC during pregnancy. Studies in rats, rabbits, and monkeys indicate **clarithromycin** does not impair fertility.
Side effects include anaphylaxis, Stevens-Johnson syndrome, arrhythmia, pseudomembranous colitis, diarrhea, nausea, abdominal pain, dyspepsia, headache, and rash.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. **Clarithromycin** crosses the human placenta to a greater degree than other macrolides (6% maternal dose), making it a candidate in treatment trials of genital *Mycoplasma* and *Ureaplasma* infections during pregnancy. Post-marketing studies are reassuring. No teratogenic effects are noted in most studies of

rats, rabbits, and monkeys. However, there are reports of a modest increase in CV malformations and cleft palate in certain rodent strains.

Breastfeeding Safety

There are no adequate reports or well-controlled studies in nursing women. **Clarithromycin** enters human breast milk, reaching levels as high as 75% of the maternal concentration.

Drug Interactions

May increase plasma **theophylline** concentrations.
May increase plasma concentrations of **carbamazepine.**
Triples the plasma concentrations of the active acid metabolite of **terfenadine** 3-fold. Concomitant administration of **clarithromycin** with **terfenadine** is contraindicated.
Simultaneous oral administration of **clarithromycin** and **zidovudine** to HIV-infected adult patients decreased **zidovudine** steady-state concentrations. Based on limited data, the steady-state **zidovudine** Cmax was increased by 2-fold but the AUC was unaffected when **clarithromycin** was administered 2-4h prior to **zidovudine.**
Administration of **clarithromycin** and **ritonavir** increased **clarithromycin** AUC 77% and decreased **clarithromycin** AUC 100%. Dosage adjustments should be considered in patients with renal impairment.
May potentiate the effects of the oral anticoagulants.
May increase **digoxin** levels, producing clinical signs consistent with toxicity, including potentially fatal arrhythmias.
Administration with **ergotamine** or **dihydroergotamine** has been associated with acute ergot toxicity.
There have been post-marketing reports of drug interactions and CNS effects (e.g., somnolence and confusion) with the concomitant use of **triazolam.**
May increase concentrations of HMG-CoA reductase inhibitors (e.g., **lovastatin, simvastatin**).
There are reports of CYP3A-based interactions of **clarithromycin** with **alfentanil, bromocriptine, carbamazepine, cilostazol, cyclosporine, disopyramide, methylprednisone, quinidine, rifabutin,** and **tacrolimus.**
Concomitant administration of **clarithromycin** with **astemizole, cisapride, pimozide,** or **terfenadine** is contraindicated.

References

Amsden GW. Clin Ther 1996; 18:56-72.
Drinkard CR, Shatin D, Clouse J. Pharmacoepidemiol Drug Saf 2000; 9:549-56.
Einarson A, Phillips E, Mawji F, et al. Am J Perinatol 1998; 15:523-5.
Gilljam M, Berning SE, Peloquin CA, et al. Eur Respir J 1999; 14:347-51.
Jacoby EB, Porter KB. Am J Perinatol 1999; 16:85-8.
Jover-Diaz F, Robert-Gates J, Andreu-Gimenez L, Merino-Sanchez J. Infect Dis Obstet Gynecol 2001; 9:47-9.
Rouveix B, Levacher M, Giroud JP. Rev Pneumol Clin 1999; 55:338-43.
Sedlmayr T, Peters F, Raasch W, Kees F. Geburtshilfe Frauenheilkd 1993; 53:488-91.
Witt A, Sommer EM, Cichna M, et al. Am J Obstet Gynecol 2003; 188:816-9.

Summary

Pregnancy Category: C
Lactation Category: U

- **Clarithromycin** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

- High placental transfer during the 1st trimester makes it an attractive agent for the treatment of *Mycoplasma* and *Ureaplasma* infections.

Clavulanate potassium—(Augmentin; Augmentin ES-600; Augmentin XR)

International Brand Name—Aclam (Indonesia); Ambilan (Peru); Amocla (Korea); Amocla Duo (Korea); Amoclan (Israel, Korea); Amoclav (Germany); Amolanic (Korea); Amolanic Duo (Korea); Amometin (Korea); Amoxiclav (Mexico); Amoxiclav-BID (Mexico); Amoxiclav-Teva (Israel); Amoxi Plus (Paraguay); Amoxsiklav (Thailand); Amoxsiklav 3X (Thailand); Amoxsiklav Forte (Thailand); Amoxxlin (Korea); Ancla (Indonesia); Auclatin Duo Dry Syrup (Korea); AugMaxcil (South Africa); Augmentan (Germany); Augmentin (China, Costa Rica, Dominican Republic, Ecuador, El Salvador, Guatemala, Honduras, Hong Kong, India, Japan, Korea, Malaysia, Nicaragua, Panama, Peru, Thailand, Uruguay, Venezuela); Augmentine (Spain); Augmex (Singapore); Augpen (Thailand); Augucillin Duo (Korea); Augurcin (Philippines); Ausclav (Australia); Ausclav Duo 400 (Australia); Ausclav Duo Forte (Australia); Auspilic (Indonesia); Bactiv (Philippines); Bactoclav (Philippines); Bioclavid (Germany, Philippines); Bioclavid Forte (Philippines); Cavumox (Thailand); Clacillin Duo Dry Syrup (Korea); Clamax (Korea); Clamentin (South Africa); Clamobit (Indonesia); Clamonex (Korea, Singapore); Clamovid (Hong Kong, Malaysia, Singapore); Clamoxin (Mexico); Clamoxyl (Australia); Clamoxyl Duo 400 (Australia); Clamoxyl DuoForte (Australia); Clarin-Duo (Korea); Clavamox (Israel); Clavinex (Chile, Ecuador, Peru); Clavoxil (Brazil); Clavoxilin Plus (Peru); Clavulin (Canada, Colombia, Costa Rica, Dominican Republic, El Salvador, Guatemala, Honduras, Nicaragua, Panama, South Africa); Clavulin Duo Forte (Australia); Clavulox Duo (Argentina, Paraguay); Clavumox (Germany, Peru, South Africa); Cramon Duo (Korea); Croanan Duo Dry Syrup (Korea); Curam (Australia, Colombia, Costa Rica, Dominican Republic, El Salvador, Guatemala, Malaysia, Nicaragua, Panama, Peru, Singapore, Taiwan, Thailand); Danoclav (Indonesia); Darzitil Plus (Argentina); E-Moxclav (Israel); Enhancin (Philippines, Singapore); Fleming (Hong Kong); Fugentin (Singapore); Fulgram (Dominican Republic, El Salvador, Guatemala, Honduras, Nicaragua, Panama); Fullicilina Plus (Argentina); Gumentin (Korea); Hibiotic (Israel); Inciclav (Indonesia); Klamonex (Korea); Kmoxilin (Korea); Lactamox (Korea); Lansiclav (Indonesia); Moxiclav (Israel, Singapore); Moxicle (Korea); Moxyclav (South Africa); Natravox (Philippines); Novamox (Brazil); Nufaclav (Indonesia); Palentin (Indonesia); Quali-Mentin (Hong Kong); Ranclav (South Africa, Thailand); Suplentin (Philippines); Synermox (New Zealand); Velamox CL (Peru); Vestaclav (Malaysia); Viaclav (Indonesia); Vulamox (Colombia); Xiclav (Indonesia)

Drug Class	Anti-infectives
Indications	Combined with penicillins, **amoxicillin,** and **ticarcillin** to broaden their antibacterial spectrum to cover certain gram-negative bacteria
Mechanism	β-Lactamase inhibitor
Dosage with Qualifiers	See penicillins, **amoxicillin,** and **ticarcillin.** • **Contraindications**—hypersensitivity to drug or class • **Caution**—see penicillins, **amoxicillin,** and **ticarcillin**
Maternal Considerations	See penicillins, **amoxicillin,** and **ticarcillin.** ***Side effects*** include N/V, diarrhea, abdominal pain, colitis, anorexia, and pseudomembranous colitis; at high doses, seizures, platelet dysfunction, hemolytic anemia, encephalitis, and nephritis.
Fetal Considerations	There are no well-controlled studies in human fetuses. **Clavulanate** crosses the human placenta, appearing in umbilical blood within 1h after administration, reaching a peak at 2-3h. Rodent studies are reassuring when **clavulanate** is administered concomitantly with penicillin or **amoxicillin,** revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically.

Breastfeeding Safety

While there are no reports specifically addressing the passage of **clavulanate** into the breast milk, it is generally considered compatible with breastfeeding.

Drug Interactions

Probenecid decreases the renal tubular secretion of **amoxicillin** and is not recommended.
Administration of **allopurinol** and **ampicillin** increases the incidence of rashes compared to patients receiving **ampicillin** alone.
Clavulanate may reduce the efficacy of oral contraceptives.

References

See penicillins, **amoxicillin,** and **ticarcillin.**

Summary

Pregnancy Category: B
Lactation Category: S

- **Clavulanate** is combined with penicillin, **amoxicillin,** and **ticarcillin** to broaden their antibacterial spectrum to include certain gram-negative bacteria.

Clemastine—(Allerhist-1; Contac 12 Hour Allergy; Tavist; Tavist-1)

International Brand Name—Agasten (Brazil); Aller-Eze (England); Clamist (India); Darvine (Taiwan); Histaverin (Taiwan); Marsthine (Philippines); Tavegil (Germany, Ireland, Italy, Netherlands, Spain); Tavegyl (Austria, Belgium, Bulgaria, Colombia, Czech Republic, Denmark, Ecuador, Egypt, Hungary, Indonesia, Norway, Philippines, Portugal, Sweden, Switzerland, Taiwan, Thailand); Tavist (Philippines)

Drug Class

Antihistamines, H_1

Indications

Rhinitis, urticaria

Mechanism

Antagonizes central and peripheral H_1 receptors

Dosage with Qualifiers

Allergic rhinitis—1.34-2.68mg PO bid or tid prn
Urticaria—1.34-2.68mg PO bid or tid prn; max 8.04mg qd

- **Contraindications**—hypersensitivity to drug or class, asthma, hypersensitivity, acute attacks of asthma, known alcohol intolerance
- **Caution**—glaucoma

Maternal Considerations

There are no adequate reports or well-controlled studies of **clemastine** during pregnancy. MAOIs such as **isocarboxazid, phenelzine,** or **tranylcypromine** prolong the anticholinergic effects of antihistamines. (See **chlorpheniramine.**)
Side effects include seizures, anaphylaxis, sedation, drowsiness, dizziness, agranulocytosis, dry mouth, extreme sleepiness, confusion, weakness, ringing in the ears, blurred vision, large pupils, flushing, fever, shaking, insomnia, hallucinations, and possibly seizures.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **clemastine** crosses the human placenta. Symptoms of toxicity in neonates include excitement, hyperreflexia, tremors, ataxia, fever, seizures, fixed dilated pupils, dry mouth, and facial flushing. The dose that causes seizures approximates the lethal dose. (See **chlorpheniramine.**)

Breastfeeding Safety ····· There is no published experience in nursing women. **Clemastine** enters breast milk. A 10w old breastfeeding child developed drowsiness, irritability, refusal to feed, and neck stiffness after maternal use (1mg PO bid); 20h after the last dose, the milk level was 5-10mcg/L and the plasma level 20mcg/L. Caution is advised.

Drug Interactions ····· MAOIs prolong and intensify the anticholinergic (drying) effects of antihistamines.
Antihistamines may increase the CNS depression associated with barbiturates, tranquilizers, and alcohol.

References ····· Kok TH, Taitz LS, Bennett MJ, et al. Lancet 1982; 1:914-5.

Summary ····· **Pregnancy Category: B**
Lactation Category: U (possibly NS)
- There are alternative agents for which there is more experience during pregnancy and lactation.

Clindamycin—(Cleocin; Cleocin Phosphate; Cleocin T; Clinda-Derm; Euroclin; Turimycin)

International Brand Name—Aclinda (Germany); Albiotin (Indonesia); BB (Taiwan); Bexon (Colombia); Cleocin HCl (Australia, Taiwan); Cleocin T (Korea); Cleocin Vaginal (Korea); Climadan (Indonesia, Singapore); Clinacin (Israel); Clinbercin (Indonesia); Clincin (Taiwan); Clinda (Germany); Clindabeta (France); Clindac (Malaysia); Clindacid (Paraguay); Clindacin (Israel); Clindal (Philippines); Clindamax (Peru); Clindavid (Thailand); Clinfol (Peru); Clinika (Singapore); Clinimycin (Israel); Clinott (Thailand); Dacin (Singapore); Daclin (Indonesia); Dalacin (Argentina, Denmark, Finland, India, Japan, Spain, Sweden, Venezuela); Dalacin C (Austria, Belgium, Brazil, Bulgaria, Canada, Chile, China, Colombia, Costa Rica, Czech Republic, Ecuador, El Salvador, England, Guatemala, Honduras, Hong Kong, Hungary, Indonesia, Ireland, Italy, Malaysia, Mexico, Netherlands, Nicaragua, Panama, Peru, Philippines, Poland, Portugal, Switzerland, Thailand, Uruguay); Dalacine (France); Dalcap (India); Damicine (Colombia); Ethidan (Indonesia); Euroclin (El Salvador, Honduras, Panama); Jutaclin (Germany); Klindamycin (Thailand); Lacin (Thailand); Lanacin (Israel); Librodan (Indonesia); Lindacin (Taiwan); Lindan (Indonesia); Lisiken (Mexico); Nufaclind (Indonesia); Opiclam (Indonesia); Probiotin (Indonesia); Qualiclinda (Hong Kong); Sobelin (Germany); Tidact (Philippines, Singapore, Taiwan); Trexen (Mexico); Turimycin (Germany); Zindacline (France)

Drug Class ····· Antibiotics; Dermatologics; Lincosamides

Indications ····· Infections (gram-positive aerobes: *S. aureus, S. epidermidis*, streptococci, pneumococci; gram-negative aerobes: *Bacteroides fragilis, Fusobacterium* species; gram-positive anaerobes: *Propionibacterium, Eubacterium, Actinomyces* species, peptostreptococci, *Peptococcus, Clostridia*; group B streptococcus prophylaxis in penicillin-allergic women, bacterial vaginosis, acne vulgaris)

Mechanism ····· Bactericidal—inhibits bacterial protein synthesis

Dosage with Qualifiers ····· Bacterial infections—150-450mg PO qid ×7-14d, max 4.8g/d; alternatively, 300-900mg IV q6-12h
BV—1 applicator PV qhs ×3-7d
Acne vulgaris—apply 1% gel topically bid

NOTE: available in oral, parenteral, topical, and vaginal gel formats.

- **Contraindications**—hypersensitivity to drug or class, colitis
- **Caution**—hepatic or renal failure

Maternal Considerations ····· Because of its antimicrobial spectrum, **clindamycin** is used for the treatment of serious infections caused by anaerobes,

respiratory tract infections, postpartum endometritis, pneumonitis, and soft tissue infections caused by streptococci and staphylococci. **Clindamycin** is a popular drug for the treatment of acne in reproductive-age women. Higher doses of **clindamycin** should be used during pregnancy, as its t/2 in maternal serum appears shorter during pregnancy. When combined with **gentamicin** in patients with PPROM, there is a significant reduction in the incidence of histologic chorioamnionitis, but not the frequency of funisitis. Oral **clindamycin** cures BV in 90% and maintains a normal flora in ⅔ of treated women throughout pregnancy. The literature is unclear whether **clindamycin** vaginal gel reduces the incidence of preterm delivery in women with BV—there are randomized trials to support either conclusion. It is the antibiotic of choice for prophylaxis for neonatal group B streptococcal sepsis in patients allergic to penicillin, though there is growing resistance.
Side effects include diarrhea, thrombocytopenia, anaphylaxis, esophagitis, pseudomembranous colitis, N/V, rash, and jaundice.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. **Clindamycin** crosses the human placenta, achieving fetal levels above the typical MICs. There are no reports linking **clindamycin** with fetal malformations. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically.

Breastfeeding Safety

Clindamycin enters human breast milk. While case reports describe bloody stools in nursing newborns whose mothers were treated with **clindamycin,** it is usually considered compatible with breastfeeding.

Drug Interactions

Clindamycin has neuromuscular blocking properties that may enhance the action of other neuromuscular blocking agents. **Clindamycin** may antagonize the action of **erythromycin.**

References

Bland ML, Vermillion ST, Soper DE, Austin M. Am J Obstet Gynecol 2001; 184:1125-6.
Brumfield CG, Hauth JC, Andrews WW. Am J Obstet Gynecol 2000; 182:1147-51.
Kekki M, Kurki T, Pelkonen J, et al. Obstet Gynecol 2001; 97:643-8.
Lamont RF, Duncan SL, Mandal D, Bassett P. Obstet Gynecol 2003; 101:516-22.
Ovalle A, Martinez MA, Kakarieka E, et al. J Matern Fetal Neonatal Med 2002; 12:35-41.
Philipson A. Clin Pharmacokinet 1979; 4:297-309.
Steen B, Rane A. Br J Clin Pharmacol 1982; 13:661-4.
Ugwumadu A, Manyonda I, Reid F, Hay P. Lancet 2003; 361:983-8.
Ugwumadu A, Reid F, Hay P, Manyonda I. Obstet Gynecol 2004; 104:114-9.

Summary

Pregnancy Category: B
Lactation Category: S (likely)

- An effective drug, either alone or combined with **gentamicin,** for a variety of pregnancy-related infections.
- Prophylactic **clindamycin** vaginal gel may have a role in the reduction of preterm birth.

Clofazimine—(Lamprene)

International Brand Name—Clofozine (India); Hansepran (India); Lampren (Ireland, Netherlands, Spain, Switzerland); Lamprene (England, France); Lapren (Korea); Lapren SL (Korea)

Drug Class

Antimycobacterials

Indications

Lepromatous leprosy

Mechanism

Bactericidal—preferentially binding to mycobacterial DNA

Dosage with Qualifiers

Lepromatous leprosy—100mg PO bid for 10d, then 2×/w ×4mo

- **Contraindications**—hypersensitivity to drug or class
- **Caution**—abdominal pain, diarrhea, skin discoloration, depression or suicide, skin dryness and ichthyosis; stains soft contact lenses

Maternal Considerations

Uneven distribution and prolonged retention in the tissues are special features of **clofazimine** metabolism. There are no adequate reports or well-controlled studies in pregnant women.
Side effects include hyperpigmentation of the skin and conjunctiva and abdominal pain. These effects resolve upon cessation of therapy.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. **Clofazimine** crosses the placenta, though the kinetics remain to be elucidated. Hyperpigmentation of the neonate that resolves gradually is reported in humans. Rodent studies are generally reassuring, revealing no evidence of teratogenicity despite the use of doses higher than those used clinically. However, embryotoxicity and IUGR were noted.

Breastfeeding Safety

Clofazimine is excreted in the breast milk. The average M:P ratio was 1.5, with milk levels of 1.33mg/L and an average infant daily dose of 0.2mg/kg/d. Hyperpigmentation of the newborn resolving over 5mo is reported.

Drug Interactions

No clinically significant interactions identified.

References

Farb H, West DP, Pedvis-Leftick A. Obstet Gynecol 1982; 59:122-3.
Freerksen E, Seydel JK. Arzneimittelforschung 1992; 42:1243-5.
Holdiness MR. Clin Pharmacokinet 1989; 16:74-85.
Lopes VG, Sarno EN. Rev Assoc Med Bras 1994; 40:195-201.

Summary

Pregnancy Category: C
Lactation Category: U

- **Clofazimine** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.
- There are alternative agents for which there is more experience during pregnancy and lactation.

Clofibrate—(Apoterin; Atromid-S; Cartagyl; Clofibral; Clofibrato; Clofipront; Coles)

International Brand Name—Amadol (Japan); Apoterin A (Japan); Arterioflexin (Austria); Arterol (Indonesia); Artes (Finland); Atromidin (Belgium, Denmark, Sweden); Atromid-S (Finland, Greece, Portugal); Atromid-S 500 (Dominican Republic, El Salvador, Guatemala); Cholenal (Taiwan); Clofi ICN (Netherlands); Colebron (Taiwan); Elpi 500 (Argentina); Lipilim (Hong Kong); Miscleron (Puerto Rico); Neo Atromid (Spain); Regadrin (Bulgaria); Regelan (Austria, Germany, Switzerland); Regelan N (Germany); Triglicer (Portugal); Yuclo (Japan)

Drug Class	Antihyperlipidemics
Indications	Hypercholesterolemia
Mechanism	Fibrates act through the nuclear PPAR system, which regulates lipid metabolism
Dosage with Qualifiers	Hypercholesterolemia—2g PO qd, in divided doses *NOTE: success is defined as triglyceride level reduced 20-70%, HDL increased by 10-25%, or LDL decreased.* *NOTE: may be combined with a statin-type agent.* • **Contraindications**—severe renal or hepatic dysfunction, gallbladder disease, primary biliary cirrhosis • **Caution**—significant hepatic or renal dysfunction, rhabdomyolysis, severe hyperkalemia (with preexisting renal insufficiency)
Maternal Considerations	There are no adequate reports or well-controlled studies of **clofibrate** in pregnant women. **Clofibrate** typically reduces serum cholesterol a modest amount and serum triglycerides somewhat more. Substantial reductions in cholesterol and triglycerides can occur in type III hyperlipidemia. No study has shown a convincing reduction in fatal MI. There is little information on the effect of **clofibrate** on cholesterol metabolism during human pregnancy. For that reason, women of childbearing potential taking **clofibrate** should use effective contraception. In patients who plan to become pregnant, **clofibrate** should be withdrawn several months before conception if deemed medically safe. ***Side effects*** include mild abdominal and bowel irritation, myalgia, increased CPK, gallstones, increased serum transaminase, water retention, and breast enlargement.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **clofibrate** crosses the human placenta. It does cross the rodent placenta and alters fetal cholesterol metabolism. While teratogenic studies have not demonstrated any effect attributable to **clofibrate,** it is known that serum of the rabbit fetus accumulates a higher concentration of **clofibrate** than that in the mother.
Breastfeeding Safety	There is no published experience in nursing women. It is unknown whether **clofibrate** enters human breast milk. Animal studies revealed increase in neonatal and pup mortality rates during lactation.
Drug Interactions	Enhances oral anticoagulants such that their dose may need to be halved to maintain the PT at the desired level. Displaces acidic drugs such as **phenytoin** and **tolbutamide** from their binding sites, and has been reported to increase hypoglycemia when given with **tolbutamide.**

Fulminant rhabdomyolysis has been seen as early as 3w after initiation of combined therapy with another fibrate and **lovastatin** but may be seen after several months. The possible benefits of combined therapy with **lovastatin** and a fibrate probably do not outweigh the risks of severe myopathy, rhabdomyolysis, and acute renal failure.

References

Muller DP, Pavlou C, Whitelaw AG, McLintock D. Br J Obstet Gynaecol 1978; 85:127-33.
Nyitray M, Szaszovsky E, Druga A. Arch Toxicol Suppl 1980; 4:463-5.
Ujhazy E, Onderova E, Horakova M, et al. Pharmacol Toxicol 1989; 64:286-90.
Wilson GN, King T, Argyle JC, Garcia RF. Pediatr Res 1991; 29:256-62.

Summary

Pregnancy Category: C
Lactation Category: U

- **Clofibrate** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk and there are no other reasonable options.

Clomiphene—(Clomid; Clomifene; Milophene; Serophene)

International Brand Name—Anexin (Paraguay); Biogen (Peru); Blesifen (Indonesia); Clomhexal (Australia); Clomid (Argentina, Australia, Austria, Belgium, Canada, England, France, Ireland, Italy, Japan, Malaysia, Netherlands, Philippines, South Africa, Switzerland, Taiwan, Thailand); Clomifen (Finland, Spain); Clomifil (Indonesia); Clomin (Greece); Clomiphene Serono (Philippines); Clomivid (Denmark, Norway, Sweden); Clomoval (Israel); Clonin (Taiwan); Cloprezine (Philippines); Clostil (Philippines); Clostilbegyt (Israel, Malaysia, Puerto Rico); Dufine (Portugal); Duinum (Hong Kong, Malaysia, Singapore, South Africa, Taiwan, Thailand); Dyneric (Germany); Fensipros (Indonesia); Fertilan (China, Hong Kong); Fertilphen (Indonesia); Fertin (Indonesia); Fertomid (India, South Africa); Genoclam (Indonesia); Ikaclomin (Israel); Indovar (Portugal); Mestrolin (Indonesia); Nefimol (Mexico); Ofertil (Indonesia); Omifin (Costa Rica, El Salvador, Guatemala, Honduras, Mexico, Nicaragua, Panama, Spain); Ovamit (Malaysia, Thailand); Ova-Mit (Puerto Rico); Ovipreg (India); Pergotime (Belgium, Denmark, France, Norway); Phemilon (Japan); Phenate (New Zealand); Pinfetil (Indonesia); Profertil (Indonesia); Provula (Indonesia); Serofene (Mexico, Peru); Serophene (Austria, Canada, China, Czech Republic, England, Hong Kong, Hungary, Ireland, Korea, Netherlands, South Africa, Switzerland, Taiwan, Thailand, Uruguay); Serpafar (Bulgaria, Greece); Zimaquin (Chile, Ecuador)

Drug Class

Hormones; Stimulants, ovarian

Indications

Ovulation induction

Mechanism

Binds to estrogen receptors with both stimulatory and inhibitory effects

Dosage with Qualifiers

Ovulation induction—50mg PO qd for 5d (menstrual cycle day 5-10); max 100mg PO qd

- **Contraindications**—hypersensitivity to drug or class, pregnancy, abnormal uterine bleeding, adrenal gland dysfunction, thyroid disease, pituitary tumor, endometrial cancer
- **Caution**—PCOS, hepatic failure

Maternal Considerations

There are no indications for **clomiphene** during pregnancy. Ovarian hyperstimulation may occur even when used as directed. There is an increased incidence of multiple pregnancies, including bilateral tubal pregnancy and coexisting tubal and intrauterine pregnancy.
Side effects include thromboembolism, ovarian hyperstimulation syndrome, multiple pregnancy, ovarian enlargement, N/V, hot

	flashes, abdominal distention, breast tenderness, blurred vision, headache, and abnormal uterine bleeding.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **clomiphene** crosses the human placenta. Although a myriad of fetal abnormalities are reported in pregnancies after **clomiphene**-induced ovulation, no discernable pattern has emerged. Rare ocular abnormalities (persistent hyperplastic primary vitreous and retinal aplasia) have been reported in several children of women taking high doses during pregnancy. Rodent studies revealed hydramnios and weak, edematous fetuses with wavy ribs and bone changes.
Breastfeeding Safety	There is no published experience in nursing women. It is unknown whether **clomiphene** is excreted in human milk. However, **clomiphene** can inhibit unestablished lactation and should not be used when breastfeeding is planned.
Drug Interactions	No clinically significant interactions identified.
References	Bishai R, Arbour L, Lyons C, Koren G. Teratology 1999; 60:143-5. Canales ES, Lasso P, Soria J, Zarate A. Br J Obstet Gynaecol 1977; 84:758-9. Clark JH, Guthrie SC, McCormack SA. Adv Exp Med Biol 1981; 138:87-98. Lynch A, McDuffie R Jr, Murphy J, et al. Obstet Gynecol 2002; 99:445-51. Marsala A. Panminerva Med 1978; 20:161-3. Nagao T, Yoshimura S. Teratog Carcinog Mutagen 2001; 21:213-21. Zuckerman H, Carmel S. J Obstet Gynaecol Br Commonw 1973; 80: 822-3.
Summary	**Pregnancy Category: X** **Lactation Category: U** • **Clomiphene** is contraindicated during pregnancy. • There is no indication for its use during lactation. • Patient should be evaluated carefully to exclude pregnancy prior to beginning ovulation induction.

Clomipramine—(Anafranil)

International Brand Name—Anafranil (Argentina, Brazil, Canada, Chile, China, Colombia, Ecuador, Japan, Malaysia, Mexico, Paraguay, Philippines, Taiwan, Thailand, Uruguay, Venezuela); Anafranil 25 (Indonesia); Anafranil Retard (Austria, Denmark, Finland, Netherlands, Sweden, Switzerland); Anafranil SR (Malaysia, Singapore); Clofranil (India); Clopram (Australia); Clopress (Malaysia, New Zealand); Equinorm (South Africa); Gromin (Korea); Hydiphen (Germany); Placil (Australia); Zoiral (Hong Kong)

Drug Class	Antidepressants; Tricyclics
Indications	Obsessive-compulsive disorder, depression
Mechanism	Exact mechanism unknown; inhibits NE and serotonin reuptake
Dosage with Qualifiers	Obsessive-compulsive disorder—begin 25mg PO qhs, then increase 75mg qhs; max 250mg qhs Depression—100-250mg PO qd in 3 divided doses

- **Contraindications**—hypersensitivity to drug or class, MI, glaucoma, pheochromocytoma, prior usage of MAOIs, suicidal ideation
- **Caution**—hepatic or renal dysfunction, seizure disorder

Maternal Considerations

There are no adequate reports or well-controlled studies in pregnant women. A variety of withdrawal symptoms may occur with abrupt discontinuation of **clomipramine.** Women of reproductive age are frequently prescribed TCAs, and there has been no apparent decline in prescriptions in recent years. The frequent prescription of potentially toxic agents to pregnant women may be due to increases in unplanned pregnancies in industrial countries, lack of adequate scientific evidence on the adverse effects, and conflicting needs to treat maternal diseases and to protect fetuses.
Side effects include dry mouth, sedation, headache, constipation, and seizures.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. **Clomipramine** and its major metabolite cross the human placenta, achieving F/M ratios of 0.6 and 0.8, respectively. Withdrawal symptoms, including jitteriness, tremor, and seizures, are reported in neonates whose mothers had taken **clomipramine** until delivery. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically. Neonatal **clomipramine** on days 8-21 produced behavioral and physiologic abnormalities resembling those found in adult human depression.

Breastfeeding Safety

Since only trace amounts of **clomipramine** are found in human breast milk, it is likely compatible with breastfeeding.

Drug Interactions

A dose adjustment may be necessary when given with anticholinergic or sympathomimetic drugs.
Several TCAs block the pharmacologic effects of **guanethidine, clonidine,** or similar agents, and such an effect may be anticipated with **clomipramine** because of its structural similarity to other TCAs.
Haloperidol increases the plasma concentration of **clomipramine.** Patients with low activity of CYP2D6 have higher than expected plasma concentrations of TCAs. Depending on the fraction of drug metabolized by CYP2D6, the increase in plasma concentration may be small, or quite large (8-fold increase in plasma AUC). In addition, certain drugs inhibit the activity of this isozyme and make normal metabolizers resemble "poor metabolizers." An individual who is stable on a given dose may become abruptly toxic when given one of these inhibiting drugs as concomitant therapy. The drugs that inhibit CYP2D6 include some that are not metabolized by the enzyme (**quinidine, cimetidine**) and many that are substrates for CYP2D6 (many other antidepressants, phenothiazines, and the class IC antiarrhythmics **propafenone** and **flecainide**). While all the SSRIs (e.g., **fluoxetine, sertraline, fluvoxamine,** and **paroxetine**) inhibit CYP2D6, an isozyme also involved in TCA metabolism, they vary in the extent of inhibition. The extent to which SSRI-TCA interactions may pose clinical problems will depend on the degree of inhibition and the pharmacokinetics of the SSRI involved. Furthermore, whenever one of these drugs is withdrawn from co-therapy, an increased dose of the TCA may be required.
Because **clomipramine** is highly bound to serum protein, its use in patients taking other drugs highly bound to protein (e.g., **warfarin, digoxin**) may cause an increase in plasma

concentrations of these drugs, potentially resulting in adverse effects.

References

Feng P, Ma Y, Vogel GW. Brain Res Dev Brain Res 2001; 129:107-10.
Loughhead AM, Stowe ZN, Newport DJ, et al. Biol Psychiatry 2006; 59:287-90.
Rodriguez Echandia EL, Foscolo MR, Gonzalez A. Ann N Y Acad Sci 1988; 525:80-8.
Schimmell MS, Katz EZ, Shaag Y, et al. J Toxicol Clin Toxicol 1991; 29:479-84.
Wen SW, Walker M. J Obstet Gynaecol Can 2004; 26:887-92.
Wisner KL, Perel JM, Foglia JP. J Clin Psychiatry 1995; 56:17-20.

Summary

Pregnancy Category: C
Lactation Category: S (likely)

- **Clomipramine** should be used during pregnancy only if the benefit justifies the potential perinatal risk.

Clonazepam—(Klonopin)

International Brand Name—Amotril (Israel); Clonex (Israel); Clonopam (Taiwan); Coquan (Colombia); Iktorivil (Sweden); Kenoket (Mexico); Kriadex (Mexico); Landsen (Japan); Lonazep (India); Paxam (Australia); Povanil (Thailand); Ravotril (Chile); Rivotril (Austria, Bangladesh, Belgium, Brazil, Bulgaria, Chile, Czech Republic, Denmark, England, France, Germany, Ghana, Greece, Hungary, Ireland, India, Israel, Italy, Kenya, Netherlands, New Zealand, Norway, Pakistan, Paraguay, Peru, Poland, Portugal, South Africa, Spain, Switzerland, Tanzania, Uganda, Uruguay, Venezuela, Zambia, Zimbabwe)

Drug Class

Anxiolytics; Benzodiazepines

Indications

Absence seizures, anxiety, periodic leg movement, neuralgia

Mechanism

Binds to benzodiazepine receptors

Dosage with Qualifiers

Absence seizures—0.5-5mg PO tid
Anxiety—0.25-0.5mg PO bid or tid
Panic disorder—0.5-1mg PO bid or tid
Periodic leg movement—0.5-2mg PO tid
Neuralgia—2-4mg PO qd

NOTE: treatment should not be withdrawn abruptly.

- **Contraindications**—hypersensitivity to drug or class
- **Caution**—hepatic failure

Maternal Considerations

There are no adequate reports or well-controlled studies in pregnant women. In case reports, **clonazepam** was unrelated to complications of pregnancy, labor, or delivery. Several investigators have used **clonazepam** for seizure prophylaxis in severe preeclampsia.
Side effects include respiratory depression, neutropenia, hepatic failure, ataxia, confusion, visual changes, drowsiness, and behavioral changes.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. **Clonazepam** crosses the human placenta, achieving an F:M ratio approximating 0.60. While congenital anomalies are reported in 13% of infants whose mothers took **clonazepam** during pregnancy in combination with other antiepileptic drugs, there is no pattern of anomalies. The majority

of exposed infants are normal at birth and have normal postnatal development. Most series conclude no increase in risk, but all are underpowered to detect an increased prevalence of major malformations. Exposure in the late 3rd trimester and during labor seems to carry greater risks to the perinate. While the neonatal withdrawal syndrome is rare, children born to treated women may have symptoms varying from mild sedation, hypotonia, and reluctance to suck to apnea spells, cyanosis, and impaired metabolic responses to cold stress. These symptoms can persist from hours to months after birth.

Breastfeeding Safety

There are no adequate reports or well-controlled studies in nursing mothers. **Clonazepam** enters human breast milk. Limited study suggests the breastfeeding neonate could ingest a clinically relevant amount. Breastfed newborns should be observed closely for side effects.

Drug Interactions

CYP inducers (e.g., **pheytoin, carbamazepine, phenobarbital**) induce **clonazepam** metabolism, causing an approximately 30% decrease in plasma **clonazepam** levels. Although clinical studies have not been performed, based on the involvement of the CYP3A family in **clonazepam** metabolism, inhibitors of this enzyme system, notably oral antifungal agents, should be used with caution.

CNS depression may be potentiated by alcohol; narcotics; barbiturates; nonbarbiturate hypnotics; antianxiety agents; the phenothiazine, thioxanthene, and butyrophenone classes of antipsychotic agents; MAOIs and TCAs; and other anticonvulsant drugs.

References

Eros E, Czeizel AE, Rockenbauer M, et al. Eur J Obstet Gynecol Reprod Biol 2002; 101:147-54.

Fisher JB, Edgren BE, Mammel MC, Coleman JM. Obstet Gynecol 1985; 66(3 Suppl):34S-5S.

Lin AE, Peller AJ, Westgate MN, et al. Birth Defects Res Part A Clin Mol Teratol 2004; 70:534-6.

McElhatton PR. Reprod Toxicol 1994; 8:461-75.

Soderman P, Matheson I. Eur J Pediatr 1988; 147:212-3.

Summary

Pregnancy Category: D

Lactation Category: NS (possibly)

- There is no substantive evidence that **clonazepam** alone is a teratogen in humans, though additional study is in order.
- Exposure in the late 3rd trimester and during labor seems to carry greater risks to the perinate.
- **Clonazepam** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Clonidine—(Catapres; Catapres-TTS; Duraclon)

International Brand Name—Arkamin (India); Atensina (Brazil); Caprysin (Finland); Catapres (Bangladesh, Canada, England, Hong Kong, Ireland, Korea, Malaysia, Pakistan, Puerto Rico, South Africa); Catapresan (Austria, Belgium, Bulgaria, Chile, Colombia, Denmark, Ecuador, Finland, Germany, Greece, Italy, Netherlands, Norway, Peru, Poland, Portugal, Spain, Sweden, Venezuela); Catapresan 100 (Mexico); Catapresan Depot (Czech Republic, Germany, Switzerland); Catapresan TTS (Italy); Catapressan (Argentina, France); Catapres TTS (New Zealand); Clonipresan (Paraguay); Daipres (Japan); Dixarit (Malaysia); Haemiton (Germany); Huma-Clonidine (Hungary); Hypodine (Thailand); Melzin (Philippines); Normopresan (Israel); Normopresin (Uruguay); Paracefan (Belgium); Sulmidine (Japan); Taitecin (Japan)

Drug Class ..... Adrenergic agonist, central α_2; Antihypertensives

Indications ..... Hypertension

Mechanism ..... α_2-Adrenergic receptor agonists (centrally acting)

Dosage with Qualifiers ..... Hypertension—0.1-0.3mg PO bid; max 1.2mg PO bid. Also used for analgesia or as an adjunctive anesthetic-neuraxial given IV/PO

NOTE: caution should be used due to potential rebound hypertension.

- **Contraindications**—hypersensitivity
- **Caution**—CV disease, hepatic and renal failure

Maternal Considerations ..... **Clonidine** is popular for treatment-seeking opiate abusers, particularly those with concurrent cocaine use. The abuse potential of the drug warrants further study in this high-risk population. There are no adequate reports or well-controlled studies in pregnant women. Women withdrawing from a variety of illicit narcotics or tobacco may benefit from **clonidine** initially and then **methadone** if symptoms persist. The combination of epidural **clonidine** with **bupivacaine/fentanyl** for pain control during labor improves analgesia, and reduces the supplementation rate and frequency of shivering. A similar beneficial effect is reported when combined with subarachnoid **morphine** for post–cesarean section analgesia. Though hypotension and bradycardia are drug dependent, no adverse maternal hemodynamic effects are noted if used in low doses mixed with opioids and local anesthetic. However, troublesome maternal sedation has been reported. ***Side effects*** include drowsiness, dry mouth, constipation, headache, rash, nausea, edema, and dry eyes.

Fetal Considerations ..... There are no adequate reports or well-controlled studies in human fetuses. **Clonidine** readily crosses the placenta, achieving an F:M ratio of 1. Amniotic fluid concentrations are up to 4× those in serum. Neonates of women receiving **clonidine** during labor are not sedated, but may experience some hypotension. **Clonidine** does not negatively affect the FHR pattern. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically. However, there is an increase in the rate of embryo absorption.

Breastfeeding Safety ..... **Clonidine** is concentrated in human breast milk, reaching an M:P ratio approximating 2. Caution is advised.

Drug Interactions ..... May potentiate the CNS-depressive effect of alcohol, barbiturates, or other sedating drugs.
Narcotic analgesics may potentiate the hypotensive effects of **clonidine.**
TCAs may antagonize the hypotensive effects of **clonidine.**

β-Blockers may exacerbate the hypertensive response seen with **clonidine** withdrawal. Caution is also wise in patients receiving **clonidine** with agents known to affect sinus node function or AV nodal conduction (e.g., **digitalis,** calcium channel blockers, and β-blockers).
Epidural **clonidine** may prolong the duration of pharmacologic effects of epidural local anesthetics, including both sensory and motor blockade.
The effect of **clonidine** may be reduced by TCAs.

References

Anderson F, Paluzzi P, Lee J, et al. Obstet Gynecol 1997; 90:790-4.
Aveline C, El Metaoua S, Masmoudi A, et al. Anesth Analg 2002; 95:735-40.
Dashe JS, Jackson GL, Olscher DA, et al. Obstet Gynecol 1998; 92:854-8.
Hartikainen-Sorri AL, Heikkinen JE, Koivisto M. Obstet Gynecol 1987; 69:598-600.
Paech MJ, Pavy TJ, Orlikowski CE, Evans SF. Reg Anesth Pain Med 2000; 25:34-40.
Paech MJ, Pavy TJ, Orlikowski CE, et al. Anesth Analg 2004; 98:1460-6.
Tremlett MR, Kelly PJ, Parkins J, et al. Br J Anaesth 1999; 83:257-61.
van Tuijl I, van Klei WA, van der Werff DB, Kalkman CJ. Br J Anaesth. 2006; 97:365-70.

Summary

Pregnancy Category: C
Lactation Category: NS (possibly)

- **Clonidine** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Clorazepate—(Gen-Xene; Mendon; Nevracten; Tranxene)

International Brand Name—Ansiopax (Uruguay); Ansiospaz (Peru); Anxidin (Finland); Anxielax (Thailand); Audilex (Greece); Calner (Chile); Cloramed (Thailand); Clozene (Taiwan); Covengar (Argentina); Dipot (Thailand); Disposef (Thailand); Enadine (Argentina); Flulium (Thailand); Justum (Argentina); Manotran (Thailand); Moderane (Argentina); Nansius (Dominican Republic, Spain); Novo-Clopate (Canada); Pazidium (Paraguay); Pomadom (Thailand); Posene (Thailand); Sanor (Malaysia); Serene (Thailand); Tencilan (Argentina); Trancon (Thailand); Transene (Italy); Tranxal (Israel); Tranxen (Denmark, Venezuela); Tranxene (Barbados, Belgium, Bulgaria, Curacao, Czech Republic, Ecuador, England, France, Greece, Hong Kong, Hungary, Ireland, Malaysia, Mexico, Netherlands, Netherlands Antilles, Philippines, Poland, Portugal, South Africa, Thailand); Tranxilen (Norway, Sweden); Tranxilene (Brazil); Tranxilium (Argentina, Austria, Germany, Spain, Switzerland, Taiwan); Travex (Slovenia); Trisan (Korea); Zetran-5 (Thailand)

Drug Class

Anxiolytics; Benzodiazepines; Sedatives

Indications

Anxiety, alcohol withdrawal

Mechanism

Enhances GABA effects by binding to benzodiazepine receptors

Dosage with Qualifiers

Anxiety—15-60mg PO qd in divided doses
Alcohol withdrawal—30mg ×1, then 30-60mg/d in divided doses

- **Contraindications**—hypersensitivity to drug or class, substance abuse, glaucoma, acute angina, suicidal ideation
- **Caution**—unknown

Maternal Considerations

There are no adequate reports or well-controlled studies in pregnant women. All benzodiazepine derivatives are lipophilic, undissociated agents, which readily penetrate membranes.
Clorazepate is rapidly absorbed, with peak concentrations

reached within 2h. The absorption t/2 approximates 0.77h and the elimination t/2 is 1.3h in pregnant women.
Side effects include hepatic failure, drowsiness, headache, hypotension, and dry mouth.

Fetal Considerations

There are no adequate reports or well-controlled studies in pregnant women. **Clorazepate** appears to cross the placenta more slowly than other benzodiazepines (20% compared to 85% for **diazepam**). An increased risk of malformations is reported in some studies for some benzodiazepines. The lowest effective dose of **clorazepate** should be used during delivery, because high doses are associated with floppy infant syndrome. Rodent teratogenicity studies apparently have not been performed.

Breastfeeding Safety

Clorazepate is excreted into human breast milk at low concentrations, though the kinetics remain to be detailed. As with other benzodiazepines in breast milk, caution is advised.

Drug Interactions

Animal experience indicates that **clorazepate** prolongs the sleeping time after **hexobarbital** or after alcohol, and increases the inhibitory effects of **chlorpromazine.** Clinical studies reveal increased sedation when used with hypnotic medications. **Clorazepate** may be potentiated by barbiturates, narcotics, phenothiazines, and MAOIs or other antidepressants.

References

McElhatton PR. Reprod Toxicol 1994; 8:461-75.
Patel DA, Patel AR. JAMA 1980; 244:135-6.
Rey E, d'Athis P, Giraux P, et al. Eur J Clin Pharmacol 1979; 15:175-80.

Summary

Pregnancy Category: D
Lactation Category: U

- **Clorazepate** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.
- There is less placental transport of **clorazepate** compared to **diazepam.**
- There are usually other options available for which there is more experience during pregnancy and lactation.

Clotrimazole—(Canastene; Clomaz; Clomine; Fungicide; Gyne-Lotrimin; Lotrimin; Mycelex; Mycelex-G)

International Brand Name—Agisten (Israel); Apocanda (Germany); Aristen (Hong Kong); Baby Agisten (Israel); Caginal (Thailand); Camazol (Korea); Canazol (Thailand); Candazole (Malaysia, Singapore); Candespor (South Africa); Candid (Malaysia, South Africa); Candid-V3 (Thailand); Candid-V6 (Philippines); Candimon (Mexico); Candinox (Thailand); Candizole (South Africa); Canesten (Argentina, Bangladesh, Belgium, Brazil, Chile, Costa Rica, Dominican Republic, El Salvador, France, Guatemala, Honduras, India, Israel, Japan, Nicaragua, Pakistan, Panama, Paraguay, Peru, Poland, Puerto Rico, Slovenia, Turkey, Uruguay, Venezuela); Canesten 1 (China, Korea); Canestene (Belgium); Canifug (Germany); Catima (Korea); Chingazol (Thailand); Cinabel (Mexico); Clocreme (New Zealand); Cloderm (Germany); Clogesten (Philippines); Clomacinvag (Peru); Clomaderm (South Africa); Clomazen (Taiwan); Clomizol (Dominican Republic); Clonea (Australia); Clonitia (Indonesia); Clostrin (Japan); Clotrihexal (New Zealand); Clotrimaderm (Canada, Israel, New Zealand); Cloxy (Philippines); Clozol (Peru); Clozole (Hong Kong); Cotren (Malaysia, Thailand); Covospor (South Africa); Dermasten (Mexico); Dermatin (Israel); Durafungol (Germany); Elcid (Japan); Empecid (Argentina, Japan); Epicort (Colombia); Esporex (Peru); Factodin (Greece); Fungicip (Israel); Fungicon (Thailand); Fungiderm (Indonesia); Fungistin (Philippines); Fungizid (New Zealand); Gino-Lotrimin (Colombia); Gyne Lotremin (Indonesia, Malaysia); Gyne-Lotremin (Australia, Hong Kong); Gynesol (Philippines); Gyno Canesten (Italy); Gyno-Canestene (Belgium); Holfungin (Germany); Imazol (Germany); Jenamazol (Germany); Kanezin (Taiwan); Krema-Rosa (Israel); Lotramina (Peru); Lotremin (Malaysia, Singapore); Medizol (Colombia); Micoter (Malaysia); Mycoban (South Africa); Mycocid (India); Myco-Hermal (Israel, Singapore, Taiwan); Mycoril (Singapore, Taiwan); Mycoril Spray (Hong Kong); Mycozole (Thailand); Nalbix (Portugal); Oralten Troche (Israel); Pan-Fungex (Portugal); Panmicol (Argentina); Sastid Anti-Fungal (Singapore); Sinium (India); Taon (Japan); Taraten (Thailand); Tinaderm Extra (Australia); Tricloderm (Hong Kong); Trimadan (Indonesia); Trimaze (South Africa); Vanesten (Singapore, Thailand); Warimazol (Hong Kong); Xeraspor V (South Africa)

Drug Class	Antifungals, topical; Dermatologics
Indications	Tinea pedis, cruris, versicolor, corporis; cutaneous and vulvovaginal candidiasis
Mechanism	Alters membrane permeability
Dosage with Qualifiers	Yeast infection—1% lotion bid 2-4w for cutaneous candidiasis Vaginal candidiasis—vaginal cream should be inserted qhs ×7d • **Contraindications**—hypersensitivity to drug or class • **Caution**—unknown
Maternal Considerations	There are no adequate reports or well-controlled studies in pregnant women. Vaginal candidiasis (moniliasis or thrush) is a common and frequently distressing infection for many women. Treatments for 7d may be necessary during pregnancy rather than the shorter courses more commonly used for nonpregnant women. Topical **clotrimazole** appears to be more effective than **nystatin** for treating symptomatic vaginal candidiasis in pregnancy. One case-control study concluded women treated with vaginal **clotrimazole** during pregnancy had a lower prevalence of preterm birth that could not otherwise be explained. There are no trial data to support this observation. *Candida* sepsis should be considered in the differential diagnosis of sepsis following CVS. ***Side effects*** include erythema, burning, edema, pruritus, and vaginal irritation.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **clotrimazole** crosses the human placenta. There is little maternal, systemic absorption after dermal application, and only 3-10% is absorbed after intravaginal administration (<0.03mcg/ml). Thus, considering the dose and route, it is unlikely the maternal systemic concentration will reach a clinically relevant level. One case report describes fetal death at 18w gestation in association with a retained IUD and asymptomatic intra-amniotic and fetal infection by *C. albicans.*

Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically.

Breastfeeding Safety ..... There are no adequate reports or well-controlled studies in nursing mothers. It is unknown whether **clotrimazole** enters human breast milk. However, considering the route and level of maternal systemic absorption, it is unlikely the breastfeeding neonate would ingest a clinically significant amount.

Drug Interactions ..... No clinically significant interactions identified.

References .....

Czeizel AE, Fladung B, Vargha P. Eur J Obstet Gynecol Reprod Biol 2004; 116:157-63.
Czeizel AE, Toth M, Rockenbauer M. Epidemiology 1999; 10:437-40.
Fleury F, Hughes D, Floyd R. Am J Obstet Gynecol 1985; 152:968-70.
Guaschino S, Michelone G, Stola E, et al. Biol Res Pregnancy Perinatol 1986; 7:20-2.
Segal D, Gohar J, Huleihel M, Mazor M. Scand J Infect Dis 2001; 33:77-8.
Weisberg M. Clin Ther 1986; 8:563-7.
Young GL, Jewell D. Cochrane Database Syst Rev 2000; (2);CD000225.

Summary .....

Pregnancy Category: B
Lactation Category: S (likely)

- There is no evidence that either thrush or **clotrimazole** in pregnancy is harmful to the baby.
- Treatments ×7d for vaginitis may be necessary during pregnancy in contrast to the shorter courses used in nonpregnant women.

Cloxacillin—(NOTE: This drug has been withdrawn from the US market.)

International Brand Name—Amplium; Austrastaph; Bactopen; Chuckin; Cloxapen; Methocillin; Prostafilina; Prostaphlin; Tegopen

Drug Class ..... Antimicrobials; Penicillins

Indications ..... Bacterial infection, treatment of staphylococcal mastitis

Mechanism ..... Bactericidal—inhibits bacterial wall mucopeptide synthesis

Dosage with Qualifiers .....

Bacterial infection—250-500mg PO q6h; take 1h before or after meals

*NOTE: **cloxacillin** loses potency when used with **erythromycin, gentamicin,** and **kanamycin.** It should not be added to blood products and IV lipids.*

- **Contraindications**—hypersensitivity to drug or class
- **Caution**—hepatic or renal failure

Maternal Considerations .....

Cloxacillin sodium is a broad-spectrum antibiotic effective against penicillinase-producing *Staphylococcus* and is usually combined with **ampicillin.** There are no adequate reports or well-controlled studies in pregnant women. Before its withdrawal in

the US, **cloxacillin** was used for the treatment of mastitis. There is a significant increase in the free plasma fraction of **cloxacillin** during pregnancy, beginning in the 2nd trimester and peaking at delivery. A similarly increased free-of-fraction **cloxacillin** is found in cord blood, which increases further during the 1st postnatal week. **Cloxacillin** is highly concentrated in the kidneys.
Side effects include seizures, thrombocytopenia, agranulocytosis, and renal failure.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. **Cloxacillin** crosses the human placenta. Fetal drug levels rise slowly to equilibrium within the maternal circulation 1-3h after drug administration. Thereafter, fetal drug levels exceed maternal values. AF levels are low during early gestation, rising progressively near term until they exceed maternal values 6-8h after drug administration. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically.

Breastfeeding Safety

There is no published experience in nursing mothers. **Cloxacillin** is excreted in the breast milk of both humans and cows.

Drug Interactions

Bacteriostatic antibiotics may antagonize the bactericidal effect of penicillins. Their concurrent use should be avoided.

References

Anderson JC. J Comp Pathol 1977; 87:611-21.
Brander GC, Watkins JH, Gard RP. Vet Rec 1975; 97:300-4.
Herngren L, Ehrnebo M, Boreus LO. Dev Pharmacol Ther 1983; 6:110-24.

Summary

Pregnancy Category: B
Lactation Category: U

- There are other options for which there is more experience during pregnancy and lactation.

Clozapine—(Clozaril; Entumin; Etumine)

International Brand Name—Clopine (Taiwan); Clopsine (Mexico); Elcrit (Germany); Leponex (Austria, Bulgaria, Colombia, Czech Republic, Denmark, Finland, France, Germany, Greece, Hungary, Mexico, Netherlands, Norway, Peru, Philippines, Portugal, South Africa, Spain, Sweden, Switzerland, Turkey); Lozapin (India); Lozapine (Israel); Sizopin (India); Zapen (Colombia)

Drug Class

Antipsychotics

Indications

Atypical psychosis, schizophrenia

Mechanism

Unknown; may antagonize D_2 dopamine receptors

Dosage with Qualifiers

Psychosis (schizophrenia)—begin 12.5mg PO qd or bid, increasing up to 25-50mg in 3-7d; titer to symptoms to 150-300mg PO bid; max 900mg/d

NOTE: check CBC count q2w for agranulocytosis.

- **Contraindications**—hypersensitivity to drug or class, myocarditis, myeloproliferative disorder, glaucoma, CNS depression
- **Caution**—renal or hepatic failure, seizure and cardiac disease, bone marrow suppression

Maternal Considerations

There are no adequate reports or well-controlled studies in pregnant women. **Clozapine** is a relatively new medication for treatment-resistant schizophrenia. The published experience during pregnancy is limited to case reports. It is effective in responsive patients experiencing positive (hallucinations, delusions, bizarre behavior, hostility) and negative (withdrawal, blunted emotions, lack of motivation, and inability to experience pleasure or enjoyment) symptoms. Negative symptoms seem to respond better to **clozapine** compared to traditional antipsychotics. Studies in rats revealed a rapid increase in the level of serum prolactin with peak values at 15 and 60min. Clinical experience suggests most current psychotropic drugs are relatively safe for use in pregnancy.
Side effects include agranulocytosis, leukopenia, neuroleptic malignant syndrome, thrombosis, constipation, arrhythmias, and cardiac arrest.

Fetal Considerations

There are no adequate reports or well-controlled studies in the human fetus. It is unknown whether **clozapine** crosses the human placenta. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically.

Breastfeeding Safety

There are no adequate reports or well-controlled studies in nursing women. **Clozapine** enters human breast milk, achieving an M:P ratio between 2.8 and 4.3 and a milk level of 116ng/ml. It was estimated the nursing infant would ingest <20mcg/kg/d. Animal studies suggest **clozapine** can affect neonatal behavior. If breastfeeding continues, the infant should be monitored for possible adverse effects, the drug given at the lowest effective dose, and breastfeeding avoided at times of peak drug levels.

Drug Interactions

Should not be used with agents having a well-known potential to suppress bone marrow function.
Caution is advised using it with other CNS-active drugs or alcohol.
May potentiate the hypotensive effects of antihypertensive drugs and the anticholinergic effects of atropine-type drugs. The administration of **epinephrine** should be avoided in the treatment of drug-induced hypotension because of a possible reverse **epinephrine** effect.
Clozapine is a substrate for many CYP isozymes, especially 1A2, 2D6, and 3A4. **Phenytoin, nicotine,** and **rifampin** may decrease **clozapine** plasma levels, resulting in a decrease in effectiveness of a previously effective dose.
Cimetidine, caffeine, and **erythromycin** may increase plasma levels of **clozapine,** potentially resulting in adverse effects.
Although use with **carbamazepine** is not recommended, it should be noted discontinuation of **carbamazepine** causes an increase in plasma levels.
Fluvoxamine may increase **clozapine** and its metabolites by some 3-fold. A reduced **clozapine** dose should be considered.
In 3-10% of patients there is reduced activity of certain drug-metabolizing enzymes (e.g., CYP2D6). Such "poor metabolizers" of drugs such as **debrisoquin, dextromethorphan,** the TCAs, and **clozapine** may develop higher than expected plasma concentrations when given usual doses. In addition, certain drugs that are metabolized by this isozyme, including many antidepressants (**clozapine,** SSRIs, and others), may inhibit the activity of this isozyme, and thus may make normal metabolizers resemble poor metabolizers.

Use with other drugs metabolized by CYP2D6 may require lower doses than usually prescribed for either **clozapine** or the other drug. Caution is recommended when **clozapine** is given with antidepressants, phenothiazines, **carbamazepine,** and class 1C antiarrhythmics (e.g., **propafenone, flecainide, encainide**), or those that inhibit this enzyme (e.g., **quinidine**).

References

Barnas C, Bergant A, Hummer M, et al. Am J Psychiatry 1994; 151:945.
Dickson RA, Hogg L. Psychiatr Serv 1998; 49:1081-3.
Duran A, Usur MM, Tunan S, Emul M. J Psychopharmacol 2008; 22:111-3.
Kaplan B, Modai I, Stoler M, et al. J Am Board Fam Pract 1995; 8:239-41.

Summary

Pregnancy Category: B
Lactation Category: U

- As for most psychotropic drugs, using monotherapy and the lowest effective quantity given in divided doses to minimize the peaks can minimize the risks.

Cocaine

Drug Class

Anesthetics, local; Anesthetics, topical; Sympathomimetics

Indications

Topical anesthetic for mucosa

Mechanism

Inhibits NE reuptake in the human peripheral circulation

Dosage with Qualifiers

Topical anesthesia—dose varies with the area to be anesthetized, vascularity of the tissues, individual tolerance, and the technique of anesthesia.

NOTE: highly restricted access in the US; no indication during pregnancy; for use as a topical anesthetic of mucosa only.
NOTE: the lowest dosage needed to provide effective anesthesia should be administered.

- **Contraindications**—hypersensitivity
- **Caution**—CV disease, hypertension

Maternal Considerations

Cocaine is a highly addictive drug and is abused widely. There are no adequate reports or well-controlled studies in pregnant women. Maternal **cocaine** use is a significant public health problem, particularly in urban areas and among women of low socioeconomic status. **Cocaine** stimulates isolated myometrial contractile activity, and several clinical studies report an association between **cocaine** and preterm labor. Although **cocaine** inhibits uterine neuronal and extraneuronal uptake of catecholamines, and increases circulating levels of catecholamines in experimental animals, it is unlikely that facilitation of the α-adrenergic pathway is the sole mechanism of action. **Cocaine**-exposed women have a higher risk of medical complications including syphilis, gonorrhea, and hepatitis; psychiatric, nervous, and emotional disorders; PROM and abruptio placentae; and domestic violence.

Fetal Considerations

There are no adequate reports or well-controlled studies in the human fetus. **Cocaine** crosses the human placenta and is associated with placental abruption, free radical production, and fetal encephalopathy. **Cocaine**-exposed children are at increased

risk of significant cognitive deficits, and a doubling of the rate of developmental delay during the first 2y of life. **Cocaine** has teratogenic or adverse effects on the developing brain. **Cocaine**-exposed infants require medical attention for CNS irritation, cardiac anomalies, apnea, and feeding difficulties. It is estimated $500 million (US) in additional health expenditures result from the direct hospital costs of **cocaine**-exposed neonates. Ongoing maternal drug use is associated with worse developmental outcomes among a group of drug-exposed infants. However, the prevalent belief is that the effects of **cocaine** diminish with age and are mediated largely through psychosocial factors.

Breastfeeding Safety

There are no adequate reports or well-controlled studies in nursing mothers. **Cocaine** freely enters human breast milk and is stable.

Drug Interactions

Cocaine interferes with the uptake of NE by adrenergic nerve terminals, producing sensitization to catecholamines, causing vasoconstriction and mydriasis.

References

Bailey DN. Am J Clin Pathol 1998; 110:491-4.
Bauer CR, Shankaran S, Bada HS, et al. Am J Obstet Gynecol 2002; 186:487-95.
Chasnoff IJ, Lewis DE, Squires L. Pediatrics 1987; 80:836-8.
Delaney DB, Larrabee KD, Monga M. Am J Perinatol 1997; 14:285-8.
Nassogne MC, Evrard P, Courtoy PJ. Ann N Y Acad Sci 1998; 846:51-68.
Refuerzo JS, Sokol RJ, Blackwell SC, et al. Am J Obstet Gynecol 2002; 186:1150-4.
Schuler ME, Nair P, Kettinger L. Arch Pediatr Adolesc Med 2003; 157:133-8.
Williams JH, Ross L. Eur Child Adolesc Psychiatry 2007; 191:378-86.

Summary

Pregnancy Category: C
Lactation Category: NS

- There are no indications for **cocaine** use during pregnancy and lactation.

Codeine

International Brand Name—Actacode (Australia); Codeine Linctus (Australia); Codein Knoll (Switzerland); Codein Kwizda (Austria); Codein Phosphate (Czech Republic); Codein Slovakofarma (Czech Republic); Codeinum Phosphorcum (Poland); Codeisan (Portugal, Spain); Codenfan (France); Codicompren Retard (Germany); Codiforton (Germany); Codipront N (Philippines); Pulmocodeina (Ecuador); Solcodein (Spain); Tricodein (Ethiopia, Germany, Kenya, Nigeria, South Africa); Tricodein Solco (Austria, Switzerland)

Drug Class

Analgesics, narcotic; Antitussives

Indications

Antitussive, expectorant

Mechanism

Opiate receptor stimulant

Dosage with Qualifiers

Pain management—15-60mg PO/IM qid
Antitussive—10-20mg PO q4-6h

NOTE: also combined with ***aspirin, acetaminophen, ibuprofen, propoxyphene,*** *and others.*

- **Contraindications**—hypersensitivity to drug or class
- **Caution**—hepatic or renal dysfunction, increased ICP, hypothyroidism, acute alcoholism, chronic lung disease

Maternal Considerations	**Codeine** is metabolized to **morphine**. There are no adequate reports or well-controlled studies in pregnant women. **Codeine** is contained in many tablets prescribed for the relief of headaches. It is commonly used alone and in combination to relieve episiotomy pain during the puerperium. Combining **codeine** with an NSAID significantly enhances pain relief. **Codeine** is not effective for the relief of uterine cramps. **Codeine** overdose may be reversed with **naloxone.** ***Side effects*** include dizziness, euphoria, N/V, constipation, dry mouth, urinary retention, and itching.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. Morphine readily crosses the placenta. Rodent studies are reassuring, revealing no evidence of teratogenicity, though IUGR is seen at doses below those producing maternal toxicity. Neonatal abstinence syndrome is reported.
Breastfeeding Safety	There are no adequate reports or well-controlled studies in nursing mothers. **Codeine** and its metabolite **morphine** are excreted in human breast milk. Breastfeeding neonates have low plasma levels during the first few days of life in part secondary to the low concentration in milk, and in part due to the small amount of milk produced. Thus, moderate **codeine** use (up to 60mg) is probably compatible with breastfeeding.
Drug Interactions	**Codeine** has additive depressant effects when used with other narcotic analgesics, general anesthetics, phenothiazines, tranquilizers, sedative-hypnotics, or other CNS depressants (including alcohol). The dosage of one or both agents should be reduced.
References	Bloomfield SS, Mitchell J, Cissell G, Barden TP. Am J Med 1986; 80:65-70. Jacobson J, Bertilson SO. J Int Med Res 1987; 15:89-95. Meny RG, Naumburg EG, Alger LS, et al. J Hum Lact 1993; 9:237-40. Williams J, Price CJ, Sleet RB, et al. Fundam Appl Toxicol 1991; 16:401-13.
Summary	**Pregnancy Category: C** **Lactation Category: S** • **Codeine** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Colchicine—(Colsalide Improved; Coluric)

International Brand Name—Artrichine (Ecuador); Colchicin (Bulgaria); Colchicine capsules (Netherlands); Colchicine Houde (South Africa); Colchicum-Dispert (Hungary); Colchily (Thailand); Colchimedio (Colombia, Dominican Republic, El Salvador, Guatemala, Honduras, Panama); Colchiquim (Mexico); Colchisol (Peru); Colcine (Thailand); Colgout (Australia, Hong Kong); Conicine (Taiwan); Goutichine (Thailand); Goutnil (India); Kolkicin (Denmark); Tolchicine (Thailand)

Drug Class	Antigouts
Indications	Gout (acute, prophylaxis), chronic familial Mediterranean fever (prophylaxis)
Mechanism	Unknown; interferes with microtubule growth affecting mitosis and other, microtubule-dependent functions

Dosage with Qualifiers

Gout (acute)—1-1.2mg PO ×1, then 0.5-0.6mg PO q1-2h; max 4-8mg PO/24h; allow 2-3d between courses; alternatively, administered 1-2mg IV load, then 0.5mg IV q6h; max 4mg; allow 7d between courses
Gout (prophylaxis)—0.6mg PO 1-4×/w
Familial Mediterranean fever (prophylaxis)—1-2mg PO in divided doses bid or tid

- **Contraindications**—hypersensitivity to drug or class; CV diseases; diarrhea, N/V, or stomach pain; blood dyscrasia
- **Caution**—hepatic or renal failure, impaired GI function

Maternal Considerations

Gout is extremely rare in pregnancy. There are no adequate reports or well-controlled studies in pregnant women. **Colchicine** is found in some herbs such as *Ginkgo biloba*. It has been used successfully to treat familial Mediterranean fever. Amniocentesis is typically recommended for women using **colchicine** at conception. **Colchicine**-induced myopathy and neuropathy appear more common than previously recognized. Patients receiving long-term therapy should be monitored carefully.
Side effects include loss of hair, GI symptoms, and loss of appetite.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. **Colchicine** crosses the human placenta. While the kinetics remain to be elucidated, it is detectable after maternal ingestion of herbal remedies where the concentration is high enough to affect neutrophil adherence. It does cross the rodent placenta, and is teratogenic at doses of 1.25 and 1.5mg/kg in mice and 10mg/kg in hamsters. Because of its mechanism of action, it is suggested women who take **colchicine** during fertilization have an increased likelihood of an aneuploid fetus. As a result, some authors do not advise discontinuation of **colchicine** before pregnancy but recommend amniocentesis for karyotyping. The evidence supporting this recommendation is scant.

Breastfeeding Safety

Colchicine is excreted into human breast milk in low quantities. It usually considered compatible with breastfeeding.

Drug Interactions

Colchicine can induce reversible malabsorption of vitamin B_{12}, apparently by altering the function of ileal mucosa.
Animals studies suggest **colchicine** may increase the response to CNS depressants and to sympathomimetic agents.

References

Ben-Chetrit E, Scherrmann JM, Levy M. Arthritis Rheum 1996; 39:1213-7.
Berkenstadt M, Weisz B, Cuckle H, et al. Am J Obstet Gynecol 2005; 193:1513-6.
Ditkoff EC, Sauer. J Assist Reprod Genet 1996; 13:684-5.
Ehrenfeld M, Brzezinski A, Levy M, Eliakim M. Br J Obstet Gynaecol 1987; 94:1186-91.
Guillonneau M, Aigrain EJ, Galliot M, et al. Eur J Obstet Gynecol Reprod Biol 1995; 61:177-8.
Petty HR, Fernando M, Kindzelskii AL, et al. Chem Res Toxicol 2001; 14:1254-8.
Tutuncu L, Atasoyu EM, Evrenkaya R, Mungen E. Arch Med Res 2006; 37:178-80.

Summary

Pregnancy Category: D
Lactation Category: S

- **Colchicine** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.
- Patients should be warned against using herbal products known to contain **colchicine.**

Colesevelam—(Welchol)

International Brand Name—None identified.

Drug Class	Antihyperlipidemics; Bile acid sequestrants
Indications	Hypercholesterolemia
Mechanism	High-capacity bile acid–binding molecule
Dosage with Qualifiers	Hypercholesterolemia—4-6 tab PO qd (1 tab = 625mg colesevelam) *NOTE: medication should be taken with food.* • **Contraindications**—hypersensitivity to drug or class • **Caution**—constipation, triglycerides elevated (>300mg/dl), dysphagia, major GI surgery
Maternal Considerations	There is no published experience with **colesevelam** during pregnancy. Malabsorption of fat-soluble vitamins might occur during use. ***Side effects*** include nausea, bloating, belching, flatulence, and weight loss.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **colesevelam** crosses the human placenta. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically.
Breastfeeding Safety	There are no adequate reports or well-controlled studies in pregnant women. It is unknown whether **colesevelam** enters human breast milk.
Drug Interactions	**Colesevelam** decreased both the C_{max} and AUC of sustained-release **verapamil** by approximately 31% and 11%, respectively. The clinical significance of this finding is unclear.
References	Marquis JK, Dagher R, Baker BA, Jones MR. Reprod Toxicol 2006; 21:197-207. Shepherd J, Packard CJ, Bicker S, et al. N Engl J Med 1980; 302:1219-22.
Summary	**Pregnancy Category: B** **Lactation Category: U** • **Colesevelam** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk. • There are other agents for which there is more experience during pregnancy and lactation.

Colestipol—(Colestid)

International Brand Name—Cholestabyl (Germany); Lestid (Denmark, Finland, Norway, Sweden)

Drug Class	Antihyperlipidemics; Bile acid sequestrants
Indications	Hypercholesterolemia, digitoxin overdose

Mechanism

Binds bile acids in the intestine, creating a nonabsorbable complex

Dosage with Qualifiers

Hypercholesterolemia—2-16g qd; begin at 2g qd or bid, increase in 2g increments at 1 or 2mo intervals
Digitoxin overdose—10g PO ×1, then 5g PO q6-8h

- **Contraindications**—hypersensitivity to drug or class
- **Caution**—constipation, vitamin absorption interference

Maternal Considerations

There are no adequate reports or well-controlled studies in pregnant women. **Colestipol** is an adjunctive therapy for the reduction of elevated serum total and LDL-C in patients with primary hypercholesterolemia (elevated LDL-C) who do not respond adequately to diet. Chronic use of **colestipol** may lead to increased bleeding secondary to the hypoprothrombinemia of vitamin K deficiency.
Side effects include nausea, bloating, belching, flatulence, and weight loss.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **colestipol** crosses the human placenta. However, it is not absorbed systemically (<0.17% of the dose), and thus should not directly cause fetal harm at the recommended dosages. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically.

Breastfeeding Safety

There are no adequate reports or well-controlled studies in breastfeeding women. **Colestipol** is not absorbed into the systemic circulation, which suggests a direct effect on breastfeeding is not possible. However, prolonged use could induce malabsorption and decrease the milk concentration of vitamins A, D, and K.

Drug Interactions

In vitro studies indicate that **colestipol** binds a number of drugs. Therefore, the interval between **colestipol** and any other medication should be as long as possible. Patients should take other drugs at least 1h before or 4h after **colestipol.**
The absorption of **chlorothiazide** as reflected in urinary excretion is markedly decreased even when administered 1h before **colestipol.**
The absorption of **tetracycline, furosemide, penicillin G, hydrochlorothiazide,** and **gemfibrozil** was significantly decreased when given simultaneously with **colestipol.**
Bile acid–binding resins may interfere with the absorption of oral phosphate supplements and **hydrocortisone.**

References

Webster HD, Bollert JA. Toxicol Appl Pharmacol 1974; 28:57-65.

Summary

Pregnancy Category: B
Lactation Category: S (likely)

- **Colestipol** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Cortisone—(Cortisyl; Cortone)

International Brand Name—Adreson (Hungary, Netherlands); Altesona (Spain); Cortate (Australia, Hong Kong, Malaysia); Cortison Ciba (Germany, Switzerland); Cortisone (France); Cortisoni Acetas (Netherlands); Cortison Nycomed (Norway); Cortogen (South Africa); Cortone Acetato (Italy); Cortone-Azetat (Austria); Scheroson (Japan)

Drug Class	Corticosteroids
Indications	Adrenal insufficiency, inflammation
Mechanism	Unknown
Dosage with Qualifiers	Adrenal insufficiency—25-300mg PO qd Inflammation suppression—25-300mg PO qd *NOTE: chronic treatment may cause adrenal suppression; use the lowest dose for shortest time. Patients with systemic infection or surgical stress require supplemental therapy.* • **Contraindications**—hypersensitivity to drug or class, CHF, active untreated infections (however, may be used in patients under treatment for tuberculous meningitis) • **Caution**—seizure disorder, diabetes, hypertension, osteoporosis, hepatic dysfunction
Maternal Considerations	There are no adequate reports or well-controlled studies in pregnant women. **Cortisone** circulates both bound and unbound, the latter active and representing a small percentage. Hepatic synthesis of the steroid-binding protein increases under the influence of estrogen during early pregnancy. Women with Cushing's disease may require additional **cortisone** to saturate the newly formed binding protein and prevent the free **cortisone** level from falling during the first 2 or 3mo of pregnancy. It is suggested but poorly documented that chronic steroid administration increases the incidence of maternal infection. Women who receive a short-term burst of steroids, such as those with PPROM, have no increased incidence of chorioamnionitis. The potent fluorinated steroids, **betamethasone** and **dexamethasone,** are more effective at accelerating fetal lung maturity than the less potent corticosteroids, **cortisol, cortisone,** and **prednisone.** ***Side effects*** include adrenal insufficiency, psychosis, immunosuppression, peptic ulcer, CHF, osteoporosis, pseudotumor cerebri, pancreatitis, hypokalemia, hypertension, Cushing features, ecchymosis, acne, and impaired wound healing.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. Primate studies suggest almost complete conversion of **cortisol** to **cortisone** by the placenta. Some suggest emotional stress during organogenesis may cause congenital malformations by increasing the level of **cortisone.** Retrospective epidemiologic studies have sought an association between oral clefting and exposure to corticosteroids. After controlling for confounding factors, it was concluded that prenatal exposure to corticosteroids increase the risk of cleft lip with or without cleft palate 6-fold. IUGR and shortening of the head and mandible are also suggested sequelae. Yet, the Collaborative Perinatal Project followed women treated during the 1st trimester and, while the number of exposures was limited, no increase in congenital malformations was detected. There was no increase in risk of anomalies after organogenesis. Women exposed to topical

cortisone during pregnancy have no significant increase in birth defects. Female rats exposed to **cortisone** *in utero* exhibit premature vaginal opening. **Cortisone** accelerates fetal rat intestinal maturation, perhaps explaining why corticosteroids decrease the incidence of NEC. In sum, the evidence that **cortisone** is a human teratogen is weak. Cortisone has been reported to reduce short-term variability of the fetal heart rate; a similar phenomenon is recognized with **betamethasone.**

Breastfeeding Safety

There are no adequate reports or well-controlled studies in breastfeeding women. **Cortisone** is present in human milk, but it is unclear whether maternal treatment increases the concentration.

Drug Interactions

Drugs that induce hepatic enzymes (e.g., **phenobarbital, phenytoin, rifampin**) may increase the clearance of corticosteroids and may require increases in corticosteroid dose to achieve the desired response.
Troleandomycin and **ketoconazole** may inhibit the metabolism of corticosteroids and thus decrease their clearance. The dose of corticosteroid should be titrated to avoid steroid toxicity.
Corticosteroids may increase the clearance of chronic high-dose **aspirin.** This could lead to decreased salicylate levels or increased risk of salicylate toxicity when the corticosteroid is withdrawn.
The effect of corticosteroids on oral anticoagulants is variable. There are reports of enhanced as well as diminished effects of anticoagulants when given concurrently with corticosteroids. Coagulation indices should be monitored closely.

References

Avci S, Yilmaz C, Sayli U. J Hand Surg [Am] 2002; 27:322-4.
Collaborative Group on Antenatal Therapy. J Pediatr 1984; 104:259-67.
Cziezel A, Rockenbauer M. Teratology 1997; 56:335-340.
Dombrowski MP. Maternal Fetal Med 1996; 5:310-3.
Hansen D, Lou HC, Olsen J. Ugeskr Laeger 2001; 163:1051-7.
Israel EJ, Schiffrin EJ, Carter EA, et al. Gastroenterology 1990; 99:1333-8.
McCoy SJ, Shirley BA. Life Sci 1992; 50:621-8.
Slikker W Jr, Althaus ZR, Rowland JM, et al. J Pharmacol Exp Ther 1982; 223:368-74.
Vermillion ST, Soper DE, Bland ML, Newman RB. Am J Obstet Gynecol 2000; 183:925-9.

Summary

Pregnancy Category: C
Lactation Category: U

- **Cortisone** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Cromolyn—(Cromoglicic Acid; Cromogloz; Gastrocrom; Inostral; Intal; NasalCrom; Opticrom)

International Brand Name—Alerbul Nasal (Colombia); Alerbul Oftalmico (Colombia); Alerg (Germany); Allergo-comod (Germany); Allergocrom (Korea, Taiwan); Clesin (Korea); Cromabak (Hong Kong, Singapore); Cromadoses (France); Cromal-5 Inhaler (South Africa); Cromo-Asma (Spain); Cromogen (Israel); Cromolyn (Israel); Crom-Ophtal (Indonesia); Cromoptic (France); Cronase (Israel); Cusicrom (Taiwan); Dadcrome (Israel); DNCG Trom (Taiwan); Epicrom (Israel); Fintal (India); Frenal (Italy); Ifiral (India, Thailand); Lomudal (Belgium, Denmark, Finland, France, Greece, Italy, Netherlands, Norway, Peru, Sweden, Switzerland); Lomudal Gastrointestinum (Finland); Lomudal Nasal (Finland, Sweden); Lomudal Nesespray (Norway); Lomupren-Nasenspray (Austria); Lomusol (Austria, Belgium, France); Lomusol Forte (Netherlands); Lomusol Nasenspray (Austria); Multicrom (France); Nalcrom (Canada, England, Hong Kong, Italy, Netherlands, New Zealand, South Africa); Nasotal (Israel); Nazotral (Colombia); Noaler (Colombia); Noaler Nasal (Colombia); Opticron (France); Optrex (New Zealand); Rynacrom (Costa Rica, Dominican Republic, El Salvador, Finland, Guatemala, Honduras, Hong Kong, Israel, Korea, Malaysia, Mexico, Nicaragua, Panama, Portugal, Puerto Rico, Singapore); Rynacrom M (Hong Kong, Puerto Rico, Singapore, Thailand); Sificrom (Singapore); Vicrom (New Zealand); Vipront (Indonesia); Vistacrom (Costa Rica, Dominican Republic, El Salvador, Guatemala, Honduras, Nicaragua, Panama, South Africa); Vividrin (Malaysia, Philippines, Thailand)

Drug Class	Antiasthmatics; Mast cell stabilizers; Ophthalmics
Indications	Mastocytosis, food allergies, inflammatory bowel disease, chronic and exercise-induced asthma, allergic rhinitis and conjunctivitis
Mechanism	Inhibits mast cell degranulation, though unclear if this is its mechanism in asthma
Dosage with Qualifiers	Mastocytosis—200mg PO qid Food allergy—200mg PO qid Inflammatory bowel disease—200mg PO qid Asthma and exercise-induced asthma (chronic treatment)—20mg NEB qid Allergic rhinitis—1 puff per nostril bid or tid (5.2mg/spray) Allergic conjunctivitis, vernal keratitis—1 gtt OS/OD 4-6×/d • **Contraindications**—hypersensitivity to drug or class • **Caution**—arrhythmia
Maternal Considerations	**Cromolyn** is taken daily to prevent symptoms. It is available in an MDI or a nebulizer solution. There are no adequate reports or well-controlled studies in pregnant women. There is an increase in adverse outcomes during pregnancy in women whose asthma is poorly controlled. Intranasal corticosteroids are considered first-line therapy, followed by 1st-generation antihistamines. Rodent studies using parenterally administered drug were not associated with adverse effects. ***Side effects*** include bronchospasm, anaphylaxis, throat irritation, dry throat, bitter taste, cough, wheezing, and dizziness.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **cromolyn** crosses the human placenta. Rodent studies are reassuring, revealing no evidence of teratogenicity despite the use of doses higher than those used clinically. Adverse fetal effects (increased resorptions and decreased fetal weight) were noted only at very high parenterally administered doses that produced maternal toxicity.
Breastfeeding Safety	There are no adequate reports or well-controlled studies in breastfeeding women. It is unknown whether **cromolyn** enters human breast milk. Early prophylaxis against food allergies appears to be best achieved by breastfeeding. Exclusive

	breastfeeding should be encouraged for as long as possible when there is a family history of allergy.
Drug Interactions	No clinically relevant interactions found.
References	Ashton MJ, Clark B, Jones KM, et al. Toxicol Appl Pharmacol 1973; 26:319-28. Gerrard JW, Shenassa M. Ann Allergy 1983; 51:300-2. Gilbert C, Mazzotta P, Loebstein R, Koren G. Drug Saf 2005; 28:707-19. Popescu IG, Comanescu C, Murariu D, Stancu C. Med Interne 1981; 19:185-9. Schatz M. Semin Perinatol 2001; 25:145-52.
Summary	**Pregnancy Category: B** **Lactation Category: S** (likely) • **Cromolyn** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk. • Virtually none of the commonly used asthma medications are contraindicated during pregnancy if their use is justified by the severity of the asthma in pregnancy.

Cyanocobalamin—(Antipernicin; B-12-1000; Berubigen; Betalin 12; Betlovex; Blu-12; Cobal; Cobalparen; Cobavite; Cobex; Cobolin-M; Compensal; Corubeen; Corubin; Cpc-Carpenters; Crystamine; Crysti-12; Cyanocob; Cyanoject; Cyano-Plex; Cyomin; Cytacon; Cytaman; Depinar; Depo-Cobolin; Docemine; Dodecamin; La-12; Lifaton; Nascobal; Neurin-12; Neurodex; Neuroforte-R; Norivite; Ottovit; Pan B-12; Primabalt; Rubesol-1000; Rubisol; Rubivite; Rubramin Pc; Ruvite; Shovite; Sytobex; Vibal; Vibisone; Vitabee 12; Vita Liver; Vitamin B-12; Vita-Plus B-12; Yobramin)

International Brand Name—Arcored (Indonesia); Bedoc (Greece); Bedodeka (Israel); Behepan (Denmark, Sweden); Betolvex (Denmark, Finland, Norway, Sweden, Switzerland); Bevitex (Israel); Cobalin (Israel); Cobalmed (South Africa); Cobamin Ophth Soln (Hong Kong); Compensal 25,000 (Mexico); Creliverol-12 (Peru); Cytamen (Argentina, Australia, England, Ireland, Turkey); Dobetin (Italy); Hematolamin (Japan); Lagavit B12 (Israel, Puerto Rico); Lifaton B12 (Spain); Nascobal Intranasal Gel (Israel); Norivite-12 (South Africa); Redisol (Japan, Thailand); Rojamin (Ecuador); Rubramin (Philippines); Rubranova (Mexico); Vicapan N (Germany); Vitamina B12-Ecar (Colombia); Vitarubin (Switzerland)

Drug Class	Hematinics; Vitamins/minerals
Indications	Vitamin B_{12} deficiency, pernicious anemia
Mechanism	Coenzyme involved in major biochemical reactions
Dosage with Qualifiers	Vitamin B12 deficiency—30mcg qd ×5-10d, then 100-1000mcg SC/IM qmo; PO route can be used for maintenance Pernicious anemia—100mcg qd ×6-7d, then 100-1000mcg SC/IM qmo Recommended daily allowance—6mcg PO qd

- **Contraindications**—hypersensitivity to drug or class
- **Caution**—pruritus, diarrhea, urticaria

Maternal Considerations

"Intrinsic factor" is essential for the adequate alimentary absorption of **cyanocobalamin.** The recommended daily intake is 4mcg. **Cyanocobalamin** deficiency and the compensatory rise in homocysteine are significant risk factors for CV disease. There are no adequate reports or well-controlled studies in pregnant women. **Cyanocobalamin** deficiency has been linked to early pregnancy loss.
Side effects include anaphylaxis, thrombosis, pruritus, diarrhea, and urticaria.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. There is efficient transfer of **cyanocobalamin** against a concentration gradient from mother to fetus by 16w gestation. IUGR fetuses have impaired hepatic **cyanocobalamin** storage ability. In one study, AF **cyanocobalamin** levels were lower when the fetus had an NTD. Increased **folate** intake reduces the risk of NTD and possibly other malformations. Evidence suggests the beneficial effect of **folate** is related to improved function of methionine synthase, a **cyanocobalamin**-dependent enzyme converting homocysteine to methionine. Rodent teratogenicity studies have not been performed.

Breastfeeding Safety

While there are no adequate reports or well-controlled studies in breastfeeding women, **cyanocobalamin** is generally considered safe for breastfeeding women in therapeutic doses. The recommended daily intake is 4mcg.

Drug Interactions

Chloramphenical may decrease the efficacy of **cyanocobalamin** by interferring with RBC maturation.
Omeprazole may decrease absorption.

References

Abbas A, Snijders RJ, Nicolaides KH. Br J Obstet Gynaecol 1994; 101:215-9.
Abbas A, Snijders RJ, Sadullah S, Nicolaides KH. Fetal Diagn Ther 1994; 9:14-8.
Berg MJ, Van Dyke DC, Chenard C, et al. J Am Diet Assoc 2001; 101:242-5.
Economides DL, Ferguson J, Mackenzie IZ, et al. Br J Obstet Gynaecol 1992; 99:23-5.
Fairfield KM, Fletcher RH. JAMA 2002; 287:3116-26.
Reznikoff-Etievant MF, Zittoun J, Vaylet C, et al. Eur J Obstet Gynecol Reprod Biol 2002; 104:156-9.
Walker MC, Smith GN, Perkins SL, et al. Am J Obstet Gynecol 1999; 180:660-4.

Summary

Pregnancy Category: C
Lactation Category: S
- **Cyanocobalamin** is contained in most prenatal vitamin tablets, though the evidence it improves pregnancy outcome overall is weak.

Cyclamate

International Brand Name—None identified.

Drug Class	Artificial sweetener
Indications	Food sweetener
Mechanism	Stimulation of the sweet receptors
Dosage with Qualifiers	Food sweetener—max 1.5g qd • **Contraindications**—hypersensitivity • **Caution**—unknown
Maternal Considerations	**Cyclamate** is 30× sweeter than sucrose and has been used in foods since the 1950s. It was removed from food products in the US and Canada in the 1970s after several animal studies suggested it posed an increased risk of papillary carcinoma of the bladders in rats fed the maximum dietary level. However, there are no adequate well-controlled studies in human subjects, and epidemiologic study does not suggest an increased incidence of cancer in humans. While still banned in the US, it is available in Canada and Europe. The scientific community is reviewing current data that may support **cyclamate** approval again.
Fetal Considerations	No adequate or well-controlled studies have been performed in human fetuses. **Cyclamate** crosses the human placenta. Rodent teratogenicity studies reveal no increase in adverse outcomes.
Breastfeeding Safety	There is no published experience in nursing women. It is unknown whether **cyclamate** enters human breast milk.
Drug Interactions	No clinically relevant interactions identified.
References	Massobrio M, Coppo F, Rappelli F. Minerva Ginecol 1971; 23:507-35. Oser BL, Carson S, Cox GE, et al. Toxicology 1975; 4:315-30. Pitkin RM, Reynolds WA, Filer LJ Jr. Am J Obstet Gynecol 1970; 108:1043-50. Schmahl D, Habs M. Arzneimittelforschung 1980; 30:1905-6. Ward VL, Zeman FJ. J Nutr 1971; 101:1635-46.
Summary	**Pregnancy Category: D** **Lactation Category: U** • Artificial sweetener of unclear risk during pregnancy and lactation.

Cyclobenzaprine—(Flexeril)

International Brand Name—Cyben (Korea); Flexiban (Italy, Portugal); Tensodox (Peru); Yurelax (Spain)

Drug Class	Muscle relaxants
Indications	Muscle spasm
Mechanism	Believed to act centrally

Dosage with Qualifiers

Muscle spasm—10mg PO tid; max 40-60mg/d

- **Contraindications**—hypersensitivity to drug or class, prior use of MAOIs in the last 14d, hyperthyroidism, recent MI, arrhythmias
- **Caution**—glaucoma

Maternal Considerations

Cyclobenzaprine relieves skeletal muscle spasm of local origin without interfering with muscle function. It is ineffective in muscle spasm due to CNS disease. There is no published experience with **cyclobenzaprine** during pregnancy.
Side effects include arrhythmias, seizures, MI, hepatitis, N/V, dry mouth, dizziness, asthenia, dyspepsia, blurred vision, and nervousness.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **cyclobenzaprine** crosses the human placenta. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically.

Breastfeeding Safety

There is no published experience in nursing women. It is unknown whether **cyclobenzaprine** enters human breast milk.

Drug Interactions

May have life-threatening interactions with MAOIs.
May enhance the effects of alcohol, barbiturates, and other CNS depressants.

References

Harwood MI, Chang SI. J Fam Pract 2002; 51:118.
Kobayashi H, Hasegawa Y, Ono H. Eur J Pharmacol 1996; 311:29-35.
Stein WM, Read S. J Pain Symptom Manage 1997; 14:255-8.

Summary

Pregnancy Category: B
Lactation Category: U

- There is no published experience during pregnancy.

Cyclophosphamide—(Cytokan; Cytoxan; Endoxon; Neosar; Neosar for Injection)

International Brand Name—Alkyroxan (Korea); Carloxan (Denmark); Ciclofosfamida (Colombia, Peru); Ciclolen (Mexico); Cicloxal (Spain); Cycloblastin (South Africa); Cycloblastine (Belgium, Netherlands); Cyclo-Cell (Germany); Cyclophar (Philippines); Cyclostin (Germany); Cyclostin N (Germany); Cytophosphan (Israel); Endoxan (Austria, Belgium, Bulgaria, China, Germany, Greece, Hungary, Israel, Japan, New Zealand, Portugal, Russia, South Africa, Turkey); Endoxana (England, Ireland); Endoxan Asta (Philippines); Endoxan-Asta (Argentina, Australia, Costa Rica, Dominican Republic, El Salvador, France, Guatemala, Honduras, Hong Kong, India, Indonesia, Israel, Italy, Malaysia, Netherlands, Nicaragua, Panama, Philippines, Switzerland, Taiwan, Thailand); Endoxon-Asta (Australia); Enduxan (Brazil); Genoxal (Mexico, Spain); Ledoxan (Philippines); Ledoxina (Mexico); Lyophilisate (Indonesia); Procytox (Canada); Sendoxan (Denmark, Finland, Norway, Sweden); Syklofosfamid (Finland, Taiwan, Turkey)

Drug Class

Antineoplastics, alkylating agent; Antirheumatics

Indications

Chemotherapy (cancer: ovary, bladder, lung, esophageal, cervical, breast, gastric, lymphoma, myeloma, sarcoma, gestational trophoblastic disease), mycosis fungoides, immune disorders such as rheumatoid arthritis

Mechanism

Alkylates and cross-links DNA (nitrogen mustard)

Dosage with Qualifiers

Chemotherapy—varies depending on tumor and protocol
Mycosis fungoides—2-3mg/kg PO qd
Rheumatoid arthritis—1.5-3mg/kg PO qd

NOTE: hydration is essential.

- **Contraindications**—hypersensitivity to drug or class, bone marrow depression
- **Caution**—renal or hepatic failure, leukopenia, thrombocytopenia, recent radiation, recent chemotherapy

Maternal Considerations

Cyclophosphamide is an alkylating agent used to treat cancer of the ovary, breast, and blood and lymph systems. Transient sterility is common after **cyclophosphamide,** and there is a risk of secondary malignancy. There are no adequate reports or well-controlled studies in pregnant women. Multiple case reports suggest it can be used with a good pregnancy outcome, though the loss rate in women with lupus may be increased after 1st trimester administration.
Side effects include infertility, CHF, malignancy, anaphylaxis, leukopenia, thrombocytopenia, cardiomyopathy, alopecia, rash, headache, N/V, dizziness, and stomatitis.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. **Cyclophosphamide** crosses the human placenta, though the kinetics remain to be detailed. Population studies have not convincingly demonstrated teratogenicity in humans, though neonatal hematologic suppression and secondary malignancies in the offspring are reported. Studies conducted in rodents suggest an increased incidence of fetal malformations and decreased implantation.

Breastfeeding Safety

Cyclophosphamide enters human breast milk in high concentration and is generally considered not compatible with breastfeeding. Neonatal neutropenia has been reported.

Drug Interactions

The rate of metabolism and the leukopenic activity of **cyclophosphamide** are increased by chronic administration of high doses of **phenobarbital.**
Causes a marked and persistent inhibition of cholinesterase activity and may thus potentiate the effect of **succinylcholine.** The anesthesiologist should be notified if the patient was treated within 10d of general anesthesia.

References

Altintas A, Vardar MA. Eur J Gynaecol Oncol 2001; 22:154-6.
Amato D, Niblett JS. Med J Aust 1977; 1:383-4.
Ben-Arie A, Piura B, Biran H, et al. Acta Obstet Gynecol Scand 2001; 80:672-3.
Clowse ME, Magder L, Petri M. Lupus 2005; 14:593-7.
Enns GM, Roeder E, Chan RT, et al. Am J Med Genet 1999; 86:237-41.
Kart Koseoglu H, Yucel AE, Kunefeci G, et al. Lupus 2001; 10:818-20.
Meirow D, Epstein M, Lewis H, et al. Hum Reprod 2001; 16:632-7.
Ozalp SS, Yalcin OT, Tanir HM. Eur J Gynaecol Oncol 2001; 22:221-2.
Peters BG, Bray JJ, Masidonski P, Mahon SM. Oncol Nurs Forum 2001; 28:639-42.
Sharon N, Neumann Y, Kenet G, et al. Pediatr Hematol Oncol 2001; 18:247-52.
Zemlickis D, Lishner M, Erlich R, Koren G. Teratog Carcinog Mutagen 1993; 13:139-43.

Summary	**Pregnancy Category: D** **Lactation Category: NS** • **Cyclophosphamide** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk. • Breastfeeding should be avoided during therapy.

Cycloserine—(Cicloserina; Cyclorin; Seromycin)

International Brand Name—Closina (Australia); Cyclomycin (Japan); Cyclorine (India); Cycosin (India); Orientomycin (Japan)

Drug Class	Antimycobacterials
Indications	Active pulmonary and extrapulmonary TB
Mechanism	Interferes with the synthesis of the bacterial cellular wall
Dosage with Qualifiers	TB—250mg PO q12h ×2w; continue 0.5-1g/d in divided doses based on blood levels (max 1g/d) • **Contraindications**—epilepsy, depression, severe anxiety, psychosis, severe renal insufficiency, alcoholism • **Caution**—drowsiness, headache, mental confusion, tremors, vertigo, loss of memory, psychoses
Maternal Considerations	There are no adequate reports or well-controlled studies of **cycloserine** in pregnant women. The published experience is limited to case reports with no obvious pregnancy-related adverse effects.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **cycloserine** crosses the human placenta. No teratogenic effects have been described in human fetuses.
Breastfeeding Safety	**Cycloserine** is excreted into human breast milk in small quantities, though the kinetics remain to be detailed. No adverse effects have been reported. It is generally considered compatible with breastfeeding.
Drug Interactions	Use with **ethionamide** may potentiate neurotoxic side effects. Alcohol increases the possibility and risk of epileptic episodes. Use with **isoniazid** may result in increased incidence of CNS effects, such as dizziness or drowsiness. Dosage adjustment may be necessary.
References	Lessnau KD, Qarah S. Chest 2003; 123:953-6. Sanguigno N. Scand J Respir Dis Suppl 1970; 71:178-9. Tran JH, Montakantikul P. J Hum Lact 1998; 14:337-40.
Summary	**Pregnancy Category: C** **Lactation Category: S** • **Cycloserine** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Cyclosporine—(Ciclosporin; Neoral; Sandimmune; SangCya)

International Brand Name—Cipol (Korea); Cipol-N (Korea); Consupren (Israel, Thailand); Deximune (Israel); Gengraf (Hong Kong); Implanta (China, Korea); Imusporin (Colombia, India); Sandimmun (Bangladesh, Bulgaria, Canada, Ecuador, India, Israel, Mexico, Netherlands, Pakistan, Peru, Poland, Slovenia, South Africa, Taiwan); Sandimmun Neoral (Australia, Austria, Canada, China, Colombia, Czech Republic, Denmark, England, Finland, Greece, Hong Kong, Indonesia, Korea, Mexico, Norway, Peru, Philippines, South Africa, Sweden, Switzerland, Thailand, Turkey); Sangcya (Israel)

Drug Class	Immunosuppressants
Indications	Prevention of transplant organ rejection
Mechanism	Believed to act through inhibition of T lymphocytes
Dosage with Qualifiers	Prevention of transplant rejection—5-10mg/kg/d PO in 2 divided doses; 5-6mg/kg IV 4-12h before surgery • **Contraindications**—hypersensitivity to drug or class, hypertension • **Caution**—hepatic or renal failure
Maternal Considerations	There are no adequate reports or well-controlled studies in pregnant women. **Cyclosporine** promotes growth of 1st trimester human cytotrophoblasts by apparently increasing their invasive ability. Successful pregnancy after solid organ transplantation is common. Preconception criteria for the optimal transplant recipient include good transplant graft function, no evidence of rejection, a minimum of 1-2y post-transplantation, and either no or well-controlled hypertension. For these women, pregnancy is generally without significant adverse effect. Because preeclampsia develops in 30% of pregnant renal transplant patients, especially those with pretransplantation arterial hypertension, BP, renal function, proteinuria, and weight should be monitored every 2-4w until the 3rd trimester, and then every week. Antihypertensive agents should be changed to those tolerated during pregnancy. **Cyclosporine** alters placental endothelin-1/NO vasoactive balance, yet newborns of transplant recipient mothers are typically AGA and normotensive. ***Side effects*** include seizures, thrombocytopenia, anaphylaxis, leukopenia, infection, hyperglycemia, hyperkalemia, and hyperuricemia.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. Transfer of **cyclosporine** across the isolated perfused placenta is poor, <5% of the maternal load. This is consistent with a case report. Most offspring have normal postnatal growth and development after maternal immunosuppressive therapy. Some studies suggest a higher risk of stillbirth, preterm delivery, and IUGR in transplant patients treated with **cyclosporine.** Whether this is due to the disease or **cyclosporine** is unknown. Preliminary evidence suggests prenatal exposure to immunosuppressive drugs does not have a profound effect on the developing immune system. Children born to transplanted women taking **cyclosporine** have normal renal function despite prolonged exposure *in utero.*
Breastfeeding Safety	There are no adequate reports or well-controlled studies in nursing mothers. **Cyclosporine** is excreted into human breast milk at low quantities, though neonatal clearance may be low. In one study, breastfed infants of treated mothers ingested less than

300mcg/d and absorbed undetectable amounts. However, in another study of 5 breastfeeding women, there was a wide range of infant exposures, and 1 infant reached a therapeutic level despite low milk concentrations. In rats, neonatal exposure to **cyclosporine** in breast milk causes significant alterations in T-cell maturation and inhibition of lymphoproliferative responsiveness to mitogen activation. In rabbits, it reduces the number of nephrons.

Drug Interactions

Drugs that may potentiate renal dysfunction include **amphotericin B,** azapropazon, **cimetidine, colchicine, diclofenac, gentamicin, ketoconazole, melphalan, naproxen, ranitidine, sulindac, tacrolimus, tobramycin, trimethoprim-sulfamethoxazole,** and **vancomycin.**

Orlistat decreases absorption and should be avoided.

Cyclosporine is extensively metabolized by CYP3A. Agents that inhibit CYP3A may decrease metabolism and increase **cyclosporine** concentrations. These include **allopurinol, amiodarone, bromocriptine, clarithromycin, colchicine, danazol, diltiazem, erythromycin, fluconazole, indinavir, itraconazole, ketoconazole, methylprednisolone, metoclopramide, nelfinavir, nicardipine, quinupristin-daldopristin, ritonavir, saquinavir,** and **verapamil.**

Grapefruit and grapefruit juice also increase **cyclosporine** blood level.

Agents that reduce **cyclosporine** levels include **carbamazepine, nafcillin, octreotide, orlistat, phenobarbital, phenytoin, rifampin,** and **ticlopidine.**

There are reports of a serious drug interaction between **cyclosporine** and the herbal dietary supplement St. John's wort. This interaction produces a marked reduction in the blood concentrations of **cyclosporine,** leading to rejection of transplanted organs and graft loss.

Clinical status and serum creatinine should be closely monitored when **cyclosporine** is used with an NSAIDs in rheumatoid arthritis patients.

Pharmacodynamic interactions have been reported to occur between **cyclosporine** and both **naproxen** and **sulindac,** in that their use is associated with decreased renal function. This interaction leads to a doubling of **diclofenac** levels and a reversible decrease in renal function. Thus, the dose of **diclofenac** should be in the lower end of the therapeutic range.

Preliminary data reveal that **methotrexate** AUC increase 30% and the AUC of its metabolite, 7-hydroxy methotrexate, decreased by 80% when administered to rheumatoid arthritis patients with **cyclosporine.**

May reduce the clearance of **digoxin, colchicine, prednisolone,** and HMG-CoA reductase inhibitors (statins). Severe digitalis toxicity has occurred within days of starting **cyclosporine** in patients taking **digoxin.** There are also reports of **colchicine**-induced myopathy and neuropathy, especially in patients with renal dysfunction.

Myotoxicity, including muscle pain and weakness, myositis, and rhabdomyolysis, is reported with co-administration with **lovastatin, simvastatin, atorvastatin, pravastatin,** and **fluvastatin.** Thus, the dose of these statins should be reduced according to label recommendations.

Hyperkalemia may result if used with potassium-sparing diuretics.

Vaccination may be less effective if given with **cyclosporine.** The use of live vaccines should be avoided.

Frequent gingival hyperplasia with **nifedipine** and convulsions with high-dose **methylprednisolone** are reported.

Psoriasis patients receiving other immunosuppressive agents or radiation therapy (including PUVA and UVB) should not receive **cyclosporine** because of the possibility of excessive immunosuppression.
For detailed information on cyclosporine drug interactions, please contact Novartis Medical Affairs Department at 888-NOW-NOVA (888-669-6682).

References

Cimaz R, Meregalli E, Biggioggero M, et al. Toxicol Lett 2004; 149:155-62.
Di Paolo S, Monno R, Stallone G, et al. Am J Kidney Dis 2002; 39:776-83.
Giudice PL, Dubourg L, Hadj-Aissa A, et al. Nephrol Dial Transplant 2000; 15:1575-9.
Moretti ME, Sgro M, Johnson DW, et al. Transplantation 2003; 75:2144-6.
Munoz-Flores-Thiagarajan KD, Easterling T, Davis C, Bond EF. Obstet Gynecol 2001; 97:816-8.
Nandakumaran M, Eldeen AS. Dev Pharmacol Ther 1990; 15:101-5.
Nyberg G, Haljamae U, Frisenette-Fich C, et al. Transplantation 1998; 65:253-5.
Padgett EL, Seelig LL Jr. Transplantation 2002; 73:867-74.
Raddadi AA, Baker Damanhoury Z. Br J Dermatol 1999; 140:1197-8.
Sgro MD, Barozzino T, Mirghani HM, et al. Teratology 2002; 65:5-9.
Tendron A, Decramer S, Justrabo E, et al. J Am Soc Nephrol 2003; 14:3188-96.
Wu A, Nashan B, Messner U, et al. Clin Transplant 1998; 12:454-64.
Yan F, Li D, Sun X, Zhu Y, et al. Zhonghua Fu Chan Ke Za Zhi 2002; 37:74-6.

Summary

Pregnancy Category: C
Lactation Category: S (likely)
- **Cyclosporine** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Cyproheptadine—(Actinal; Aptide; Cyheptin; Huavine; Ioukmin; Nekomin; Oractine; Periactin; Setomin)

International Brand Name—Adekin (Greece); Antisemin (Taiwan); Apeton 4 (Indonesia); Ciplactin (India); Ciproral (Germany); Ciprovit-A (Peru); Cyheptine (Thailand); Cylat (Indonesia); Cyproatin (Japan); Cyprogin (Hong Kong, Thailand); Cypro H (Taiwan); Cypromin (Japan); Cyprono (Thailand); Cyprosian (Thailand); Cytadine (Taiwan); Ennamax (Indonesia); Glocyp (Indonesia); Heptasan (Indonesia); Ifrasal (Japan); Istam-Far (Greece); Klarivitina (Spain); Kulinet (Greece); Periactine (France); Peritol (India, Puerto Rico); Petina (Malaysia); Pilian (Malaysia); Pronicy (Indonesia); Sinapdin (Indonesia); Trimetabol (Colombia)

Drug Class

Antihistamines, H_1; Antihistamines, sedating

Indications

Allergic rhinitis

Mechanism

Central and peripheral H_1 receptor antagonist, serotonin receptor antagonist

Dosage with Qualifiers

Allergic rhinitis—4mg PO tid

- **Contraindications**—hypersensitivity to drug or class, gastric ulcer, glaucoma, MAOIs used up to 14d prior, bladder neck obstruction
- **Caution**—unknown

Maternal Considerations

There are no adequate reports or well-controlled studies in pregnant women. **Cyproheptadine** is used to prevent or relieve symptoms of rhinitis (inflammation of the mucous membranes of the nasal passages, often associated with hay fever and other seasonal allergies); skin itching and hives; and tissue swelling (angioedema). It is also used to stimulate appetite in women with anorexia nervosa (8mg PO qid).
Side effects include agranulocytosis, dry mouth, N/V, urinary retention, dizziness, headache, rash, diarrhea, weight gain, and glucose intolerance.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **cyproheptadine** crosses the human placenta. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically. **Cyproheptadine** alters insulin-secreting beta cell function in the fetal rat pancreas when given to pregnant rats at a dose that has no apparent effects on the maternal pancreas.

Breastfeeding Safety

There is no published experience in nursing women. It is unknown whether **cyproheptadine** enters human breast milk.

Drug Interactions

MAOIs prolong and intensify the anticholinergic effects of antihistamines.
Antihistamines may have an additive effect with alcohol and other CNS depressants (e.g., hypnotics, sedatives, tranquilizers, antianxiety agents).

References

Chow SA, Fischer LJ. Drug Metab Dispos 1987; 15:740-8.
Chow SA, Fischer LJ. Toxicol Appl Pharmacol 1986; 84:264-77.
Kasperlik-Zaluska A, Migdalska B, Hartwig W, et al. Br J Obstet Gynaecol 1980; 87:1171-3.
Rodriguez Gonzalez MD, Lima Perez MT, Sanabria Negrin JG. Teratog Carcinog Mutagen 1983; 3:439-46.

Summary

Pregnancy Category: B
Lactation Category: U
- There are alternative, selective agents for which there is more experience during pregnancy and lactation.

Cytarabine—(Cytosar-U; Tarabine PFS)

International Brand Name—Alexan (Austria, Belgium, Bulgaria, China, Czech Republic, Denmark, England, Germany, Hong Kong, Hungary, Indonesia, Ireland, Italy, Malaysia, Mexico, Philippines, Portugal, South Africa, Sweden, Switzerland, Thailand, Turkey); Arabitin (Japan); Aracytin (Colombia, Greece, Italy); Aracytine (France); Citarabina (Peru); Cytarine (India, Thailand); Cytonal (Turkey); Cytosar (Austria, Belgium, Bulgaria, Canada, China, Czech Republic, Denmark, England, Finland, Ghana, Hong Kong, Hungary, Kenya, Netherlands, Norway, Philippines, Portugal, South Africa, Sweden, Switzerland, Tanzania, Uganda, Zambia); Cytosar U (New Zealand); Cytosa U (Korea); Iretin (Japan); Laracit (Mexico); Novumtrax (Mexico); Udicil (Germany); Udicil CS (Germany)

Drug Class

Antineoplastics, antimetabolite

Indications

Leukemia

Mechanism

Interferes with RNA and DNA chain elongation after incorporation

Dosage with Qualifiers

Cancer—varies with protocol; most recommend 100mg/m^2/d by continuous IV infusion (days 1-7) or 100mg/m^2 IV q12h (days 1-7)
AML—30mg/m2 q4d until CSF findings are normal (intrathecal administration)

- **Contraindications**—hypersensitivity to drug or class, pregnancy, infertility
- **Caution**—renal or hepatic failure

Maternal Considerations

There are no adequate reports or well-controlled studies in pregnant women. The coexistence of leukemia and pregnancy is extremely rare. **Cytarabine** is used during pregnancy to achieve remission of the acute episodes. It is an essential component of the drug regimen used for the treatment of AML. Once remission is achieved, the dose should be readjusted.
Side effects include anemia, bruising, N/V, hair loss, leukopenia, bone marrow suppression, and pancreatitis.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. **Cytarabine** does appear to cross the human placenta, though the kinetics remain to be detailed. In humans, **cytarabine** is associated with fetal brachycephaly, hypoplasia of the anterior cranial base and the midface, cranial synostoses, IUGR, neonatal leukopenia, and elevation of neonatal hepatic transaminases. Unaffected neonates appear to mature normally. In rodents, **cytarabine** causes microcephalia and joint anomalies.

Breastfeeding Safety

There are no adequate reports or well-controlled studies in nursing women. It is unknown whether **cytarabine** enters human breast milk.

Drug Interactions

In vitro, cytarabine may decrease the efficacy of **gentamicin** for certain *Klebsiella pneumoniae* strains.
May reduce **fluorocytosine** efficacy.

References

Caligiuri MA, Mayer RJ. Semin Oncol 1989; 16:388-96.
Cantini E, Yanes B. South Med J 1984; 77:1050-2.
Fassas A, Kartalis G, Klearchou N, et al. Nouv Rev Fr Hematol 1984; 26:19-24.
Ono-Yagi K, Ohno M, Iwami M, et al. Acta Neuropathol 2000; 403-8.
Requena A, Velasco JG, Pinilla J, Gonzalez-Gonzalez A. Eur J Obstet Gynecol Reprod Biol 1995; 63:139-41.

Summary

Pregnancy Category: D
Lactation Category: U

- **Cytarabine** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.
- **Cytarabine** would appear to be a modest human teratogen.

Dacarbazine—(DTIC-Dome)

International Brand Name—Dacarbazin (Czech Republic); Dacarbazine DBL (Malaysia); Dacarbazine Dome (Denmark); Dacarbazine for Injection (Australia); Dacatic (Finland); Deticene (Czech Republic, France, Greece, Hong Kong, Israel, Italy, Malaysia, Mexico, Netherlands, Portugal, Russia, Switzerland, Turkey); Detimedac (Germany); DTI (Korea); DTIC (Austria, Canada, Germany, Japan, Sweden); D.T.I.C. (Australia); DTIC Dome (Ireland); DTIC-Dome (Belgium, England, Korea, New Zealand, Spain, Switzerland, Taiwan); D.T.I.C.-Dome (South Africa); DTIC-VHB (India)

Drug Class ..... Antineoplastics, alkylating agent

Indications ..... Melanoma, Hodgkin's disease

Mechanism ..... Primary action appears to be alkylation of nucleic acids

Dosage with Qualifiers .....

Melanoma, Hodgkin's disease—numerous dosing schedules depend on disease, response, and concomitant therapy: 375mg/m^2; 850mg/m^2; 250mg/m^2/d ×5d; 2-4.5mg/kg/d ×10d; 650-1450mg/m^2 are the most frequent regimens; intra-arterial administration is no longer recommended

- **Contraindications**—hypersensitivity to drug or class
- **Caution**—hepatic or renal dysfunction

Maternal Considerations .....

There are no adequate reports or well-controlled studies in pregnant women. There are many case reports of **dacarbazine** use during pregnancy with a good outcome.
Side effects include leukopenia, alopecia, thrombocytopenia, anorexia, N/V, hepatotoxicity, diarrhea, fever, myalgias, hepatic or renal dysfunction, and photosensitivity.

Fetal Considerations .....

There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **dacarbazine** crosses the human placenta. No teratogenic effects are described in human fetuses, and long-term follow-up studies of children exposed *in utero* in the 1st trimester are reassuring. **Dacarbazine** is both teratogenic and embryotoxic in rodents when given at multiples of the MRHD.

Breastfeeding Safety .....

There are no adequate reports or well-controlled studies in nursing women. It is unknown whether **dacarbazine** enters human breast milk.

Drug Interactions ..... No clinically significant interactions identified.

References .....

Aviles A, Diaz-Maqueo JC, Talavera A, et al. Am J Hematol 1991; 36:243-8.
Aviles A, Neri N. Clin Lymphoma 2001; 2:173-7.
Green DM, Zevon MA, Lowries G, et al. N Engl J Med 1991; 325:141-6.

Summary .....

Pregnancy Category: C
Lactation Category: U

- **Dacarbazine** should be used during pregnancy and lactation only if the benefit justifies the potential risk.
- Women of childbearing potential should use contraception during therapy and for at least 4mo after completion of therapy.

Daclizumab—(Zenapax)

International Brand Name—Zenapax (Argentina, Brazil, Canada, Chile, Colombia, Hong Kong, Israel, Mexico, Paraguay, Peru, Philippines, Taiwan, Uruguay, Venezuela)

Drug Class	Immunosuppressants; Monoclonal antibodies
Indications	Prevention of transplanted kidney rejection
Mechanism	IL-2 receptor antagonist
Dosage with Qualifiers	Prevention of transplant rejection—1.0mg/kg IV q14d ×5 doses *NOTE: begin within 24h pretransplant; interacts with echinacea.* • **Contraindications**—hypersensitivity to drug or class • **Caution**—unknown
Maternal Considerations	There is no published experience in pregnant women. It is recommended that women of childbearing potential use contraception before and during therapy, and for 4mo after completion of therapy with **daclizumab.** ***Side effects*** include pulmonary edema, renal tubular necrosis, N/V, diarrhea, constipation, abdominal or chest pain, dyspepsia, tremor, headache, edema, dizziness, dysuria, dyspnea, fever, acne, and cough.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **daclizumab** crosses the human placenta. No teratogenic effects are described in human fetuses. Animal teratogenicity studies have not been conducted.
Breastfeeding Safety	There are no published reports in nursing mothers. It is unknown whether **daclizumab** enters human breast milk.
Drug Interactions	In a large clinical study of cardiac transplants, **daclizumab** as part of an immunosuppression regimen including **cyclosporine, mycophenolate mofetil,** and corticosteroids was associated with an increase in mortality, particularly in patients receiving concomitant antilymphocyte antibody therapy and in patients who developed severe infections.
References	There is no published experience in pregnancy or during lactation.
Summary	**Pregnancy Category: C** **Lactation Category: U** • **Daclizumab** should be used during pregnancy and lactation only if the benefit justifies the potential risk.

Dactinomycin—(Cosmegen)

International Brand Name—Ac-De (Mexico, Peru); Cosmegen (Argentina, Brazil, Canada, Japan, Korea, Paraguay, Philippines, South Africa, Taiwan, Thailand); Cosmegen Lyovac (England, Hong Kong); Cosmogen (Israel); Cosmogen Lyovac (Hong Kong, Malaysia); Dacmozen (India); Lyovac (England); Trepar (Philippines)

Drug Class	Antineoplastics, antibiotics
Indications	GTN, Wilms' tumor, uterine carcinoma, Ewing's sarcoma
Mechanism	Inhibits RNA and protein synthesis
Dosage with Qualifiers	GTN—12mcg/kg IV ×5d Wilms' tumor—15mcg/kg IV ×5d Rhabdomyosarcoma—15mcg/kg IV ×5d Ewing's sarcoma—protocols vary; most recommend dose should not exceed 15mcg/kg or 400-600mcg/m^2 IV qd ×5d • **Contraindications**—hypersensitivity to drug or class, herpes zoster, varicella infection • **Caution**—hepatic or renal dysfunction (may enhance radiation injury to tissues)
Maternal Considerations	**Dactinomycin** is a derivative of *Streptomyces parvulus* and extensively used for the treatment of GTN. No deleterious long-term effects are described in women treated with combination regimens that include **dactinomycin** for germ cell ovarian cancer. The impact on future fertility appears low. Although remission rates of 80-90% are reported for **dactinomycin,** women with **methotrexate**-resistant GTN have a much lower remission rate (60%). Prediction of remission may be more closely related to hCG levels than the WHO score alone. There are no adequate reports or well-controlled studies of **dactinomycin** in pregnant women. ***Side effects*** include aplastic anemia, thrombocytopenia, leukopenia, pancytopenia, flushing, alopecia, acute folliculitis, N/V, fever, lethargy, abdominal pain, myalgias, anorexia, increased LFTs, hepatotoxicity, GI ulceration, pharyngitis, and stomatitis. Tissue necrosis after extravasation may manifest days to weeks after treatment.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **dactinomycin** crosses the human placenta. No teratogenic effects are described in humans. In rodents, it is both embryotoxic and teratogenic when given at multiples of the MRHD.
Breastfeeding Safety	There is no published experience in nursing women. It is unknown whether **dactinomycin** enters human breast milk. It is generally considered incompatible with breastfeeding.
Drug Interactions	**Dactinomycin** may interfere with bioassay procedures that determine antibacterial drug levels.
References	Chen LM, Lengyel ER, Bethan Powell C. Gynecol Oncol 2004; 94:204-7. Goldstein DP. Surg Forum 1967; 18:426-8. Kendall A, Gillmore R, Newlands E. Curr Opin Obstet Gynecol 2002; 14:33-8. Matsui H, Suzuka K, Iitsuka Y, et al. Gynecol Oncol 2000; 78:28-31.

Nagai K, Ikenoue T, Mori N. J Matern Fetal Med 2001; 10:136-40.
Suzuka K, Matsui H, Iitsuka Y, et al. Obstet Gynecol 2001; 97:431-4.

Summary

Pregnancy Category: C
Lactation Category: U

- **Dactinomycin** should be used during pregnancy and lactation only if the benefit justifies the potential risk.

Dalteparin—(Fragmin)

International Brand Name—Fragmin (Brazil, Canada, Chile, Colombia, Ecuador, Hong Kong, India, Japan, Korea, Peru, Philippines, Singapore, South Africa, Taiwan); Fragmine (France); Fragmin P Forte (Germany)

Drug Class

Anticoagulants; Low-molecular-weight heparins

Indications

Prophylaxis and treatment for DVT, unstable angina

Mechanism

Binds to antithrombin III and accelerates its inhibition of thrombin and factor Xa

Dosage with Qualifiers

DVT prophylaxis—begin 2500U SC/IV 1-2h preoperatively, then qd ×5-14d; increase dose to 5000U SC in high-risk women or during pregnancy
DVT treatment—200U/kg/d SC in divided doses; max 18,000U/dose, overlap with oral anticoagulation 2-3d
Unstable angina—120U/kg; max 10,000U SC q12h

*NOTE: 2500U SC qd is of similar antithrombotic efficacy to 5000U of unfractionated **heparin** bid.*

- **Contraindications**—hypersensitivity to drug or class, active bleeding, thrombocytopenia, epidural catheters, antibodies to drug, prosthetic heart valve, spinal puncture
- **Caution**—diabetic retinopathy, hepatic or renal dysfunction, recent surgery or stroke, pregnancy, GI bleeding

Maternal Considerations

Dalteparin is a LMWH (5000MW) with improved bioavailability, increased plasma elimination t/2, and greater factor Xa inhibitory activity compared to unfractionated **heparin. Dalteparin** given once or twice daily (IV or SC) is as effective as unfractionated **heparin** for the initial treatment of acute DVT. LMWHs are increasingly popular during pregnancy for the treatment of various thrombophilias and the antiphospholipid syndrome, though evidence of their efficacy remains limited. LMWHs differ in pharmacologic profiles. The mean retention time of anti-Xa activity varies from 5.2h (**dalteparin**) to 7h (**enoxaparin, nadroparin**). The bioavailability of a prophylactic dose of LMWHs range from 86% (**dalteparin**) to 98% (**enoxaparin, nadroparin**). Though equal in efficacy and amenable to once-daily dosing for prophylaxis in the nonpregnant patient, they are more expensive than unfractionated **heparin** and have the same risks. **Heparin** and heparin products are not treatments for preeclampsia. However, women with ACE insertion/deletion polymorphism are at increased risk of recurrent disease in a subsequent pregnancy, and 5000IU **dalteparin** daily reportedly decreases the risk of recurrence.
The therapeutic dose of **dalteparin** during pregnancy is based on maternal weight. Interpatient variability is wide during pregnancy and clearance significantly enhanced. Peak anti-Xa levels occur at

4h postbolus in pregnancy, compared with 2h in the nonpregnant state. The mean anti-Xa levels at 12, 24, and 36w gestation are each significantly reduced 2h postinjection, compared with the nonpregnant state. The lowest dose-response curve was at 36w gestation. The initial prophylactic dose for most pregnant women in the 1st trimester is 5000U daily. Anti-Xa activity is measured after initiating therapy, and again periodically (at least each trimester) to confirm the adequacy of the prophylactic or therapeutic dose. A dose of 5000U SC should produce an anti-Xa activity of 0.20-0.40U/ml (0.4-0.7U/ml for full anticoagulation) 3h after injection. Women treated with LMWHs for prevention of thromboembolic complications are at risk of developing an epidural or spinal hematoma after neuraxial anesthesia. It is prudent to wait at least 12h after the removal of an epidural catheter before re-initiating LMWH. LMWHs are best replaced with unfractionated **heparin** at 36w because of their long t/2s, and inability to rapidly measure residual activity (anti-Xa levels). One prospective study of bone density in women receiving LMWH found no significant change in mean bone density between baseline and 6w postpartum. Another suggested any decrease was consistent with the normal decline associated with pregnancy.

Side effects include bleeding, thrombocytopenia, fever, pruritus, osteoporosis, easy bruising, epistaxis, injection site reaction, and elevated LFTs.

Fetal Considerations

Dalteparin, similar to other LMWHs and unfractionated **heparin,** does not cross the placenta. It is generally safe and effective for the noted indications during pregnancy. Rodent studies are reassuring, revealing no evidence of teratogenicity despite the use of doses higher than those used clinically.

Breastfeeding Safety

Only trace amounts of **dalteparin** (2500U ×1 IU, and measured as anti-Xa activity) enter human breast milk. It is highly unlikely that puerperal treatment would have any clinically relevant effect on the nursing infant.

Drug Interactions

Dalteparin should be used with care in patients receiving oral anticoagulants, platelet inhibitors, and thrombolytic agents because of increased risk of bleeding.

References

Barbour LA, Oja JL, Schultz LK. Am J Obstet Gynecol 2004; 191:1024-9.

Blomback M, Bremme K, Hellgren M, Lindberg H. Blood Coagul Fibrinolysis 1998; 9:343-50.

Carlin AJ, Farquharson RG, Quenby SM, et al. Hum Reprod 2004; 19:1211-4.

Dunn CJ, Jarvis B. Drugs 2000; 60:203-37.

Ensom MH, Stephenson MD. J Soc Gynecol Investig 2004; 11:377-83.

Farquharson RG, Sephton V, Quenby SM. J Soc Gynecol Investig 2003; 10(Suppl):308A.

Laurent P, Dussarat GV, Bonal J, et al. Drugs 2002; 62:463-77.

Mello G, Parretti E, Fatini C, et al. Hypertension 2005; 45:86-91.

O'Shaughnessy DF. Hematology 2000; 4:373-80.

Rey E, Rivard GE. Int J Gynaecol Obstet 2000; 71:19-24.

Richter C, Sitzmann J, Lang P, et al. Br J Clin Pharmacol 2001; 52:708-10.

Rodgers MA, Kahn SR, Cranney A, et al. J Thromb Haemost 2007; 5:1600-8.

Samama MM, Gerotziafas GT. Semin Thromb Hemost 2000; 26(Suppl 1):31-8.

Sephton V, Farquharson RG, Topping J, et al. Obstet Gynecol 2003; 101:1307-11.
Ulander V, Stenqvist P, Kaaja R. Thromb Res 2002; 106:13.

Summary

Pregnancy Category: B
Lactation Category: S

- **Dalteparin** should be used during pregnancy only if the benefit justifies the potential perinatal risk.
- The possibility of once-daily administration and the reduced need for laboratory monitoring may translate into a cost advantage compared to unfractionated **heparin** or **warfarin.** Unfortunately, *this is not true during pregnancy,* where the increased clearance generally necessitates twice-daily dosing and serial measurement of anti-Xa activity.
- **Dalteparin** may reduce the risk of recurrent preeclampsia or IUGR.
- LMWHs are best replaced with unfractionated **heparin** at around 36w because of their long t/2s, possible need for surgical delivery and/or neuraxial anesthesia, and inability to quickly obtain anti-Xa levels.
- LMWHs may have lower frequencies of thrombocytopenia and osteoporosis compared to unfractionated **heparin.**

Danazol—(Danocrine; Danatrol; Danogen; Danokrin; Ectopal; Zoldan-A)

International Brand Name—Anargil (Hong Kong, Malaysia, Thailand); Azol (Australia, Malaysia, Taiwan); Bonzol (Japan); Cyclomen (Canada); Danasin (Turkey); Danatrol (Belgium, France, Greece, Italy, Netherlands, Portugal, Spain, Switzerland); Danazol (Korea, Poland); Danazol Jean Marie (Hong Kong); Danazol-Ratiopharm (Germany); Danocrine (Australia, Denmark, Finland, Hong Kong, Indonesia, Israel, Norway, Sweden); Danodiol (Egypt, Ghana, Iran, Iraq, Kenya, Kuwait, Mauritius, Puerto Rico, Tanzania); Danogar (Chile); Danogen (India, Russia); Danokrin (Austria); Danol (Czech Republic, England, Hungary, Ireland, Israel); Danoval (Bulgaria, Hungary, Poland); Danzocurine (Korea); Dorink (Taiwan); D-Zol (New Zealand); Ectopal (Taiwan, Thailand); Gonablok (India); Kendazol (Mexico); Ladazol (South Africa); Ladogal (Argentina, Bolivia, Brazil, Canada, Chile, Colombia, Ecuador, Malaysia, Mexico, Paraguay, Peru, Philippines, Taiwan, Thailand, Uruguay, Venezuela); Nazol (Malaysia); Norciden (Mexico); Vabon (Malaysia, Thailand); Winobanin (Germany); Zendol (India); Zoldan-A (Mexico)

Drug Class — Hormones, other gynecologic

Indications — Endometriosis, fibrocystic breast disease, hereditary angioedema

Mechanism — Suppression of the pituitary-ovarian axis

Dosage with Qualifiers

Endometriosis—begin 200-400mg PO bid depending on severity; continue for 3-6mo trial
Fibrocystic breast disease—50-200mg PO bid for 2-6mo, then adjust dose
Hereditary angioedema—200mg PO tid until response, then half dose for 1-3mo

NOTE: begin during menstruation.

- **Contraindications**—hypersensitivity to drug or class, undiagnosed genital bleeding, pregnancy, breastfeeding, porphyria
- **Caution**—hepatic, renal or cardiac dysfunction, epilepsy, migraine

Maternal Considerations

There are no indications during pregnancy for **danazol.** It should be discontinued if the patient becomes pregnant. **Danazol** is not

an effective contraceptive. It decreases the maternal progesterone level if taken during the 1st trimester.
Side effects include alteration of the lipid profile (low HDL), contraceptive failure, pseudotumor cerebri, weight gain, acne and seborrhea, mild hirsutism, virilization, edema, hair loss, hoarseness, menstrual irregularities, flushing, sweating, vaginal dryness, reduction in breast size, hypertension, anxiety, and thromboembolism.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **danazol** crosses the human placenta. Though the FDA classifies **danazol** as category X, there is no reason *a priori* to terminate an exposed pregnancy. **Danazol** can have an androgenic effect on female fetuses (vaginal atresia, clitoral hypertrophy, labial fusion, ambiguous genitalia). Thus, exposed fetuses should undergo a detailed ultrasound examination. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically. **Danazol** is associated with inhibition of fetal development in rabbits.

Breastfeeding Safety

There is no published experience in nursing women. It is unknown whether **danazol** enters human breast milk. It is generally considered contraindicated during breastfeeding.

Drug Interactions

Prolongation of PT occurs in patients stabilized on **warfarin.** **Danazol** may cause an increase in **carbamazepine.**

References

Bianchi S, Busacca M, Agnoli B, et al. Hum Reprod 1999; 14:1335-7.
Brunskill PJ. Br J Obstet Gynaecol 1992; 99:212-5.
Igarashi M, Iizuka M, Abe Y, Ibuki Y. Hum Reprod 1998; 13:1952-6.
Kingsbury AC. Med J Aust 1985; 143:410-1.
Rabe T, Kiesel L, Franke C, et al. Biol Res Pregnancy Perinatol 1984; 5:149-52.
Schwartz R. Am J Dis Child 1982; 136:474.
Zayed F, Abu-Heija A. Obstet Gynecol Surv 1999; 54:121-30.

Summary

Pregnancy Category: X
Lactation Category: NS (possibly)

- There are no indications for **danazol** during pregnancy; it is considered contraindicated.
- A pregnancy test is recommended immediately prior to initiating therapy.
- **Danazol** may virilize a female fetus (vaginal atresia, clitoral hypertrophy, labial fusion, urogenital sinus defect, ambiguous genitalia), but these abnormalities have not been reported if discontinued by 8w.

Dantrolene—(Danlene; Dantralen; Dantrium; Dantrium IV)

International Brand Name—Anorex (Korea); Dantamacrin (Austria, Bulgaria, Switzerland); Dantrium (Belgium, Canada, Chile, Denmark, England, France, Greece, Ireland, Italy, Japan, Netherlands, Portugal, South Africa); Dantrolen (Austria, Bulgaria, Czech Republic, Russia)

Drug Class	Muscle relaxants
Indications	Chronic spasticity, malignant hyperthermia
Mechanism	Interferes with the release of the calcium from sarcoplasmic reticulum
Dosage with Qualifiers	Chronic spasticity—begin 25mg PO qd; max 400mg/d Malignant hyperthermia prevention—4-8mg/kg/d PO q6-8h 1-2d preoperatively with last dose 3-4h prior to surgery; same dose postcrisis Malignant hyperthermia crisis—1-2.5mg/kg IV ×1, may repeat q5min until patient improves; max 10mg/kg Neuroleptic malignant syndrome—1mg/kg IV ×1, repeat until symptoms improve; max 10mg/kg *NOTE: monitor LFTs.* • **Contraindications**—hypersensitivity to drug or class, cirrhosis • **Caution**—age >35y, pulmonary disease, cardiomyopathy
Maternal Considerations	There are no adequate reports or well-controlled studies of **dantrolene** in pregnant women, though it has been used for both the prevention and treatment of acute malignant hyperthermia and neuroleptic malignant syndrome, where it may be lifesaving. However, prevention of malignant hypertension is not usually recommended. Instead, a nontriggering anesthetic should be selected. ***Side effects*** include hepatic dysfunction, pleural effusion, pericarditis, constipation, bowel obstruction, abdominal pain, diarrhea, dizziness, pruritus, vomiting, tachycardia, depression, seizure, headache, aplastic anemia, and myalgia.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. It readily crosses the placenta, achieving equal maternal and fetal whole blood levels by delivery. No adverse neonatal effects are reported. **Dantrolene** is embryocidal in rodents when administered at a multiple of the MRHD.
Breastfeeding Safety	**Dantrolene** is excreted in human breast milk, but the peak concentration reported is small and unlikely to produce neonatal levels as high as fetal levels. Though the kinetics remain to be detailed, **dantrolene** is likely compatible with breastfeeding.
Drug Interactions	Binding to plasma proteins is reduced by **warfarin** and **clofibrate,** and increased by **tolbutamide.** The combination of IV **dantrolene** and calcium channel blockers, such as **verapamil,** should not be used together for the management of malignant hyperthermia until further research is completed. May potentiate **vecuronium**-induced neuromuscular block. Use with CNS depressants such as sedatives and tranquilizing agents may result in increased drowsiness.
References	Ben Abraham R, Cahana A, Krivosic-Horber RM, Perel A. Q J Med 1997; 90:13-8.

Fricker RM, Hoerauf KH, Drewe J, Kress HG. Anesthesiology 1998; 89:1023-5.
Russell CS, Lang C, McCambridge M, Calhoun B. Obstet Gynecol 2001; 98:906-8.
Shime J, Gare D, Andrews J, Britt B. Am J Obstet Gynecol 1988; 159:831-4.

Summary

Pregnancy Category: C
Lactation Category: S (likely)
- **Dantrolene** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Dapsone—(Avlosulfon; Dapsoderm-X; Dapson)

International Brand Name—Avlosulfon (Canada); Daps (Argentina); Dapsoderm-X (Mexico); Dapson (Denmark, Egypt, Netherlands, Norway, Sweden); Dapsona (Paraguay); Dapsone (Australia); Dapson-Fatol (Germany); Diaphenylsulfon (Hungary, Netherlands); Disulone (Czech Republic, Poland); Dopsan (Thailand); Lennon-Dapsone (South Africa); Lepravir (Philippines); Novasulfon (Mexico); Protogen (Japan); Servidapsone (Thailand); Sulfona (Portugal, Spain)

Drug Class

Antimycobacterials

Indications

PCP, dermatitis herpetiformis, malaria suppression, leprosy

Mechanism

Bactericidal/bacteriostatic by some unknown mechanism

Dosage with Qualifiers

PCP—100mg PO qd; usually given with **trimethoprim** (20mg/kg qd ×3w)
Dermatitis herpetiformis—begin 50mg PO qd, increase to 300mg qd as needed
Malaria suppression—100mg PO qw, give with **pyrimethamine** 12.5mg PO qw
Leprosy prophylaxis—100mg PO qd ×24mo
Leprosy treatment—50mg PO qd

- **Contraindications**—hypersensitivity to drug or class
- **Caution**—cardiac, renal or hepatic dysfunction, G6PD deficiency

Maternal Considerations

There are no adequate reports or well-controlled studies of **dapsone** in pregnant women. **Dapsone,** alone or in combination with **pyrimethamine, trimethoprim-sulfamethoxazole,** or **pentamidine,** is the most commonly used drug for PCP prophylaxis. **Dapsone** should be administered in combination with one or more antileprosy drugs to avoid resistance. **Dapsone** should also be considered during pregnancy in areas where *P. falciparum* resistance to **chloroquine** and **pyrimethamine-sulfadoxine** is rapidly increasing. Mild degrees of hemolysis occur consistently with continued therapy but may be less likely with intermittent treatment. Most reported adverse effects have occurred after long-term use.
Side effects include hemolysis, aplastic anemia, peripheral neuropathy, N/V, abdominal pains, pancreatitis, vertigo, blurred vision, tinnitus, insomnia, fever, headache, fatigue, malaise, psychosis, pulmonary eosinophilia, albuminuria, nephrotic syndrome, renal papillary necrosis, exfoliative dermatitis, erythema multiforme, toxic epidermal necrolysis, phototoxicity, drug-induced lupus-like syndrome, and infectious mononucleosis–like syndrome.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. Transfer across the human placenta likely occurs, as there are reports of neonatal methemoglobinemia after maternal **dapsone. Dapsone** appears unassociated with fetal abnormalities in humans. Rodent teratogenicity studies have not been performed.

Breastfeeding Safety

Dapsone is excreted in breast milk in substantial amounts, with the unsupplemented breastfed infant receiving some 15% of the maternal dose. Hemolytic reactions can occur in newborns. Caution is advised. Breastfeeding is contraindicated in HIV-infected nursing women where formula is available to reduce the risk of neonatal transmission.

Drug Interactions

Rifampin lowers **dapsone** 7- to 10-fold by enhancing plasma clearance.
Folic acid antagonists such as **pyrimethamine** may increase the likelihood of hematologic reactions.

References

Bhargava P, Kuldeep CM, Mathur NK. Int J Lepr Other Mycobact Dis 1996; 64:457-8.
Brabin BJ, Eggelte TA, Parise M, Verhoeff F. Drug Saf 2004; 27:633-48.
Edstein MD, Veenendaal JR, Newman K, Hyslop R. Br J Clin Pharmacol 1986; 22:733-5.
Erstad BL. Clin Pharm 1992; 11:800-5.
Kabra NS, Nanavati RN, Srinivasan G. Indian Pediatr 1998; 35:553-5.
Kahn G. J Am Acad Dermatol 1985; 13:838-9.
Lush R, Iland H, Peat B, Young G. Aust N Z J Med 2000; 30:105-7.

Summary

Pregnancy Category: C
Lactation Category: S (likely)

- **Dapsone** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.
- Hemolysis in neonates is the most common adverse effect seen in patients with or without G6PD deficiency.

Daunorubicin—(Cerubidine; DaunoXome)

International Brand Name—Daunoxome (Sweden)

Drug Class

Antineoplastics, antibiotics

Indications

HIV-associated Kaposi's sarcoma, AML, acute lymphoblastic leukemia

Mechanism

Inhibits topoisomerase and binds DNA

Dosage with Qualifiers

Kaposi's sarcoma—dose varies with protocol; most recommend 40mg/m^2 IV
AML—dose varies with protocol; most recommend 40mg/m^2 IV
Acute lymphoblastic leukemia—dose varies with protocol; most recommend 40mg/m^2 IV

- **Contraindications**—hypersensitivity to drug or class
- **Caution**—hepatic, renal, or cardiac dysfunction; myelosuppression

Maternal Considerations

Daunorubicin is an anthracycline antibiotic. **Daunoxome** is an encapsulated form designed to maximize selectivity for solid tumors such as Kaposi's sarcoma. The specific mechanism by which the **daunorubicin** citrate liposome delivers the drug to solid tumors is not known. It is also commonly used in combination with other drugs for the treatment of breast cancer. There are no adequate reports or well-controlled studies of **daunorubicin** in pregnant women. There are multiple reports of its use during pregnancy with a successful outcome.
Side effects include bone marrow suppression, hepatic and cardiac toxicity, alopecia, N/V, diarrhea, mucositis, back pain, flushing, chest tightness, fever, and local tissue necrosis at the site of drug extravasation.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. **Daunorubicin** crosses the human placenta, but in the isolated perfused model the global transfer was <3%.
Not surprisingly, there are multiple reports of its use during pregnancy, including 1st trimester, either without evidence of an adverse fetal effect or, on occasion, with a report of anemia, thrombocytopenia, and neutropenia. Though children (and presumably fetuses) have greater sensitivity to the cardiotoxic effects of **daunorubicin** than adults, there are no such reports in exposed fetuses. Short-term follow up has been encoraging.
Rodent studies reveal, at doses a fraction of those used in the human, an increased prevalence of anophthalmia, microphthalmia, and incomplete ossification when given alone, and esophageal atresia with tracheoesophageal fistula if **daunorubicin** is combined with **doxorubicin.**

Breastfeeding Safety

Daunorubicin is excreted into human breast milk, but in the only case reported, the total amount delivered in the milk (maximum concentration of active antibiotic: 0.24mg/L) was negligible.

Drug Interactions

No clinically significant interactions identified.

References

Achtari C, Hohlfeld P. Am J Obstet Gynecol 2000; 183:511-2.
Dezube BJ. Expert Rev Anticancer Ther 2002; 2:193-200.
Egan PC, Costanza ME, Dodion P, et al. Cancer Treat Rep 1985; 69:1387-89.
Grohard P, Akbaraly JP, Saux MC, et al. J Gynecol Obstet Biol Reprod (Paris) 1989; 18:595-600.
Kerr JR. Pharmacotherapy 2005; 25:438-41.
Leslie KK. Clin Obstet Gynecol 2002; 45:153-64.
Merei JM, Farmer P, Hasthorpe S, et al. Anat Rec 1997; 249:240-8.

Summary

Pregnancy Category: D
Lactation Category: S (likely)

- **Daunorubicin** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Deferoxamine—(Desferal)

International Brand Name—Desferal (Argentina, Brazil, Canada, Chile, China, Hong Kong, India, Indonesia, Korea, Taiwan, Thailand, Venezuela); Desferin (Spain)

Drug Class	Antidotes; Chelators
Indications	Iron toxicity
Mechanism	Chelation
Dosage with Qualifiers	Acute iron intoxication—1g IM ×1, then 500mg IM q4h ×2, may repeat; do not exceed 6g/24h Chronic iron overload—500-1000mg IM qd, plus 2000mg IV (not to exceed 15 mg/kg/h) with each transfused unit of PRBCs • **Contraindications**—hypersensitivity to drug or class, severe renal disease or anuria • **Cautions**—IV route should be used only in instances of CV collapse or with blood transfusion
Maternal Considerations	There are no adequate reports or well-controlled studies of **deferoxamine** in pregnant women. There are case reports of its use during pregnancy and lactation in women with transfusion-dependent homozygous β-thalassemia. ***Side effects*** include ocular disturbances such as blurred vision, cataracts, and decreased acuity, color perception, and night vision; injection site irritation; pruritus, tachycardia; hypotension; shock; N/V; diarrhea; and abdominal pain.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **deferoxamine** crosses the human placenta. However, there are over 50 published cases without evidence of adverse fetal effects. One recent case suggested decreased fetal iron. Rodent studies reveal an increased incidence of delayed ossification and skeletal anomalies when administered at multiples of the MRHD.
Breastfeeding Safety	There are no adequate reports or well-controlled studies in nursing women. It is unknown whether **deferoxamine** enters human breast milk. Case reports suggest **deferoxamine** therapy does not alter the iron content of human breast milk.
Drug Interactions	Treatment in combination with **prochlorperazine** may lead to temporary impairment of consciousness. Imaging results may be distorted by the rapid urinary excretion of **deferoxamine**-bound gallium-67. **Deferoxamine** should be discontinued 48h prior to scintigraphy.
References	Pafumi C, Zizza G, Caruso S, et al. Ann Hematol 2000; 79:571-3. Pearson HA. J Pediatr Hematol Oncol 2007; 29:160-2. Perniola R, Magliari F, Rosatelli MC, De Marzi CA. Gynecol Obstet Invest 2000; 49:137-9. Singer ST, Vichinsky EP. Am J Hematol 1999; 60:24-6. Surbek DV, Glanzmann R, Nars PW, Holzgreve W. J Perinat Med 1998; 26:240-3.
Summary	**Pregnancy Category: C** **Lactation Category: U** • **Deferoxamine** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Delavirdine—(Rescriptor)

International Brand Name—None identified.

Drug Class	Non-nucleoside reverse transcriptase inhibitors; Retrovirals
Indications	HIV
Mechanism	NNRTI that induces allosteric changes in HIV-1 reverse transcriptase, rendering it incapable of converting viral RNA to DNA
Dosage with Qualifiers	HIV—400mg PO tid • **Contraindications**—hypersensitivity to drug or class • **Caution**—unknown
Maternal Considerations	There are no adequate reports or well-controlled studies in pregnant women. Because **delavirdine** increases the plasma concentrations of several protease inhibitors, it may also be beneficial as a component of salvage therapy in combination with protease inhibitors. ***Side effects*** include skin rash (up to 20%), angioedema, Stevens-Johnson syndrome, anemia, GI bleeding, pancreatitis, thrombocytopenia, neutropenia, pancytopenia, granulocytosis, fatigue, N/V, diarrhea, abdominal pain, hematuria, dry skin, elevated LFTs, flu-like symptoms, bradycardia, headache, anxiety, and edema.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **delavirdine** crosses the human placenta. In rodents, **delavirdine** causes embryotoxicity and VSDs at doses that are multiples of the MRHD.
Breastfeeding Safety	There is no published experience in nursing women. It is unknown whether **delavirdine** enters human breast milk. Breastfeeding is contraindicated in HIV-infected nursing women where formula is available to reduce the risk of neonatal transmission.
Drug Interactions	**Delavirdine** has numerous recognized and predicted drug interactions. All prescribers should review the package insert before adding a new drug. **Delavirdine** inhibits the metabolism of many drugs (e.g., antiarrhythmics, calcium channel blockers, sedative-hypnotics, and others), and *serious and/or life-threatening drug interactions* may result from the inappropriate use of some drugs. Further, some drugs markedly reduce **delavirdine** plasma concentrations, resulting in suboptimal antiviral activity and the emergence of drug resistance. Inhibits CYP3A and to a lesser extent CYP2C9, CYP2D6, and CYP2C19. Administration with drugs primarily metabolized by CYP3A (e.g., HMG-CoA reductase inhibitors and **sildenafil**) may increase plasma levels of the co-administered drug that increase or prolong both therapeutic or adverse effects. Use of **lovastatin** or **simvastatin** is not recommended, and caution should be exercised if **delavirdine** must be used with other HMG-CoA reductase inhibitors also metabolized by CYP3A4 (e.g., **atorvastatin, cerivastatin**). The risk of myopathy, including rhabdomyolysis, may be increased when **delavirdine** in this circumstance.

The use of **St. John's wort** with NNRTIs, including **delavirdine,** may substantially decrease NNRTI concentrations and lead to the loss of virologic response and the emergence of resistance to **delavirdine** or to the class of NNRTIs.
Use with drugs that induce CYP3A, such as **rifampin** and **rifabutin,** may decrease **delavirdine** plasma concentrations, reduce its therapeutic effect, and increase the chance of resistance to this class of NNRTIs. Not surprisingly, drugs that inhibit CYP3A may increase **delavirdine** plasma concentrations.
Phenytoin, phenobarbital, and **carbamazepine** may lead to loss of virologic response and possible resistance to **delavirdine** or to the class of NNRTIs.
Cisapride, pimozide, astemizole, and **terfenadine** are *contraindicated due to the potential for serious and/or life-threatening reactions* such as cardiac arrhythmias.
Dihydroergotamine, ergonovine, ergotamine, and **methylergonovine** may cause serious and/or life-threatening reactions such as acute ergot toxicity characterized by peripheral vasospasm and ischemia of the extremities and other tissues.
Use with **nifedipine**-like calcium channel antagonists *is contraindicated as it may trigger* serious and/or life-threatening reactions such as cardiac arrhythmias.
Administration of **didanosine** (buffered tablets) and **delavirdine** should be separated by at least 1h.
A dose reduction of either **saquinavir** or **indinavir** should be considered when given with **delavirdine.**
Delavirdine may increase the concentrations of **amiodarone, bepridil, clarithromycin, cyclosporine, flecainide, lidocaine** (systemic), **methadone, quinidine, propafenone, rapamycin, tacrolimus,** and **warfarin.**
Delavirdine increases immunosuppressant concentrations.

References ..... There is no published experience in pregnancy or during lactation.

Summary .....

Pregnancy Category: C
Lactation Category: U

- **Delavirdine** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.
- Physicians are encouraged to register pregnant women under the Antiretroviral Pregnancy Registry (1-800-258-4263) for a better follow-up of the outcome while under treatment with **delavirdine.**

Demecarium—(Humorsol; Tosmilen)

International Brand Name—Tosmilen (Bulgaria, Japan)

Drug Class ..... Cholinesterase inhibitors; Miotics; Ophthalmics

Indications ..... Open-angle glaucoma

Mechanism ..... Cholinesterase inhibitor

Dosage with Qualifiers .....

Glaucoma—1-2 gtt (0.125% or 0.25%) in the affected eye

- **Contraindications**—hypersensitivity to drug or class, uveal inflammation, glaucoma associated with iridocyclitis

- **Caution**—narrow angle-closure glaucoma, bronchial asthma, spastic GI disturbances, peptic ulcer, pronounced bradycardia and hypotension, recent MI, epilepsy, parkinsonism

Maternal Considerations

Demecarium is a cholinesterase inhibitor with sustained activity. It produces miosis and ciliary muscle contraction, and should be used only when shorter acting miotics have proved inadequate. There is no published experience with **demecarium** during pregnancy.
Side effects include salivation, urinary incontinence, diarrhea, profuse sweating, muscle weakness, respiratory difficulties, shock, cardiac irregularities, stinging, burning, tearing, lid muscle twitching, and headache.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **demecarium** crosses the placenta. Considering the dose and route, it is unlikely the maternal systemic concentration will reach clinically relevant level. Rodent teratogenicity studies have apparently not been performed.

Breastfeeding Safety

There is no published experience in nursing women. It is unknown whether **demecarium** enters human breast milk. However, considering the indication and dosing, **demecarium** use is unlikely to pose a clinically significant risk to the breastfeeding neonate.

Drug Interactions

Demecarium may intensify the responses to **succinylcholine** or other anticholinesterase agents.

References

There is no published experience in pregnancy or during lactation.

Summary

Pregnancy Category: X
Lactation Category: U
- **Demecarium** should be used during pregnancy only if the benefit justifies the potential risk.
- There are alternative agents for which there is more experience regarding use during pregnancy and lactation.

Demeclocycline—(Bioterciclin; Clortetrin; Declomycin; Ledermycin)

International Brand Name—Declomycin (Canada); Ledermicina (Italy, Peru); Ledermycin (Australia, Austria, Belgium, England, India, Ireland, Japan, Korea, Netherlands); Ledermycine (France)

Drug Class

Antibiotics; Tetracyclics

Indications

Bacterial infections (gram-negative microorganisms: *H. ducreyi* (chancroid), *Yersinia pestis, Francisella tularensis, P. pestis, P. tularensis, Bartonella, Bacteroides* species, *Vibrio* species, *Brucella, E. coli, Enterobacter aerogenes, Shigella, H. influenzae, Klebsiella;* gram-positive microorganisms: *S. aureus, S. pyogenes, S. faecalis, S. pneumoniae, N. gonorrhoeae, Listeria monocytogenes, Clostridium, B. anthracis, Fusobacterium fusiforme* [Vincent's infection], Rickettsiae, *T. pallidum, Actinomyces*, amebiasis)

Mechanism

Bacteriostatic—inhibits protein synthesis

Dosage with Qualifiers

Bacterial infection, amebiasis, rickettsiae—150mg PO qid or 300mg PO bid
Gonorrhea—600mg PO ×1; follow with 300mg q12h ×4d

NOTE: renal dosing.

- **Contraindications**—hypersensitivity to drug or class, diabetes insipidus
- **Caution**—hepatic or renal dysfunction

Maternal Considerations

There are no adequate reports or well-controlled studies of **demeclocycline** during pregnancy. Outside of pregnancy, **demeclocycline** may cause diabetes insipidus–like syndrome (polyuria, polydipsia, and weakness) that is nephrogenic in origin, dose-dependent, and reversible on discontinuation.
Side effects include photosensitization, diabetes insipidus syndrome, pseudotumor cerebri, thrombocytopenia, hemolytic anemia, hepatic or renal dysfunction, increased BUN, glossitis, enterocolitis, acute fatty liver disease, and vaginal candidiasis.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **demeclocycline** crosses the human placenta. Other tetracyclines may cause a permanent discoloration of the teeth (yellow-gray/brown teeth) when given during the latter half of pregnancy, or during childhood prior to 8 years of age. In rodents, exposure to **demeclocycline** is associated with tooth discoloration. Exposure to other tetracyclines is associated with delayed bone growth.

Breastfeeding Safety

There is no published experience in nursing women. It is unknown whether **demeclocycline** enters human breast milk. It likely enters human breast milk, as do other tetracyclines, and is generally considered incompatible with breastfeeding.

Drug Interactions

Tetracyclines may depress plasma prothrombin activity necessitating a decrease in anticoagulant dosage.
May interfere with the bactericidal action of penicillins.
May render oral contraceptives less effective. Breakthrough bleeding has been reported.

References

Hendeles L, Trask PA. J Am Dent Assoc 1983; 107:12.
Iwamoto HK, Brennan WR. Toxicol Appl Pharmacol 1969; 14:33-40.
Jha VK, Jayachandran C, Singh MK. Vet Res Commun 1989; 13:225-30.
Thomas JP, Bradley EL Jr. Ala J Med Sci 1973; 10:89-97.
Zyngier S, Schmuziger P. Rev Farm Bioquim Univ Sao Paulo 1970; 8:173-6.

Summary

Pregnancy Category: D
Lactation Category: NS

- There are alternative agents during pregnancy for almost all indications.

Desipramine—(Deprexan; Norpramin; Pertofrane)

International Brand Name—Deprexan (Israel); Nebril (Argentina); Norpramin (Canada, Mexico); Nortimil (Italy); Pertofran (Austria, Belgium, England, France, Netherlands, New Zealand); Petylyl (Bulgaria, Czech Republic, Germany, Poland, Russia)

Drug Class	Antidepressants; Tricyclics
Indications	Depression
Mechanism	Unknown; inhibits NE and serotonin reuptake
Dosage with Qualifiers	Depression—Begin 25-75mg PO qam, increase gradually to a maximum of 300mg/d (typical 100-200mg qd) • **Contraindications**—hypersensitivity to drug or class, usage of MAOIs in the past 14d, CAD • **Caution**—heart disease, glaucoma, thyroid disease, seizure disorder
Maternal Considerations	Depression is a commonly overlooked and undertreated disorder during pregnancy and the puerperium. Pregnancy is not a reason *a priori* to discontinue psychotropic drugs. Women with a history of depression are at high risk for recurrence during pregnancy and the puerperium. TCAs continue to be widely used during pregnancy, but remain inadequately studied. **Desipramine** is a metabolite of **imipramine. Desipramine** lowers the threshold for seizures. There are no adequate reports or well-controlled studies of **desipramine** in pregnant women. There are marked interindividual differences during pregnancy in the metabolism of TCAs. TCAs are effective for the treatment of postpartum depression. ***Side effects*** include stroke, MI, arrhythmias, thrombocytopenia, seizures, urinary retention, and glaucoma.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **desipramine** crosses the human placenta. No evidence of teratogenicity is seen in rhesus monkey fetuses exposed to **imipramine** despite a high incidence of maternal toxicity and abortion. A large body of study on the impact of *in utero* exposure to **desipramine** on postnatal neurologic function is inconclusive.
Breastfeeding Safety	**Desipramine** is excreted in small quantities into human breast milk, but is not detectable in the blood of breastfeeding newborns. No adverse effects are reported in breastfeeding neonates.
Drug Interactions	Metabolized by CYP2D6, and the activity of 2D6 is reduced in 7-10% of Caucasians (“poor metabolizers”). Poor metabolizers have higher than expected plasma concentrations of TCAs when given usual doses. The increase in plasma concentration may be small, or quite large (up to an 8-fold increase in the AUC). The drugs that inhibit CYP2D6 include both those that are not metabolized by the enzyme (**quinidine, cimetidine**) and those that are substrates (other antidepressants, phenothiazines, and the class IC antiarrhythmics **propafenone** and **flecainide**). All SSRIs (e.g., **fluoxetine, sertraline, paroxetine**) inhibit CYP2D6 to varying degrees. The extent to which this interaction creates a clinical problem will depend on the degree of inhibition and the pharmacokinetics of the SSRI involved. Caution is

indicated in co-administration and in switching from one class to the other.
Close supervision and careful adjustment of dosage are required when **desipramine** is given concomitantly with anticholinergic or sympathomimetic drugs.
Patients should be warned that their response to alcohol may be exaggerated while taking **desipramine**.
Both the sedative and anticholinergic effects of the major tranquilizers are additive to those of **desipramine.**

References

Gelenberg AJ, Wojcik JD, Lydiard RB, et al. J Clin Psychiatry 1984; 45:54-9.
Sjoqvist F, Bertilsson L. Adv Biochem Psychopharmacol 1984; 39:359-72.
Stancer HC, Reed KL. Am J Psychiatry 1986; 143:1597-600.
Wen SW, Walker M. J Obstet Gynaecol Can 2004; 26:887-92.
Ware MR, DeVane CL. J Clin Psychiatry 1990; 51:482-4.
Wisner KL, Parry BL, Piontek CM. N Engl J Med 2002; 347:194-9.
Yoshida K, Smith B, Craggs M, Kumar RC. J Affect Disord 1997; 43:225-37.

Summary

Pregnancy Category: C
Lactation Category: S

- TCAs are effective second-line therapies (behind SSRIs) for postpartum depression.
- Pregnancy is not a reason *a priori* to discontinue psychotropic drugs.

Desmopressin—(DDAVP Desmopressin; Octim)

International Brand Name—Adiuretin-SD (Bulgaria, Czech Republic, Hungary, Poland); DDAVP (Brazil, Canada, Chile, Italy, South Africa, Taiwan); DDAVP Desmopressin (Portugal); Defirin (Greece); Desmopressin Nasal Solution (Japan); Desmospray (England, Ireland); Desmotab (England, Ireland); D-VOID (India); Minirin (Austria, China, Denmark, Finland, France, Germany, Israel, Korea, Malaysia, Mexico, Norway, Philippines, Sweden, Switzerland, Taiwan, Turkey); Minirin DDAVP (Greece, Hong Kong, Israel, Italy, Thailand); Minrin (Belgium, Netherlands); Minurin (Spain); Nocutil (England, Ireland); Nucotil nasenspray (Germany); Octim (France); Octostim (Finland, Hong Kong, Korea, Netherlands, New Zealand, Norway, Philippines, Sweden, Switzerland); Octostim Nasal Spray (Korea); Presinex (England, Ireland)

Drug Class

Antidiuretics; Hormones

Indications

Diabetes insipidus, vWD, factor VIII deficiency, nocturnal enuresis

Mechanism

Synthetic analog of hormone arginine vasopressin

Dosage with Qualifiers

Diabetes insipidus—10-40mcg NAS qhs; 1-2mcg SC/IV bid also acceptable (10mcg = 40U)
vWD—0.3mcg/kg IV ×1; alternatively NAS to provide 300mcg
Factor VIII deficiency—0.3mcg/kg IV ×1; alternatively NAS ×1
Nocturnal enuresis—10-40mcg NAS qhs

- **Contraindications**—hypersensitivity to drug or class, CAD, type IIB vWD
- **Caution**—hyponatremia, electrolyte imbalance

Maternal Considerations

The metabolic clearance rate of AVP increases 4-fold during human pregnancy. As opposed to natural hormone,

desmopressin (1-deamino-[8-D-arginine]vasopressin) has no uterotonic action in antidiuretic doses. It is the treatment of choice for most patients with type I vWD. Types II and III are usually unresponsive, and best treated with either FFP or concentrates containing von Willebrand factor. There is a high risk of delayed postpartum hemorrhage in vWD type I, especially during the first week. The risk is independent of the factor VIII level during the 3rd trimester, and reflects the rapid clearance of the various factor VIII components postpartum. The risk of postpartum hemorrhage is especially high in women with type II or III vWD, and **desmopressin** is effective prophylaxis in responsive women. Hemorrhage may occur up to 5w postpartum. Administer **desmopressin** at least 30min prior to a surgical procedure to maintain hemostasis during the procedure and immediately postoperatively. It is also effective treatment for women who develop transient diabetes insipidus during late pregnancy and/or the immediate puerperium. Maternal **desmopressin** use reduces and stabilizes plasma osmolality and increases AF volume. It has been proposed as a possible treatment of oligohydramnios and, if given intra-amniotically, polyhydramnios.
Side effects include hyponatremia, cerebral edema, rhinitis, flushing, abdominal pain, and thrombotic accidents.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. There is no detectable transfer of **desmopressin** at therapeutic maternal drug concentrations. No adverse fetal effects are reported when **desmopressin** is used during human pregnancy. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically. In sheep, intra-amniotic **desmopressin** inhibits fetal urination without CV effect or change in fetal swallowing.

Breastfeeding Safety

There are no adequate reports or well-controlled studies in nursing women. A single study found minimal **desmopressin** in human breast milk after a single nasal spray. Considering the dose and dosing frequency, it seems unlikely a significant quantity would reach the breastfeeding neonate. It has been used to treat diabetes insipidus during the puerperium.

Drug Interactions

Large doses of **desmopressin** may enhance the response to other pressor agents, which dictates careful patient monitoring.

References

Brewster UC, Hayslett JP. Obstet Gynecol 2005; 105:1173-6.
Burrow GN, Wassenaar W, Robertson GL, Sehl H. Acta Endocrinol (Copenh) 1981; 97:23-5.
Chediak JR, Alban GM, Maxey B. Am J Obstet Gynecol 1986; 155:618-24.
Davison JM, Sheills EA, Philips PR, et al. Am J Physiol 1993; 264:F348-53.
Kouides PA. Best Pract Res Clin Haematol 2001; 14:381-99.
Kullama LK, Nijland MJ, Ervin MG, Ross MG. Am J Obstet Gynecol 1996; 174:78-84.
Lee CA, Abdul-Kadir R. Semin Hematol 2005; 42:42-8.
Nichols WL, Hultin MB, James AH, et al. Haemophilia 2008; 14:171-232.
Ray JG, Boskovic R, Knie B, et al. Clin Biochem 2004; 37:10-3.
Ross MG, Cedars L, Nijland MJ, Ogundipe A. Am J Obstet Gynecol 1996; 174:1608-13.
Siristatidis C, Salamalekis E, Iakovidou H, Creatsas G. J Matern Fetal Neonatal Med 2004; 16:61-3.

Summary

Pregnancy Category: B
Lactation Category: S

- **Desmopressin** is effective therapy for women with either diabetes insipidus, or type I vWD during pregnancy, if necessary, or in the puerperium.

Dexamethasone—(Aeroseb-Dex; Corotason; Curson; Decaderm; Decadron; Decarex; Decaspray; Decofluor; Desigdron; Dexone; Dms; Hexadrol; Isopto; Lebedex; Lozusu; Maxidex; Millicorten; Mymethasone; Predni; Taidon)

International Brand Name—Adrecort (Mexico); Alfalyl (Colombia); Alin (Costa Rica, Dominican Republic, El Salvador, Guatemala, Mexico, Nicaragua, Panama); Artrosone (Spain); BiDexol (Thailand); Cetadexon (Indonesia); Corsona (Indonesia); Cortidex (Indonesia); Cortidexason (Germany); Dabu (Japan); Danasone (Indonesia); Decadran (Spain); Decadron (Argentina, Brazil, Canada, Denmark, Ecuador, Finland, Germany, Greece, Hong Kong, Italy, Japan, Mexico, Netherlands, Norway, Paraguay, Poland, Portugal, Russia, Sweden, Switzerland, Taiwan, Thailand); Decdan (India); Decilone (Philippines); Dectancyl (Israel); Deltafluorene (Malaysia); Desalark (Italy); Desigdron (Philippines); Dexacort (Peru); Dexacortal (Sweden); Dexagel (Taiwan); Dexalien (Uruguay); Dexalocal (Dominican Republic, El Salvador, Guatemala, Honduras, Hong Kong, Switzerland); Dexame (Japan); Dexamed (Malaysia, Singapore); Dexametason (Finland); Dexamethason (Hungary); Dexamethasone (Greece, Israel, New Zealand); Dexamonozon (Germany); Dexano (Thailand); Dexa-P (Thailand); Dexasone (Canada, Hong Kong, Thailand); Dexasone S (Japan); Dexmethsone (Australia, Hong Kong); Dexona (Israel, India); Dextrasone (Malaysia); Dibasona (Mexico); Fortecortin (Austria, Bulgaria, Czech Republic, Germany, Russia, Switzerland); Isopto-Dex (Germany); Isopto-Maxidex (Argentina, Finland, Norway, Paraguay, Sweden); Loverine (Japan); Maxidex (Bulgaria); Mexasone (Singapore); Oftan-Dexa (Finland); Oradexon (Belgium, Chile, Czech Republic, Finland, Greece, Hungary, Indonesia, Israel, Netherlands, Peru, Taiwan, Turkey); Pidexon (Indonesia); Predni-F (Germany); Santenson (Japan); Santeson (Philippines); Sawasone (Japan); Spersadex (Norway); Sterasone (Philippines); Thilodexine (Greece); Vexamet (Philippines); Visumetazone (Italy); Wymesone (India)

Drug Class

Corticosteroids

Indications

Accelerating fetal lung maturity, adrenal insufficiency, inflammatory states, congenital adrenal hyperplasia, allergic reactions, testing for Cushing's syndrome, cerebral edema, shock

Mechanism

Unknown

Dosage with Qualifiers

Prevention of RDS in preterm neonates—6mg IM q12h ×4 doses
Adrenal insufficiency—0.03-0.15mg/kg PO/IV/IM qd
Inflammatory states—0.75-9mg PO/IV/IM qd
Inflammatory ocular—1-2 gtt q1-6h
Congenital adrenal hyperplasia—0.03-0.15 mg/kg/d in 2-4 divided doses
Allergic reactions—0.75-9mg PO qd
Diagnostic test for Cushing's disease—2.0mg of dexamethasone PO q6h for 48h; 24h urine collection required to calculate 17-hydroxycorticosteroid production
Cerebral edema—10mg IV, then 4mg IM q6h
Shock—1-6mg/kg IV q2-6h prn
Postoperative N/V—4-5mg IV

NOTE: also available in a multitude of preparations for dermatologic and ophthalmologic uses; inhalation: 1 puff = 100mcg; 3 puffs = 3-4 puffs/d. Equivalent doses: dexamethasone 0.75mg = methylprednisolone 4mg = hydrocortisone 20mg.

- **Contraindications**—hypersensitivity to drug or class, fungal infections, active untreated infections (however, may be used in patients under treatment for tuberculosis meningitis), and lactation

- **Caution**—seizure disorder, diabetes, hypertension, osteoporosis, hepatic dysfunction

■ Maternal Considerations

Dexamethasone is used widely during pregnancy for the acceleration of fetal lung maturity. A comparison of PO (8mg) versus IM (6mg) dosing reveals similar bioavailability as determined by the AUC and terminal t/2s. Most large studies conclude the risk of maternal infection in women after PPROM is not increased by **dexamethasone.** It may transiently cause an abnormal glucose tolerance test, and will worsen diabetes mellitus. Large doses such as those given to hasten the fetal lung maturation are associated with pulmonary edema, especially when combined with a tocolytic agent in the setting of an underlying infection. **Dexamethasone** does not reduce the maternal perception of fetal movements and short-term variability. It is not contraindicated in women with severe preeclampsia requiring preterm delivery. Women chronically treated must be monitored closely for hypertension or glucose intolerance, and treated with stress replacement doses postoperatively and postpartum. **Dexamethasone** is an effective antiemetic after general anesthesia for pregnancy termination. There are as yet uncorroborated reports that IV **dexamethasone** helps modify the clinical course of the so-called HELLP syndrome both ante- and postpartum. It may also reduce itching in women with intrahepatic cholestasis of pregnancy.

Side effects include immunosuppression, pancreatitis, fluid retention, CV failure, pseudotumor cerebri, suppression of growth and development in children, myositis, Cushing's disease, decreased carbohydrate tolerance, osteoporosis, hepatic dysfunction, thromboembolism, insomnia, and anxiety.

■ Fetal Considerations

Antenatal corticosteroid administration is the only therapy conclusively demonstrated to reduce the perinatal morbidity and death associated with preterm delivery. Newborns of treated women have lower incidences of RDS, NEC, and IVH and shorter hospital stays. Therapy for pulmonary maturity should be limited to no more than 2 courses. The route of administration is apparently important, as neonatal outcome is worse when **dexamethasone** is given PO compared to IM to hasten lung maturation. **Dexamethasone** readily crosses the human placenta unmetabolized. Infants of women treated chronically should be carefully observed for signs of hypoadrenalism. Complete fetal heart block has been treated with **dexamethasone** with positive result. Some studies suggest that, in contrast to **betamethasone, dexamethasone** does not alter biophysical parameters of the fetus (i.e., fetal breathing) when administered for the enhancement of lung maturation. However, oligohydramnios is reportedly more common. When initiated by 6-7w, **dexamethasone** can prevent or diminish virilization due to congenital adrenal hyperplasia. PO dosing is equal to IM for the suppression of unconjugated estriol levels in the 3rd trimester. It is continued until a definitive diagnosis is established by DNA analysis of chorionic villi at 11-13w. One observational study concluded that children subjected to multiple antenatal doses of **dexamethasone** to enhance pulmonary maturity were more likely to develop leukomalacia and neurodevelopmental abnormalities at 2y old than those treated with either **betamethasone** or single doses of **dexamethasone.** This remains to be confirmed. Some suggest emotional stress during organogenesis can cause congenital malformations by increasing the level of **cortisone.** Corticosteroids produce oral clefting in some rodents. Some epidemiologic studies conclude, after controlling for confounding

factors, that prenatal exposure to corticosteroids adds a 6-fold increase in the risk for cleft lip with or without cleft palate, IUGR, and shortening of the head and mandible. In contrast, the Collaborative Perinatal Project followed women treated during the 1st trimester. While the number of exposures was limited, no increase in congenital malformations was detected. There was no increased risk of anomalies after organogenesis. Antenatal **dexamethasone** for fetal lung maturation is associated with diminished growth (12g at 24-26w, 63g at 27-29w, 161g at 30-32w, and 80g at 33-34w gestation) and decreased myelination in several animal models. The long-term impacts of these effects remain to be established. Corticosteroids (e.g., **cortisone**) accelerate fetal rat intestinal maturation, perhaps explaining why corticosteroids decrease the incidence of NEC.

Breastfeeding Safety

There are no adequate reports or well-controlled studies in breastfeeding women. **Dexamethasone** is excreted into human breast milk, but it is unclear whether maternal treatment increases the concentration of **cortisone** in breast milk.

Drug Interactions

Aminoglutethimide may diminish the adrenal suppression produced by corticosteroids.
There are case reports of cardiac enlargement, CHF, and hypokalemia when corticosteroids are administered with potassium-depleting agents such as **amphotericin B** and diuretics.
Macrolide antibiotics can decrease corticosteroid clearance.
Anticholinesterase agents and corticosteroids may produce severe weakness in patients with myasthenia gravis. When possible, anticholinesterase agents should be withdrawn at least 24h before initiating corticosteroid therapy.
May reduce the response to **warfarin.**
May decrease serum concentrations of **isoniazid.**
Cholestyramine may increase corticosteroid clearance.
The activity of both **cyclosporine** and corticosteroids may be increased when used together. Convulsions have been reported with this concurrent use.
False-negative results have been reported in patients undergoing a **dexamethasone** suppression test when also treated with **indomethacin.**
Ephedrine may increase clearance, decreasing blood levels and lessening physiologic activity.
CYP3A4 inducers (e.g., barbiturates, **phenytoin, carbamazepine, rifampin**) may enhance corticosteroid metabolism, requiring an upward dose adjustment.
Inhibitors of CYP3A4 (e.g., **ketoconazole, erythromycin**) may increase plasma concentrations of corticosteroids.
A moderate inducer of CYP3A4; use with other drugs metabolized by CYP3A4 (e.g., **indinavir, erythromycin**) may increase their clearance, resulting in decreased plasma concentration.
Ketoconazole may decrease the metabolism of corticosteroids by up to 60%, leading to an increased risk of corticosteroid side effects. Further, it alone can inhibit adrenal corticosteroid synthesis and cause adrenal insufficiency during corticosteroid withdrawal.
Use of **aspirin** and othe NSAIDs increases the risk of GI side effects.
The clearance of salicylates may be increased with concurrent use of corticosteroids.
Corticosteroids may suppress reactions to skin tests.
Toxic epidermal necrolysis has been reported when **dexamethasone** is used with **thalidomide.**

Patients on corticosteroid therapy may have diminished responses to toxoids and live or inactivated vaccines; routine administration should be deferred until after corticosteroid therapy is discontinued.

References

Bloom SL, Sheffield JS, McIntire DD, Leveno KJ. Obstet Gynecol 2001; 97:485-90.
Brownfoot FC, Crowther CA, Middleton P. Cochrane Database Syst Rev 2008; (4):CD006764.
Egerman RS, Mercer BM, Doss JL, Sibai BM. Am J Obstet Gynecol 1998; 179:1120-3.
Egerman RS, Pierce WF 4th, Andersen RN, et al. Obstet Gynecol 1997; 89:276-80.
Egerman RS, Walker, RA, Mercer BM, et al. Am J Obstet Gynecol 1998; 179:1234-6.
Elimian A, Garry D, Figueroa R, et al. Obstet Gynecol 2007; 110:26-30.
Fujii Y, Uemura A. Obstet Gynecol 2002; 99:58-62.
Goldenberg RL, Wright LL. Obstet Gynecol 2001; 97:316-7.
Guinn DA, Atkinson MW, Sullivan L, et al. JAMA 2001; 286:1581-7.
Isler CM, Barrilleaux PS, Magann EF, et al. Am J Obstet Gynecol 2001; 184:1332-7.
Lammert F, Marschall HU, Matern S. Curr Treat Options Gastroenterol 2003; 6:123-132.
Moritz K, Butkus A, Hantzis V, et al. Endocrinology 2002; 143:1159-65.
Mushkat Y, Ascher-Landsberg J, Keidar R, et al. Eur J Obstet Gynecol Reprod Biol 2001; 97:50-2.
Nevagi SA, Kaliwal BB. Indian J Exp Biol 2001; 39:1163-5.
New MI. Curr Urol Rep 2001; 2:11-8.
Ritzen EM. Semin Neonatol 2001; 6:357-62.
Roberts D, Dalziel S. Cochrane Database Syst Rev 2006; (3):CD004454.
Spiliotis BE. J Pediatr Endocrinol Metab 2001; 14:1299-302.
Spinillo A, Viazzo F, Colleoni R, et al. Am J Obstet Gynecol 2004; 191:217-24.
Wong JP, Kwek KY, Tan JY, Yeo GS. Aust N Z J Obstet Gynaecol 2001; 41:339-41.

Summary

Pregnancy Category: C
Lactation Category: U

- **Dexamethasone** is effective for the reduction of neonatal RDS and other complications of prematurity.
- There is no evidence of increased benefit after 2 courses; there is some evidence of fetal harm.

Dexchlorpheniramine—(Dexchlor; Dex-Cpm; Mylaramine; Polaramine)

International Brand Name—Dapriton (Hong Kong); Delamin (Taiwan); Destramin (Bulgaria); Dexferin (Taiwan); Isomerine Repetabs (Paraguay); Liramin (Venezuela); Nasamine (Thailand); Polamec (Indonesia); Polamine (Malaysia); Polaramin (Denmark, Italy, Japan, Norway, Sweden); Polaramine (Belgium, Brazil, Colombia, France, Hong Kong, Indonesia, Malaysia, Mexico, Netherlands, Puerto Rico, Spain, Switzerland, Taiwan); Polaramine (non-prescription) (Australia); Polaramine Repetabs (France, Greece); Polaramin Prolongat (Finland); Polaramin Prolongatum (Sweden); Polaramin Prolong Depottab (Norway); Polarist (Indonesia); Polaronil (Austria); Polazit (Japan); Rhiniramine (Singapore); Rhiniramine SR (Hong Kong, Singapore); Somin (Malaysia); Tomin (Taiwan); Trenelone (Portugal)

Drug Class	Antihistamines, H_1; Decongestants
Indications	Allergic rhinitis, anaphylaxis
Mechanism	Antagonizes central and peripheral H_1 receptors
Dosage with Qualifiers	Allergic rhinitis—2-4mg PO q4-6h; max 24mg/24h Anaphylaxis—5-20mg SC/IM q6-12h prn; max 40mg/24h • **Contraindications**—see **Chlorpheniramine** • **Caution**—see **Chlorpheniramine**
Maternal Considerations	**Dexchlorpheniramine** is the active metabolite of **chlorpheniramine.** There are no adequate reports or well-controlled studies in pregnant women, and its safety during pregnancy is not established. However, **chlorpheniramine** is widely available in OTC preparations and has not been implicated with adverse effects during pregnancy. ***Side effects*** include hypotension, dry mouth, N/V, and constipation.
Fetal Considerations	**Dexchlorpheniramine** has not been incriminated as a human teratogen. (See **Chlorpheniramine.**)
Breastfeeding Safety	There are no adequate reports or well-controlled studies in nursing women. It is unknown whether **dexchlorpheniramine** enters human breast milk. There are no reports of adverse effects on the breastfeeding neonate despite widespread availability.
Drug Interactions	May cause severe hypotension when given in conjunction with an MAOI. Sedative effects are potentiated by alcohol and other sedative drugs. The action of oral anticoagulants may be inhibited by antihistamines.
References	See **Chlorpheniramine.**
Summary	**Pregnancy Category: B** **Lactation Category: S** • **Dexchlorpheniramine** should be used during pregnancy and lactation only if the benefit justifies the potential risk.

Dexmedetomidine—(Precedex)

International Brand Name—Precedex (Israel)

Drug Class

Adrenergic agonists; α_2-agonist, central; Analgesics, non-narcotic; Anesthesia, adjunct; Sedatives

Indications

Sedation of ventilated patients

Mechanism

Selective α_2-adrenoceptor agonist

Dosage with Qualifiers

Sedation—begin 1mcg/kg IV over 10min, then 0.2-0.7mcg/kg/h IV
Anesthetic adjunct—0.5-0.6mcg/kg IV
Postoperative pain—0.4mcg/kg IV

NOTE: avoid abrupt withdrawal.

- **Contraindications**—hypersensitivity to drug or class
- **Caution**—CV disease, bradycardia, 2nd/3rd degree heart block, sick sinus syndrome, hypotension, transient hypertension, hypovolemia, diabetes mellitus, hepatic or renal dysfunction, adrenal insufficiency, tachycardia, anemia, thirst

Maternal Considerations

There are no adequate reports or well-controlled studies of **dexmedetomidine** in pregnant women. **Dexmedetomidine** enhances rat myometrial contractility *in vitro*.
Side effects include bradycardia, hypotension, atrial fibrillation, pulmonary edema, pleural effusion, bronchospasm, hypokalemia, leukocytosis, adrenal insufficiency, and N/V.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. **Dexmedetomidine** crosses the human placenta, which also binds a large fraction, delaying transfer. Rodent studies are generally reassuring, revealing no evidence of teratogenicity, though embryotoxicity and IUGR occurs in some models. It is a potent neuroprotector that has been explored in perinatal models.

Breastfeeding Safety

There is no published experience in nursing women. It is unknown whether **dexmedetomidine** enters human breast milk. **Dexmedetomidine** is excreted into rodent milk. Considering its indications, it is unlikely to pose a clinically significant risk to women who choose to breastfeed.

Drug Interactions

Administration with anesthetics, sedatives, hypnotics, and opioids is likely to lead to enhanced effects. This effect has been confirmed with **sevoflurane, isoflurane, propofol, alfentanil,** and **midazolam,** though no pharmacokinetic interactions have been demonstrated.

References

Ala-Kokko TI, Pienimaki P, Lampela E, et al. Acta Anaesthesiol Scand 1997; 41:313-9.
Hayashi Y, Maze M. Br J Anaesth 1993; 71:108-18.
Karaman S, Evren V, Firat V, Cankayali I. Adv Ther 2006; 23:238-43.
Laudenbach V, Mantz J, Lagercrantz H, et al. Anesthesiology 2002; 96:134-41.
Peden CJ, Prys-Roberts C. Br J Anaesth 1992; 68:123-5.

Summary

Pregnancy Category: C
Lactation Category: U

- **Dexmedetomidine** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Dexmethylphenidate—(Focalin)

International Brand Name—None identified.

Drug Class	CNS stimulants
Indications	ADD
Mechanism	Unknown; stimulates CNS activity
Dosage with Qualifiers	ADD—begin 2.5mg PO bid; increase by 5-10mg/d qw, max dose 20mg/d • **Contraindications**—hypersensitivity to drug or class, history of severe anxiety, glaucoma, motor tics, MAOI use within 14d • **Caution**—CV disease, hypertension, seizure disorder, psychosis, substance abuse, hyperthyroidism
Maternal Considerations	There are no published reports of **dexmethylphenidate** use during pregnancy. ***Side effects*** include seizures, dependency, arrhythmia, angina, thrombocytopenia, leukopenia, nervousness, insomnia, abdominal pain, headache, dizziness, palpitations, blurred vision, anorexia, weight loss, dyskinesia, and rash.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **dexmethylphenidate** crosses the human placenta. Rodent studies are reassuring, revealing no evidence of teratogenicity, though delayed ossification is seen at the highest dose level. However, there is concern that antenatal exposure may lead to behavioral abnormalities based on rodent and human study of related drugs (**amphetamine** and **methamphetamine**).
Breastfeeding Safety	There is no published experience in nursing women. It is unknown whether **dexmethylphenidate** enters human breast milk.
Drug Interactions	May decrease the effectiveness of drugs used to treat hypertension. As a result, it should be used cautiously with pressor agents. May inhibit the metabolism of coumarin anticoagulants, anticonvulsants (e.g., **phenobarbital, phenytoin, primidone**), and some antidepressants (TCAs [e.g., **imipramine, clomipramine, desipramine**] and SSRIs). Downward dose adjustments may be required. Serious adverse events have been reported when used with **clonidine,** though no causality has been established. Should not be used in patients being treated (currently or within the proceeding 2w) with MAOIs.
References	National Toxicology Program. NTP CERHR MON 2005; (16):vii-III1.
Summary	**Pregnancy Category: C** **Lactation Category: U** • **Dexmethylphenidate** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Dextroamphetamine—(Amphaetex; Das; Dexampex; Dexedrina; Dexedrine; Dextrostat; Ferndex; Oxydess; Spancap No. 1)

International Brand Name—Dexamphetamini Sulfas (Switzerland); Dexedrine (Canada, England, Ireland); Dexedrine Spansule (Canada)

Drug Class	Adrenergic agonists; Amphetamines; CNS stimulants
Indications	ADHD, narcolepsy, obesity
Mechanism	CNS stimulant
Dosage with Qualifiers	ADHD—5mg PO qd/bid; increase up to 5mg/w prn, max 40mg qd Narcolepsy—10-60mg PO qd; begin 10mg PO qd and increase 10mg/w if necessary Obesity—5-30mg PO qd 30min before breakfast • **Contraindications**—hypersensitivity to drug or class, hypertension, glaucoma, hyperthyroidism, Tourette's syndrome • **Caution**—mild hypertension
Maternal Considerations	There are no adequate reports or well-controlled studies of **dextroamphetamine** in pregnant women. There are case reports of its use for the treatment of narcolepsy during pregnancy. Since amphetamines are used to decrease appetite and maintain adequate body weight, its usage during pregnancy should be discouraged once pregnancy is diagnosed. ***Side effects*** include arrhythmia, palpitation, insomnia, irritability, dry mouth, diarrhea, tremor, anorexia, and personality changes.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. Amphetamines cross the human placenta. One case report describes severe congenital body deformity, tracheoesophageal fistula, and anal atresia in the newborn of a mother who took **dextroamphetamine** throughout the 1st trimester. Epidemiologic study reveals that birth weight is unaffected if discontinued prior to 28w, but is significantly lower if discontinued later. Mouse transport is also confirmed (approximately 18% after 1h). **Dextroamphetamine** is embryotoxic and teratogenic when administered to some but not all rodents.
Breastfeeding Safety	Amphetamines are excreted in human milk and are generally considered incompatible with breastfeeding.
Drug Interactions	GI acidifying agents (e.g., **guanethidine, reserpine, ascorbic acid,** fruit juices) lower absorption of amphetamines. Urinary acidifying agents (e.g., ammonium chloride, sodium acid phosphate) increase urinary excretion. Adrenergic blockers are inhibited by amphetamines. GI alkalinizing agents (e.g., sodium bicarbonate) increase absorption of amphetamines. Urinary alkalinizing agents (e.g., **acetazolamide,** some thiazides) decrease urinary excretion. **Desipramine** or **protriptyline** and possibly other TCAs may cause a striking and sustained increase in the concentration of **dextroamphetamine** in the brain as well as potentiating CV effects. MAOIs, as well as a metabolite of **furazolidone,** slows the metabolism of amphetamines, increasing their effect on NE release, and causing headaches and other signs of hypertensive crisis. Fatalities are reported.

Chlorpromazine and **haloperidol** block **dopamine** and NE reuptake, inhibiting their central effects. They can be used to treat amphetamine poisoning.
Amphetamines may delay intestinal absorption of **ethosuximide.**
Amphetamines potentiate the analgesic effect of **meperidine.**
Urinary excretion of amphetamines is increased, and efficacy is reduced, by acidifying agents used in **methenamine.**
In cases of **propoxyphene** overdose, amphetamine CNS stimulation is potentiated and fatal convulsions can occur.
Amphetamines inhibit the hypotensive effect of veratrum alkaloids.

References

Briggs GG, Samson JH, Crawford DJ. Am J Dis Child 1975; 129:249-50.
Hoover-Stevens S, Kovacevic-Ristanovic R. Clin Neuropharmacol 2000; 23:175-81.
Naeye RL. Pharmacology 1983; 26:117-20.
Shah NS, Yates JD. Arch Int Pharmacodyn Ther 1978; 233:200-8.

Summary

Pregnancy Category: C
Lactation Category: NS

- **Dextroamphetamine** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.
- There are few indications for **dextroamphetamine** during pregnancy, which would preclude its temporary cessation.

Dextromethorphan—(Aquabid-Dm; Biophen-Dm; Bio-Tuss Dm; Broncot; Dectuss DM; Equi-Tuss Dm; Fenex Dm; Gani-Tuss-Dm Nr; Genophen-Dm Elixir; Guaibid Dm; Guiadrine Dm; Guaifenesin Dm; Guaifenesin w/Dextromethorphan; Humibid DM; Iodur-Dm; Iofen-Dm Nf; Iogan-Dm; Iophen D-C; Iophen-DM; Io Tuss-Dm; Iotuss-Dm; Mucobid Dm; Muco-Fen-Dm; Myodine Dm; Numobid Dx; Oridol Dm; Pancof-HC; Phenergan w/ Dextromethorphan; Phen-Tuss DM; Pherazine DM; Promethazine w/DM; Prothazine; Q-Mibid-Dm; RobafenDm; Roganidin-Dm; Sil-O-Tuss Dm; Sudal-DM; Tosmar Dm; Tri-Onex Dm; Tusnel; Tusside; Tussidin Dm; Tussidin Dm Nr; Tussin Dm; Tussi-Organidin DM; Tussi-Organidin DM NR; Tussi-Organidin DM-S NR; Tussi-R-Gen Dm; Tusso-DM)

International Brand Name—None identified.

Drug Class ..... Antitussives; Expectorants

Indications ..... Cough

Mechanism ..... Suppression of the cough center

Dosage with Qualifiers

Antitussive—10-30mg PO q4h; max 120mg qd (contains alcohol)

NOTE: may be combined with ***guaifenesin*** *or* ***promethazine.***

- **Contraindications**—hypersensitivity to drug or class, use of MAOIs in the last 14d
- **Caution**—concomitant use of serotonergic drugs

Maternal Considerations

There are no adequate reports or well-controlled studies of **dextromethorphan** in pregnant women. It is commonly found in many OTC preparations. No adverse pregnancy outcomes are associated with its use.
Side effects include abuse, serotonin syndrome, sedation, dizziness, and abdominal pain.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **dextromethorphan** crosses the human placenta. The wide and long-term clinical experience suggests any fetal risk of **dextromethorphan**-containing cough preparations is small. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than that used clinically. Several rodent studies suggest **dextromethorphan** may have a beneficial effect on the developing brain chronically exposed to **morphine. Dextromethorphan** is a teratogen in the chick embryo, a poor model for such studies.

Breastfeeding Safety

There are no adequate reports or well-controlled studies in nursing women. It is unknown whether **dextromethorphan** enters human breast milk. However, the wide and long-term clinical experience suggests any risk to the breastfeeding neonate is small.

Drug Interactions

No clinically relevant interactions identified.

References

Debus O, Kurlemann G, Gehrmann J, Krasemann T. Chest 2001; 120:1038-40.
Einarson A, Lyszkiewicz D, Koren G. Chest 2001; 119:466-9.
Martinez-Frias ML, Rodriguez-Pinilla E. Teratology 2001; 63:38-41.
Yang SN, Liu CA, Chung MY, et al. Hippocampus 2006; 16:521-30.

Summary

Pregnancy Category: C
Lactation Category: S

- **Dextromethorphan** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Dextrothyroxine—(Choloxin)

International Brand Name—None identified.

Drug Class

Antihyperlipidemics

Indications

Hypercholesterolemia

Mechanism

Stimulates hepatic catabolism and excretion of cholesterol

Dosage with Qualifiers

Hypercholesterolemia—begin 1-2mg PO qd; increase to max 4-8mg/d

- **Contraindications**—hypersensitivity to drug or class, cardiac arrhythmia, tachycardia, CHF
- **Caution**—hepatic or renal dysfunction

Maternal Considerations	**Dextrothyroxine** is the dextrorotatory isomer of **thyroxine.** There is a single report of its use during pregnancy in the successful treatment of thyroid hormone resistance syndrome (RTH). RTH is characterized by an elevated serum thyroxine, inappropriately "normal" TSH, and reduced thyroid hormone responsiveness associated with point mutations in the thyroid hormone receptor-β gene. ***Side effects*** include angina, arrhythmia, MI, insomnia, nervousness, palpitations, tremors, loss of weight, changes in libido, and gallstones.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **dextrothyroxine** crosses the human placenta. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically.
Breastfeeding Safety	There is no published experience in nursing women. It is unknown whether **dextrothyroxine** enters human breast milk.
Drug Interactions	No clinically relevant interactions identified.
References	Sarkissian G, Dace A, Mesmacque A, et al. Thyroid 1999; 9:165-71.
Summary	**Pregnancy Category: C** **Lactation Category: U** • **Dextrothyroxine** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Dezocine—(Dalgan)

International Brand Name—None identified.

Drug Class	Analgesics, narcotic
Indications	Moderate to severe pain
Mechanism	Binds to various opiate receptors
Dosage with Qualifiers	Pain, moderate to severe—begin 5mg IV q2-4h or 10mg IM q3-6h; max dose 10mg IV and 20mg IM • **Contraindications**—hypersensitivity to drug or class • **Caution**—head injury, hepatic or renal dysfunction, sulfite allergy, drug dependency, biliary surgery, impaired lung function
Maternal Considerations	**Dezocine** is a synthetic opioid agonist-antagonist. There is no published experience with **dezocine** during pregnancy. ***Side effects*** include respiratory depression or arrest, hypotension, nausea, vomiting, dizziness, headache, pruritus, euphoria, and anxiety.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **dezocine** crosses the human placenta. Evidence of rodent teratogenicity is noted in the manufacturer's information, but not detailed.

Breastfeeding Safety	There is no published experience in nursing women. It is unknown whether **dezocine** enters human breast milk.
Drug Interactions	No clinically relevant interactions identified.
References	There is no published experience during pregnancy or lactation.
Summary	**Pregnancy Category: C** **Lactation Category: U** • **Dezocine** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk. • There are alternative agents for which there is more experience during pregnancy and lactation.

Diatrizoate—(Amidotrizoate; Angiovist 282; Berlex; Bolus Infusion Set; Burron Infusion Set; Cystografin; Cystografin Dilute; Cystografin Dilute w/Set; Hypaque; Hypaque-Cysto; Hypaque-Cysto 100Ml/300Ml; Hypaque-Cysto 250Ml/500Ml; Hypaque Meglumine; Reno-M-30; Reno-M-60; Reno-M-Dip; Urovist Cysto; Urovist Cysto 100Ml in 300Ml; Urovist Cysto 300Ml in 500Ml; Urovist Cysto Pediatric; Urovist Meglumine; Urovist Meglumine DIU/CT)

International Brand Name—None identified.

Drug Class	Diagnostics, nonradioactive
Indications	Retrograde cystourethrography
Mechanism	Radiographic contrast agent
Dosage with Qualifiers	Retrograde cystourethrography—25-300ml instilled within the urinary bladder *NOTE: also used for IV contrast.* • **Contraindications**—hypersensitivity to drug or class • **Caution**—sensitivity to iodine, UTI
Maternal Considerations	There are no adequate reports or well-controlled studies of **diatrizoate** in pregnant women. **Diatrizoate** is a contrast agent frequently used to study bladder structure or function and fallopian tube patency, and in the past for a variety of fetal imaging studies. ***Side effects*** include hematuria, retrograde infection, renal failure, hypersensitivity, and anaphylactic reaction.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **diatrizoate** crosses the human placenta. Postnatally, **diatrizoate** is used diagnostically to distinguish NEC from microcolon of prematurity. Rodent teratogenicity studies have not been performed.
Breastfeeding Safety	A single report suggests that a small amount of **diatrizoate** may be excreted into human breast milk. However, considering the

	indication and dosing, one-time **diatrizoate** use is unlikely to pose a clinically significant risk to the breastfeeding neonate.
Drug Interactions	No clinically significant interactions identified.
References	Krasna IH, Rosenfeld D, Salerno P. J Pediatr Surg 1996; 31:855-8. Harman CR, Menticoglou SM, Bowman JM, Manning FA. Fetal Ther 1989; 4:78-82. Samuel N, Dicker D, Landman J, et al. J Ultrasound Med 1986; 5:425-8. Weyrauch U, Volkhardt V, Speck U. Rofo 1977; 127:275-6
Summary	**Pregnancy Category: C** **Lactation Category: U** • **Diatrizoate** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Diazepam—(Alupram; Anlin; Baogin; Britazepam; Centrazepam; Chuansuan; Desloneg; Diastat; Diatran; Dizac; Euphorin; Evacalm; Jinpanfan; Mandro; Meval; Nellium; Nerozen; Nixtensyn; Notense; Parzam; Pomin; Rival; Tensium; Tranquil; Valitran; Valium; Valrelease; Winii; Zepaxid)

International Brand Name—Alboral (Mexico); Aliseum (Italy); Amiprol (Argentina); Ansiolin (Italy); Anxionil (Philippines); Apo-diazepam (Canada); Apozepam (Denmark, Sweden); Armonil (Argentina); Arzepam (Mexico); Assival (Israel); Atensine (Ireland); Azedipamin (Japan); Benzopin (South Africa); Best (Argentina); Betapam (South Africa); Calmpose (India); Caudel (Argentina); Compaz (Brazil); Desconet (Argentina); Diaceplex (Spain); Dialar (England); Diano (Thailand); Diapam (Finland, Russia, Thailand, Turkey); Diapanil (Mexico); Diapax (Japan); Diapin (Taiwan); Diapine (Malaysia, Thailand); Diapo (Malaysia); Diaquel (South Africa); Diazem (Turkey); Diazemuls (England, Italy, Netherlands); Diazepan (Costa Rica, Dominican Republic, El Salvador, Guatemala, Honduras, Nicaragua, Panama, Spain); Diazepin (Indonesia); Dipaz (Ecuador); Dipezona (Argentina); Doval (South Africa); Drenian (Spain); Dupin (Taiwan); DZP (Malaysia); Elcion CR (India); Eridan (Italy); Euphorin P (Japan); Gewacalm (Austria); Gradual (Argentina); Gubex (Argentina); Horizon (Japan); Kratium 2 (Hong Kong); Lembrol (Argentina); Lovium (Indonesia); Melode (Korea); Mentalium (Indonesia); Noan (Brazil, Italy); Ortopsique (Mexico); Paceum (Switzerland); Pacitran (Peru); Pax (South Africa); Paxum (India); Placidox 2 (India); Placidox 5 (India); Placidox 10 (India); Plidan (Argentina); Propam (New Zealand); Psychopax (Austria, Switzerland); Relanium (Bulgaria, Poland, Russia); Reliver (Japan); Reposepan (Peru); Saromet (Argentina); Simasedan (Argentina); Sipam (Thailand); Sonacon (Japan); Stesolid (Czech Republic, Denmark, England, Finland, Germany, Hungary, Indonesia, Netherlands, Norway, Sweden, Switzerland, Taiwan, Thailand); Stesolid Rectal Tube (Germany, Hong Kong); Tranquirit (Italy); Trazepam (Philippines); Valaxona (Denmark); Valiquid (Germany); Valium (Argentina, Australia, Brazil, Canada, Costa Rica, Dominican Republic, Ecuador, El Salvador, Guatemala, Honduras, India, Indonesia, Korea, Malaysia, Mexico, Nicaragua, Panama, Paraguay, Peru, Philippines, Taiwan, Thailand, Uruguay, Venezuela); Valpam (Australia); Vanconin (Taiwan); Vatran (Italy); Vazen (Peru); Vivol (Canada)

Drug Class	Anxiolytics; Benzodiazepines; Muscle relaxants
Indications	Anxiety, alcohol withdrawal, seizure disorder, status epilepticus, muscle spasm
Mechanism	Binds benzodiazepine and possibly GABA receptors centrally
Dosage with Qualifiers	Anxiety—2-10mg IV/IM tid or qid Alcohol withdrawal—5mg PO tid or qid prn Seizure disorder—2-10mg PO bid or qid Status epilepticus—5-10mg IV q10-15min Muscle spasm—2-10mg PO bid or qid

- **Contraindications**—hypersensitivity to drug or class, glaucoma, CNS depression, shock, coma, and barbiturate and alcohol use
- **Caution**—renal or hepatic dysfunction, psychosis, pulmonary dysfunction

Maternal Considerations

There are no adequate reports or well-controlled studies of **diazepam** in pregnant women. It is a beneficial adjunct to IV fluids and vitamins for the treatment of 1st trimester hyperemesis. **Diazepam** was previously used for prophylaxis and treatment of eclamptic convulsions, but proved less effective than **magnesium sulfate.** Pregnancy may unmask a preexisting potential for chorea (chorea gravidarum), and benzodiazepines may aid chorea control. **Diazepam** is a useful antianxietal in women undergoing fetal therapy procedures. **Flumazenil** (a specific benzodiazepine receptor antagonist) is indicated for complete or partial reversal of the sedative effects, or treatment of a **benzodiazepine** overdose.
Side effects include severe burning and vascular irritation, withdrawal syndrome, hepatic toxicity, pancytopenia, neutropenia, hypotension, N/V, vertigo, blurred vision, and rash.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. **Diazepam** rapidly crosses the human placenta, with the F:M ratio approaching unity within 15min of maternal injection and exceeding the maternal level within several hours of administration during labor. Decreased fetal movement frequently accompanies IV administration. Several studies that suggested an increased risk of fetal malformation when **diazepam** is used during the 1st trimester have not been confirmed subsequently. Postnatal follow-up until age 4y is likewise reassuring, revealing no adverse effects on neurodevelopment. Prolonged CNS depression may occur in neonates, apparently due to their inability to metabolize **diazepam.** The shortest course and the lowest dose should be used when indicated during pregnancy. Some newborns exposed antenatally exhibit either the floppy infant syndrome or marked neonatal withdrawal symptoms. Symptoms vary from mild sedation, hypotonia, and reluctance to suck to apneic spells, cyanosis, and impaired metabolic responses to cold stress. Such symptoms may persist for hours to months after birth. Rodent studies suggest an increased incidence of fetal malformations (skeletal defects) when administered at much higher doses than ones used clinically. Further, a large body of rodent behavioral studies reveals behavioral alterations that persist into adulthood.

Breastfeeding Safety

Diazepam is excreted into human breast milk to a limited degree. The maximum neonatal exposure is estimated at 3% of the maternal dose. Problems may arise if the neonate is premature, or the maternal dose particularly high. Neonatal lethargy, sedation, and weight loss have been reported, but their attribution to **diazepam** is not always clear.

Drug Interactions

Phenothiazines, narcotics, barbiturates, MAOIs, and other antidepressants may potentiate the action of **diazepam.**
Cimetidine may delay **diazepam** clearance.
Valproate may potentiate the CNS-depressant effects.
In vitro studies of human liver suggest CYP2CI9 and CYP3A4 are the principal isozymes involved in the initial oxidative metabolism of **diazepam.** Potential inhibitors of CYP2CI9 (e.g., **cimetidine, quinidine, tranylcypromine**) and CYP3A4 (e.g., **ketoconazole, troleandomycin, clotrimazole**) may decrease

diazepam elimination, while inducers of CYP2CI9 (e.g., **rifampin**) and CYP3A4 (e.g., **carbamazepine, phenytoin, dexamethasone, phenobarbital**) may increase the rate of elimination.
Diazepam could interfere with the metabolism of CYP2CI9 (e.g., **omeprazole, propranolol, imipramine**) and CYP3A4 substrates (e.g., **cyclosporine, paclitaxel, terfenadine, theophylline, warfarin**).

References

Belfort MA, Anthony J, Saade GR. Semin Perinatol 1999; 23:65-78.
Borgatta L, Jenny RW, Gruss L, et al. J Clin Pharmacol 1997; 37:186-92.
Brandt R. Arzneimittelforschung 1976; 26:454-7.
Chatterjee A, Mukheree J. J Obstet Gynaecol Res 1997; 23:289-93.
Chien PF, Khan KS, Arnott N. Br J Obstet Gynaecol 1996; 103:1085-91.
Ditto A, Morgante G, la Marca A, De Leo V. Gynecol Obstet Invest 1999; 48:232-6.
Duley L, Henderson-Smart D. Cochrane Database Syst Rev 2000; (0):CD000127.
Gidai J, Acs N, Banhidy F, Czeizel AE. Toxicol Ind Health 2008; 24:29-39.
Golbe LI. Neurol Clin 1994; 12:497-508.
Gulmezoglu AM, Duley L. BMJ 1998; 316:975-6.
Iqbal MM, Sobhan T, Aftab SR, Mahmud SZ. Del Med J 2002; 74:127-35.
Iqbal MM, Sobhan T, Ryals T. Psychiatr Serv 2002; 53:39-49.
Jauniaux E, Jurkovic D, Lees C, et al. Hum Reprod 1996; 11:889-92.
Kjaer D, Horvath-Puho E, Christensen J, et al. Pharmacoepidemiol Drug Saf 2007; 16:181-8.
Levy M, Spino M. Pharmacotherapy 1993; 13:202-11.
McElhatton PR. Reprod Toxicol 1994; 8:461-75.
[No authors]. Lancet 1995; 345:1455-63.
Stahl MM, Saldeen P, Vinge E. Br J Obstet Gynaecol 1993; 100:185-8.
Suita S, Taguchi T, Yamanouchi T, et al. J Pediatr Surg 1999; 34:1652-7.
Wang C, Cheng Y, Liang J. Hunan Yi Ke Da Xue Xue Bao 1999; 24:53-5.

Summary

Pregnancy Category: D
Lactation Category: S (likely)

- **Diazepam** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.
- Many indications for **diazepam** have other alternative agents considered to have a higher safety margin during pregnancy and lactation.

Diazoxide—(Hyperstat; Proglycem)

International Brand Name—Eudemine (England, Korea); Hyperstat (Canada); Proglicem (France, Israel, Italy, Netherlands, Switzerland); Proglycem (Canada, Greece, Korea)

Drug Class

Antihypertensives; Antihypoglycemics

Indications

Hypertension

Mechanism

Directly relaxes peripheral arteriole smooth muscle

Dosage with Qualifiers

Hypertension—1-3mg/kg IV q5-15min; max 150mg IV

- **Contraindications**—hypersensitivity to drug or class, sulfonamides or thiazide diuretics
- **Caution**—CAD

Maternal Considerations

The mechanism of action of **diazoxide** remains unclear. It inhibits the production of IL-10 and the proinflammatory cytokines TNF-α and IL-6 by placentas and peripheral blood mononuclear cells. The choice of antihypertensive depends in part on physician experience, and in part on what is known about adverse maternal and fetal side effects. **Diazoxide** has been used for the treatment of severe hypertension during pregnancy, but is associated with a high risk of hypotension and its attendant fetal distress. Smaller (15mg IU) but more frequent dosing reduces that risk. There are many alternatives, including **labetalol, ketanserin, hydralazine, nitroprusside, nicardipine** (in low doses), and **nifedipine,** of seemingly equal efficacy with much lower complication rates.
Side effects include arrhythmias, seizures, MI, hyperglycemia, hypotension, N/V, weakness, and CHF.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. **Diazoxide** crosses the human placenta, though the kinetics remain to be elucidated. Rodent studies are generally reassuring, revealing no evidence of teratogenicity, though IUGR is seen at the highest doses.

Breastfeeding Safety

There is no published experience in nursing women. It is unknown whether **diazoxide** enters human breast milk.

Drug Interactions

Diazoxide is highly bound to serum proteins and can be expected to displace other bound substances such as bilirubin or **warfarin** and its derivatives, and thus cause higher blood levels.
Hypotension may occur if administered within 6h of another antihypertensive medication such as **hydralazine, reserpine, alphaprodine, methyldopa,** β-blockers, **prazosin, minoxidil,** the nitrites, and other papaverine-like compounds.
May potentiate the actions of other antihypertensive agents.
Use with thiazides or other commonly used diuretics may potentiate the hyperuricemic and antihypertensive effects of **diazoxide.**

References

Duley L, Henderson-Smart DJ, Meher S. Cochrane Database Syst Rev 2006; (3):CD001449.
Hennessy A, Thornton CE, Makris A, et al. Aust N Z J Obstet Gynaecol 2007;47:279-85.
Lowe SA, Rubin PC. J Hypertens 1992; 10:201-7.
Michael CA. Aust N Z J Obstet Gynaecol 1986; 26:26-9.
Xu B, Makris A, Thornton C, et al. J Hypertens 2006; 24:915-22.

Summary	**Pregnancy Category: C** **Lactation Category: U** • **Diazoxide** is indicated outside pregnancy for the rapid reduction of BP. • There are many other alternatives (e.g., **labetalol, ketanserin, nifedipine**) during pregnancy of seemingly equal efficacy.

Dichlorphenamide—(Daranide; Defenamida)

International Brand Name—None identified.

Drug Class	Carbonic anhydrase inhibitors
Indications	Glaucoma (open-angle)
Mechanism	Carbonic anhydrase inhibitors decrease intraocular pressure by reducing aqueous humor inflow
Dosage with Qualifiers	Glaucoma—100-200mg PO q12h until response, then maintain 25-50mg PO qd to tid • **Contraindications**—hypersensitivity to drug or class • **Caution**—hypokalemia
Maternal Considerations	There is no published experience with **dichlorphenamide** during pregnancy. **Dichlorphenamide** should be used cautiously as it may produce brisk diuresis followed by hypokalemia. ***Side effects*** include constipation, anorexia, N/V, weight loss, urinary frequency, renal colic, renal calculi, skin rash, headache, weakness, pruritus, leukopenia, agranulocytosis, thrombocytopenia, nervousness, sedation, depression, confusion, dizziness, and paresthesias of the hands, feet, and tongue.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **dichlorphenamide** crosses the human placenta. Rodent studies reveal skeletal anomalies at high doses.
Breastfeeding Safety	There is no published experience in nursing women. It is unknown whether **dichlorphenamide** enters human breast milk.
Drug Interactions	No clinically relevant interactions identified.
References	Hallesy DW, Layton WM Jr. Riv Patol Nerv Ment 1966; 87:6-8. Purichia N, Erway LC. Dev Biol 1972; 27:395-405.
Summary	**Pregnancy Category: B** **Lactation Category: U** • **Dichlorphenamide** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Diclofenac—(Berifen Gel; Blesin; Cataflam; Clofen; Diclofenac Sodium; Oritaren; Silino; Voltaren)

International Brand Name—Abdiflam (Indonesia); Abitren (Israel); Acuflam (Philippines); Allvoran (Germany); Almiral (Hong Kong, Malaysia, Singapore, Taiwan); Almiral Gel (Singapore); Almiral SR (Hong Kong, Malaysia); Alonpin (Japan); Apo-Diclofenac EC (New Zealand); Arcanafenac (South Africa); Arthrifen (Philippines); Artren (Colombia, Ecuador); Artrenac (Mexico); Artrites (Colombia); Artrites Retard (Colombia); Berafen Gel (Paraguay); Berifen (Indonesia); Berifen Gel (Costa Rica, Dominican Republic, El Salvador, Guatemala, Honduras, Nicaragua, Panama); Betaren (Israel); Bolabomin (Japan); Calozan (Costa Rica, Dominican Republic, El Salvador, Guatemala, Honduras, Nicaragua, Panama); Cataflam (Belgium, Chile, China, Greece, Hong Kong, Hungary, Indonesia, Mexico, Netherlands, New Zealand, Peru, Portugal, South Africa, Taiwan, Turkey); Cataflam DD (Ecuador); Cataflam Drops (Malaysia); Cataflam Emulgel (Brazil, Chile, Venezuela); Catanac (Indonesia); Catas (Korea); Cencenag (Thailand); Clo-Far (Mexico); Clofec (Thailand); Clonac (Australia); Clonaren (Philippines); Clonodifen (Mexico); Cordralan (Peru); Curinflam (Argentina, Hong Kong); DDL plaster (Korea); Decrol (Korea); Deflam-K (Taiwan); Depain (Korea); Depain Plaster (Korea); Diceus (Taiwan); Diclax (New Zealand); Diclax SR (New Zealand); Diclo (Singapore); Diclo-Basan (Switzerland); Diclobene (Austria); Diclodoc (Germany); Diclofen (Taiwan, Thailand); Diclofenac (Colombia); Diclofen Cremogel (Israel); Dicloflam (South Africa); Diclohexal (Australia); Diclomax (India, Republic of Yemen); Diclomol (Thailand); Diclon (Denmark); Dicloran Gel (India, South Africa); Dicloren (Taiwan); Diclosian (Thailand); Diclotec (Canada); Diclowal (Costa Rica, Dominican Republic, El Salvador, Guatemala, Honduras, Nicaragua, Panama); Dicsnal (Japan); Difen (Thailand); Difena (Taiwan); Difenac (Japan, South Africa, Thailand); Difenol Gel (Hong Kong); Difnal K (Malaysia); Dioxaflex (Mexico); Divoltar (Indonesia); Doflastad (Philippines); Doflex (India); Dolaren (Mexico); Dolflam-Retard (Mexico); Doloflam (Philippines); Dolotren (Dominican Republic, El Salvador, Guatemala, Honduras, Nicaragua, Panama, Taiwan); Dolotren Gel (Taiwan); Dosanac (Thailand); Dycon SR (Philippines); E (Greece); Ecofenac (Switzerland); Eflagen (Indonesia); Epifenac (Israel); Eslofen (Philippines); Evadol (Mexico); Fenadium (Malaysia); Fenaspec (Philippines); Flameril (New Zealand); Flector (France); Flexagen (South Africa); Flogofenac (China); Flogosin D (Uruguay); Flogozan (Costa Rica, Dominican Republic, El Salvador, Guatemala, Honduras, Nicaragua, Panama); Fortfen SR (South Africa); Freejex (Korea); Hizemin (Japan); Imflac (Australia); Inac (Singapore); Inac gel (Singapore); Inflamac (Switzerland); Inflanac (Hong Kong, Malaysia, Thailand); Jonac Gel (India); Kadiflam (Indonesia); Klotaren (Indonesia); Lesflam (Singapore); Lifenac (Mexico); Lofenac (Thailand); Lotirac (Korea); Magluphen (Austria); Merflam (Indonesia); Monoflam (Czech Republic, Germany); Myfenax (Thailand); Naboal (Japan); Nac Gel (India); Naclof (Ecuador, Hong Kong, Korea, Philippines, South Africa, Taiwan, Thailand); Nacoflar (Indonesia); Nadifen (Indonesia); Nepenthe (Philippines); Novo–Difenac (Hong Kong); Novolten (China); Ofenac (Korea); Olfen (China, Hong Kong); Olfen-75 SR (Hong Kong, Malaysia); Olfen Gel (Singapore, Thailand); Olfen Roll-On (Israel); Optanac (Indonesia); Osteoflam (India); Painstop (Taiwan); Panamor (South Africa); Profenac (Israel); Relaxyl Gel (India); Remethan (Germany, Malaysia, Singapore); Remethan Gel (Taiwan); Ren (Hong Kong); Renvol Emulgel (Indonesia); Rewodina (Germany, Malaysia, Russia); Rhewlin (Singapore); Rhewlin Forte (Singapore); Rhewlin SR (Singapore); Rolactin (Korea); Savismin (Japan); Sefnac (Thailand); Soproxen (Thailand); Staren (Taiwan); Sting Gel (Singapore); Tigen Plaster (Korea); Toraren (Korea); Tsudohmin (Japan); Uniclonax (Philippines); Uniren (Singapore); Valentac (Korea); Vartelon (Hong Kong); Vartelon Gel (Hong Kong); Voldic (Israel); Voldic Emulgel (Israel); Volero (Korea); Volfenac (Costa Rica, Dominican Republic, El Salvador, Guatemala, Honduras, Nicaragua, Panama); Volna-K (Taiwan); Volta (Thailand); Voltadex Emulgel (Indonesia); Voltalen (New Zealand); Voltalen Emulgel (New Zealand); Voltaren (Argentina, Austria, Belgium, Bulgaria, Canada, China, Colombia, Czech Republic, Denmark, Ecuador, Finland, Germany, Hong Kong, Indonesia, Italy, Japan, Korea, Malaysia, Mexico, Netherlands, Norway, Paraguay, Philippines, Poland, Portugal, Russia, Spain, Sweden, Switzerland, Taiwan, Thailand, Turkey, Uruguay, Venezuela); Voltaren Acti-Go (Israel); Voltaren Colirio (Paraguay); Voltaren Dolo (Hong Kong); Voltarene (France, Greece); Voltarene Emulgel (France); Voltaren Emulgel (Brazil, China, Colombia, Czech Republic, Germany, Greece, Hong Kong, Indonesia, Malaysia, Mexico, Peru, Philippines, South Africa, Spain, Switzerland, Taiwan, Turkey); Voltaren Forte (Philippines); Voltaren K Migraine (Germany); Voltaren Ofta (Germany, Italy, Mexico); Voltaren Oftalmico (Colombia, Uruguay, Venezuela); Voltaren Ophta (Canada); Voltaren Ophtha (Austria, Belgium, Denmark, Israel, Norway, Switzerland, Thailand); Voltaren Retard (Colombia, Mexico); Voltaren SR (Hong Kong, New Zealand, Philippines); Voltarol (England, Ireland); Voltarol Emulgel (England, Ireland); Voltrix (Brazil); Voren (China, Indonesia, Taiwan); Voren Emulgel (China); Votalen (Hong Kong); Votalen SR (New Zealand); Voveran (India); Voveran Emulgel (India); Yuren (Taiwan); Zolterol (Malaysia); Zolterol SR (Singapore)

Drug Class	Analgesics, non-narcotic; NSAID; Ophthalmics
Indications	Dysmenorrhea, mild to moderate pain, rheumatoid arthritis or osteoarthritis, ankylosing spondylitis
Mechanism	Inhibits cyclooxygenase and lipoxygenase, leading to reduced prostaglandin synthesis
Dosage with Qualifiers	Dysmenorrhea—begin 100mg PO, then 50mg PO tid Mild to moderate pain—begin 50mg PO bid to tid

Rheumatoid arthritis or osteoarthritis—50mg PO bid to tid; max 225mg qd
Ankylosing spondylitis—25mg PO qid

- **Contraindications**—hypersensitivity to drug or class, NSAID-induced asthma, nasal polyps, GI bleeding, liver
- **Caution**—hypertension, nasal polyps, CHF, GI bleeding history

■ Maternal Considerations

There are no adequate reports or well-controlled studies in pregnant women. **Diclofenac** is a short-acting NSAID with antipyretic, anti-inflammatory, and analgesic properties. It is useful for the relief of ureteral colic or postsurgical pain during pregnancy, or episiotomy after delivery. In several studies, **diclofenac** had a morphine-sparing effect. While rodent studies reveal very high doses of some NSAIDs are associated with dystocia and prolongation of pregnancy, similar studies in humans are missing for **diclofenac.** Cyclooxygenase inhibitors such as **diclofenac** may modulate the quantity and degradation of collagen in the rat cervix. **Diclofenac** does not interfere with cervical ripening induced by **misoprostol.** Like other NSAIDs, **diclofenac** alters renal function to decrease free water clearance and increases the toxicity of certain drugs such as **digoxin.** Administration at the time of egg collection in women undergoing IVF does not appear to affect implantation or pregnancy rates, while it could be effective in reducing discomfort and pain associated with oocyte retrieval.

NOTE: with caution, may be combined with ***misoprostol*** *(Arthrotec).*
Side effects include anaphylaxis, bleeding, bronchospasm, thrombocytopenia, Stevens-Johnson syndrome, interstitial nephritis, impairment of the liver and kidney function, abdominal pain, urticaria, drowsiness, and tinnitus.

■ Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. **Diclofenac** rapidly crosses the human placenta even in the 1st trimester, yielding an F:M ratio approximating unity. Premature closure of the ductus arteriosus is reported. Rodent studies are generally reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically. High doses were associated with fetal toxicity. In one recent report, the administration of **diclofenac** to the ovine fetus blunted the normal increase in cerebral blood flow following a hypoxic episode. While it is unknown whether this same response occurs in association with other NSAIDs or in the human, it suggests the need for caution administering NSAIDs to pregnant women when labor is imminent.

■ Breastfeeding Safety

There are no adequate reports or well-controlled studies of **diclofenac** in nursing women. Most NSAIDs enter human milk to some extent. The chemical structure and preliminary study suggest passage should be low and occasional use is without clinically significant risk. **Ibuprofen** is generally preferred for breastfeeding women.

■ Drug Interactions

Aspirin is not generally recommended because of the potential of increased adverse effects.
NSAIDs reportedly inhibit **methotrexate** accumulation in rabbit kidney slices. Caution should be used when administering NSAIDs with **methotrexate.**
Like other NSAIDs, **diclofenac** may affect renal prostaglandins and increase the toxicity of drugs such as **cyclosporine.**
NSAIDs may diminish the antihypertensive effect of ACEIs.

Diclofenac reduces the natriuretic effect of **furosemide** and thiazides; observe closely for signs of renal failure as well as to assure diuretic efficacy.
NSAIDs increase plasma **lithium** levels and reduce renal **lithium** clearance. Patients should be observed carefully for signs of **lithium** toxicity.
The effects of **warfarin** and NSAIDs on GI bleeding are synergistic, such that users of both drugs together have a risk of serious GI bleeding higher than users of either drug alone.

References

Akande V, Garas A, Cahill D. J Obstet Gynaecol 2006; 26:785-7.
Al-Waili NS. Arch Med Res 2001; 32:148-54.
Bienkiewicz A. Horm Metab Res 1995; 27:79-82.
Bogdanenko EV, Sviridov IuV, Sadovnikov VB, Zhdanov RI. Eksp Klin Farmakol 1999; 62:55-7.
Dodd JM, Hedayati H, Pearce E, et al. BJOG 2004; 111:1059-64.
Ergene U, Pekdemir M, Canda E, et al. Int Urol Nephrol 2001; 33:315-9.
Hohlagschwandtner M, Ruecklinger E, Husslein P, Joura EA. Obstet Gynecol 2001; 98:1089-92.
Ivy LC, Grace WC, Ben CC, Chung HP. Contraception 2003; 67:101-5.
Mas C, Menahem S. Aust N Z J Obstet Gynaecol 1999; 39:106-7.
Montenegro MA, Palomino H. J Craniofac Genet Dev Biol 1990; 10:83-94.
Needs CJ, Brooks PM. Br J Rheumatol 1985; 24:291-7.
Nishida N, Blood AB, Hunter CJ, et al. Pediatr Res 2006; 60:524-9.
Siddik SM, Aouad MT, Jalbout MI, et al. Reg Anesth Pain Med 2001; 26:310-5.
Siu SS, Yeung JH, Lau TK. Hum Reprod 2000; 15:2423-5.
Zenker M, Klinge J, Kruger C, et al. J Perinat Med 1998; 26:231-4.

Summary

Pregnancy Category: B
Lactation Category: S (likely)
- There are alternative agents for which there is more experience during pregnancy and lactation.

Dicloxacillin—(Dacocillin; Dycill; Dynapen; Maclicine; Orbenin; Pathocil; Staphcillin)

International Brand Name—Brispen (Mexico); Cloxydin (Thailand); Dacocilin (Taiwan); Diclex (Thailand); Diclixin (Peru); Diclo (Italy); Diclocil (Colombia, Costa Rica, Denmark, Ecuador, El Salvador, Finland, Greece, Guatemala, Honduras, Hong Kong, Italy, Nicaragua, Norway, Panama, Peru, Portugal, Sweden, Thailand); Diclopen-T (Ecuador); Diclox (Thailand); Dicloxin (Thailand); Dicloxman (Thailand); Dicloxno (Thailand); Dicloxsig (Australia); Diloxin (Thailand); Distaph (Australia); Dixalin (Dominican Republic, El Salvador, Panama); H.G. Dicloxacil (Ecuador); Novapen (Italy); Posipen (Costa Rica, Dominican Republic, El Salvador, Guatemala, Honduras, Mexico, Nicaragua, Panama, Peru); Staphcillin A (Japan); Uniclox (Colombia); Ziefmycin (Taiwan)

Drug Class

Antibiotics; Penicillins

Indications

Bacterial infections (gram-positive aerobes: penicillin-resistant *Staphylococcus*), osteomyelitis, mastitis

Mechanism

Bactericidal—inhibits cell wall synthesis

Dosage with Qualifiers

Skin infection—125-500mg PO q6h 1h ac or pc

Osteomyelitis—250-500mg PO q6h ac or pc
Mastitis—250-500mg PO q6h ac or pc

*NOTE: renal dosing; GI absorption of **dicloxacillin** is delayed if taken after a meal.*

- **Contraindications**—hypersensitivity to drug or class
- **Caution**—cephalosporin allergy, neonates, renal or hepatic dysfunction, and Epstein-Barr virus or CMV infections

Maternal Considerations

There are no adequate reports or well-controlled studies of **dicloxacillin** in pregnant women. **Dicloxacillin** is a penicillinase-resistant, acid-resistant semisynthetic broad-spectrum penicillin. It is an excellent drug for the treatment of postpartum mastitis. ***Side effects*** include seizures, pseudomembranous colitis, agranulocytosis, anemia, thrombocytopenia, leukopenia, epigastric or abdominal pain, N/V, diarrhea, dizziness, fatigue, fever, increased LFTs, and eosinophilia.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. **Dicloxacillin** crosses the human placenta but the fetal concentrations are relatively low, perhaps because of the high degree of maternal protein binding. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically.

Breastfeeding Safety

There is no published experience in nursing women. It is unknown whether **dicloxacillin** enters human breast milk. The extensive clinical experience with its use for mastitis is reassuring. Other penicillin agents are excreted into human breast milk, but are generally considered safe.

Drug Interactions

Tetracycline-class agents that are bacteriostatic antibiotics may antagonize the bactericidal effect of penicillins and should be avoided.

References

Anderson JC. J Comp Pathol 1977; 87:611-21.
Brander GC, Watkins JH, Gard RP. Vet Rec 1975; 97:300-4.
Depp R, Kind AC, Kirby WM, Johnson WL. Am J Obstet Gynecol 1970; 107:1054-7.
Herngren L, Ehrnebo M, Boreus LO. Dev Pharmacol Ther 1983; 6:110-24.
MacAulay MA, Berg SR, Charles D. Am J Obstet Gynecol 1968; 102:1162-8.
Pacifici GM. Int J Clin Pharmacol Ther 2006; 44:57-63.

Summary

Pregnancy Category: B
Lactation Category: S

- A drug of choice for the treatment of postpartum mastitis.

Dicyclomine—(Antispas; A-Spas; Bentyl; Bo-Cyclomine; Coochil; Dedoxia; Diciclomina; Dicyclocot; Magesan; Medispaz-Im; Protylol)

International Brand Name—Babyspasmil (Argentina); Balacon (Japan); Bentyl (Brazil, Japan, Mexico, Philippines, Taiwan); Bentylol (Canada); Clomin (South Africa, Thailand); Cyclominol (India); Diclomin (Mexico); Dicomin (Thailand); Dicymine (Hong Kong, Thailand); Dilomin (Philippines); Easy (Korea); Formulex (Canada); Lomine (Canada); Magesan P (Japan); Medicyclomine (South Africa); Merbentyl (England, Ireland, New Zealand, South Africa); Nomcramp (South Africa); Notensyl (Israel); Panakiron (Japan); Respolimin (Japan); Spasmotine (Philippines); Swityl (Taiwan)

Drug Class	Anticholinergics; Gastrointestinals
Indications	Irritable bowel syndrome
Mechanism	Decreases GI motility by inhibiting smooth muscle contractility
Dosage with Qualifiers	Irritable bowel syndrome—20mg PO qid; max 40mg PO qid • **Contraindications**—hypersensitivity to drug or class, ulcerative colitis, paralytic ileus, toxic megacolon, myasthenia gravis, reflux esophagitis, glaucoma • **Caution**—CV disease, hyperthyroidism
Maternal Considerations	There are no adequate reports or well-controlled studies of **dicyclomine** in pregnant women. ***Side effects*** include drowsiness, blurred vision, respiratory distress, tachycardia, urticaria, confusion, constipation, mydriasis, N/V, palpitations, fever, psychosis, and photophobia.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **dicyclomine** crosses the human placenta. Epidemiologic studies are reassuring. **Dicyclomine** was a component of Bendectin, a popular but no longer marketed drug used to treat N/V during pregnancy. It initially consisted of **doxylamine, dicyclomine,** and **pyridoxine; dicyclomine** was dropped from the formulation in 1976. Bendectin was ultimately discontinued in 1983 after an onslaught of lawsuits suggesting it caused congenital malformations. Subsequent studies revealed no difference in the prevalence of birth defects between mothers who had taken Bendectin during the 1st trimester and those who had not. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically.
Breastfeeding Safety	There is no published experience in nursing women. **Dicyclomine** is excreted in human milk. As there are case reports noting severe respiratory symptoms in neonates directly receiving **dicyclomine,** it is generally considered incompatible with breastfeeding.
Drug Interactions	**Amantadine,** antiarrhythmic agents of class I (e.g., **quinidine**), antihistamines, antipsychotic agents (e.g., **phenothiazines**), benzodiazepines, MAOIs, narcotic analgesics (e.g., **meperidine**), nitrates and nitrites, sympathomimetic agents, TCAs, and other drugs having anticholinergic activity may enhance the effect of **dicyclomine.** Anticholinergics antagonize the effects of antiglaucoma agents. Anticholinergic drugs in the presence of increased intraocular

pressure may be hazardous when taken concurrently with agents such as corticosteroids.
Anticholinergic agents may affect GI absorption of various drugs, such as sustained-release digoxin, causing increased concentrations.
Anticholinergic drugs may antagonize the effects of drugs that alter GI motility, such as **metoclopramide.**
Antacids may interfere with the absorption of anticholinergic agents; simultaneous use of these drugs should be avoided.

References

Boneva RS, Moore CA, Botto L, et al. Am J Epidemiol 1999; 149:717-25.
Magee LA, Mazzotta P, Koren G. Am J Obstet Gynecol 2002; 185:S256-61.
McKeigue PM, Lamm SH, Linn S, Kutcher JS. Teratology 1994; 50:27-37.

Summary

Pregnancy Category: B
Lactation Category: NS (possibly)

- **Dicyclomine** should be used during pregnancy only if the benefit justifies the potential perinatal risk.
- There are alternative agents for which there is more experience during pregnancy and lactation.

Didanosine—(DDI; Videx; Videx EC)

International Brand Name—Bandotan (Argentina); Bristol-Videx EC (Colombia); Cipladinex 100 (Colombia); Didax (Brazil); Dinex (India); Vidanovir (Hungary); Viden DDI (Colombia); Videx (Brazil, Canada, Chile, Ecuador, Egypt, Indonesia, Israel, Japan, Korea, Malaysia, Mexico, Peru, South Africa, Taiwan, Thailand, Uruguay, Venezuela); Videx EC (Hong Kong, Israel, Malaysia, Singapore, Taiwan, Thailand)

Drug Class

Antivirals; Nucleoside reverse transcriptase inhibitors

Indications

HIV

Mechanism

NRTI

Dosage with Qualifiers

HIV—200mg PO q12h

NOTE: if weight <60kg, 125mg PO q12h.

- **Contraindications**—hypersensitivity to drug or class, history of pancreatitis, neuropathy
- **Caution**—gout, neuropathy, renal or hepatic dysfunction, concomitant use of neurotoxic agents

Maternal Considerations

There are no adequate reports or well-controlled studies of **didanosine** in pregnant women. Human pharmacokinetic studies suggest maternal plasma clearance after IV administration is significantly greater antepartum than postpartum. Clearance during pregnancy is unaltered after PO administration.
Didanosine is no more effective than **zidovudine** as monotherapy. HIV patients with <400 viral copies/ml respond faster (2 consecutive viral loads <400 copies/ml) and maintain that response for 4y when given a multiregimen treatment including **didanosine, stavudine,** and **nelfinavir** compared to **lamivudine, zidovudine,** and **nelfinavir.** Resistant strains are known. **Didanosine** is a cause of diabetes mellitus. Blood glucose levels should be monitored frequently, especially when **didanosine** is combined with other drugs such as **pentamidine** and **dapsone** that cause hyperglycemia. **Didanosine** does not cure HIV, nor

does it reduce the risk of HIV transmission by sexual contact or blood contamination. Fatal lactic acidosis has been reported in pregnant women who have received a combination of **didanosine** and **stavudine.** The long-term effects of **didanosine** on both treated women and neonates are presently unknown.
Side effects include pancreatitis, neuropathy, hepatotoxicity, optic neuritis, thrombocytopenia, diabetes mellitus, N/V, diarrhea, rhabdomyolysis, rash, abdominal pain, arthralgia, and anorexia.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. **Didanosine** rapidly crosses the isolated human placenta, and efficiently crosses *in vivo* the macaque placenta. It is estimated the fetal levels would be therapeutic. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically. **Didanosine** does cross the rodent placenta.

Breastfeeding Safety

There is no published experience in nursing women. It is unknown whether **didanosine** enters human breast milk. It is generally recommended that, wherever possible, HIV-infected women not breastfeed to avoid the risk of HIV transmission to the neonate.

Drug Interactions

Didanosine has numerous recognized and predicted drug interactions. All prescribers should review the package insert before prescribing **didanosine** or adding a new drug.
Allopurinol, ganciclovir, and **tenofovir** increase the **didanosine** concentration; consult the package insert before prescribing.
Administer **didanosine** at least 2h after or 6h before **ciprofloxacin** to avoid a decrease in the **ciprofloxacin** levels.
Administer **didanosine** 1h after **delavirdine** to avoid a decrease in the **didanosine** concentration.
Administer **didanosine** 1h after **indinavir** to avoid a decrease in **indinavir** concentration.
Methadone decreases the **didanosine** concentration.
Use with drugs known to cause pancreatitis or neuropathy may increase the risk of these toxicities.
Ribavirin has been shown *in vitro* to increase intracellular triphosphate levels of **didanosine** and its use is not recommended. Fatal hepatic failure, as well as peripheral neuropathy, pancreatitis, and symptomatic hyperlactatemia/lactic acidosis, have been reported in patients receiving both.
Administer drugs such as **ketoconazole** or **itraconazole** at least 2h before **didanosine** to avoid a decrease in **ketoconazole** or **itraconazole** concentration.

References

Bardsley-Elliot A, Perry CM. Paediatr Drugs 2000; 2:373-407.
Bawdon RE, Sobhi S, Dax J. Am J Obstet Gynecol 1992; 167:1570-4.
Munshi MN, Martin RE, Fonseca VA. Diabetes Care 1994; 17:316-7.
Tuntland T, Odinecs A, Pereira CM, et al. Am J Obstet Gynecol 1999; 180:198-206.
Wang Y, Livingston E, Patil S, et al. J Infect Dis 1999; 180:1536-41.

Summary

Pregnancy Category: B
Lactation Category: U

- **Didanosine** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.
- Physicians are encouraged to register pregnant women under the Antiretroviral Pregnancy Registry (1-800-258-4263) for a

better follow-up of the outcome while under treatment with **didanosine.**

Dienestrol—(DV; Estraguard; Ortho Dienoestrol)

International Brand Name—None identified.

Drug Class	Estrogens; Hormones
Indications	Atrophic vaginitis
Mechanism	Stimulates estrogen receptors
Dosage with Qualifiers	Atrophic vaginitis—1 intravaginal application 3×/w • **Contraindications**—hypersensitivity to drug or class, history of thromboembolic disease, cancer (ovarian, uterine, breast), unexplained vaginal bleeding • **Caution**—hepatic or renal dysfunction, history of depression
Maternal Considerations	**Dienestrol** is a synthetic, nonsteroidal estrogen suitable for intravaginal use. It is also an oxidative metabolic product of **diethylstilbestrol.** Estrogen compounds are contraindicated during pregnancy. ***Side effects*** include depression, thromboembolic events (stroke, MI), endometrial carcinoma, gallbladder disease, pancreatitis, hypertension, N/V, abnormal uterine bleeding, migraine, libido change, increase in size of uterine fibromyomas, vaginal candidiasis, breast tenderness, and erythema nodosum.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **dienestrol** crosses the human placenta. The genital tract has the ability to metabolize **dienestrol.** Estrogens are contraindicated during pregnancy.
Breastfeeding Safety	There is no published experience in nursing women. It is unknown whether **dienestrol** enters human breast milk. Estrogens are usually considered incompatible with breastfeeding.
Drug Interactions	No clinically significant drug interactions were identified. However, estrogen is a potent inducer of a wide range of enzymes.
References	Harper MJ. Anat Rec 1968; 162:433-52. Korach KS, McLachlan JA. Arch Toxicol Suppl 1985; 8:33-42. Miller RK, Heckmann ME, McKenzie RC. J Pharmacol Exp Ther 1982; 220:358-65.
Summary	**Pregnancy Category: X** **Lactation Category: NS** (possibly) • **Dienestrol** is contraindicated during pregnancy and lactation.

Diethylpropion—(Depletite; Diethylpropion HCl; Dietil; Dipro; Durad; M-Orexic; Radtue; Tenuate; Tenuate Dospan; Tepanil)

International Brand Name—Apisate (Ireland); Atractil (Thailand); Delgamer (Spain); Dietil Retard (Belgium, Thailand); Dobesin (Denmark); Linea (Greece, Italy); Moderatan Diffucap (France); Neobes (Dominican Republic, El Salvador, Guatemala, Honduras, Nicaragua); Prefamone (Switzerland, Thailand); Prefamone Chronule (Belgium, France); Prothin (Hong Kong); Regenon (Austria, Belgium, Denmark, Switzerland); Regenon Reard (Germany, Thailand); Sacin (Chile); Tenuate (Canada); Tenuate Dospan (Canada, New Zealand, Peru, South Africa); Tenuate Retard (Germany)

Drug Class	Anorexiants; CNS stimulants
Indications	Obesity
Mechanism	The mechanism of appetite suppression is unknown (possible inhibitor of NE and dopamine reuptake).
Dosage with Qualifiers	Obesity—25mg PO tid before meals, or XR tab qd • **Contraindications**—hypersensitivity to drug or class, use of MAOIs within the last 14d, CV disease, glaucoma, hyperthyroidism • **Caution**—unknown
Maternal Considerations	There are no adequate reports or well-controlled studies of **diethylpropion** in pregnant women. The published experience consists of isolated case reports. ***Side effects*** include pulmonary hypertension, arrhythmias, psychosis, dry mouth, constipation, and restlessness.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **diethylpropion** crosses the human placenta. Neonatal withdrawal has been described in neonates delivered of women who used **diethylpropion** during pregnancy. There is a single case report of sacral agenesis associated with multiple anomalies of the lower limb in a woman taking **diethylpropion** during the first month of pregnancy. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically.
Breastfeeding Safety	There are no adequate reports or well-controlled studies in nursing women. **Diethylpropion** is excreted into human breast milk, though the kinetics remain to be elucidated.
Drug Interactions	Antidiabetic drug requirements (e.g., insulin) may be altered. Concurrent use with general anesthetics may result in arrhythmias. The pressor effects of **diethylpropion** and those of other drugs may be additive. Conversely, **diethylpropion** may interfere with antihypertensive drugs (e.g., **guanethidine, methyldopa**). Concurrent use of phenothiazines may antagonize the anorectic effect of **diethylpropion.**
References	Abraham E. Clin Orthop 1979; 145:168-71. Boileau PA. Appl Ther 1968; 10:763-5. Silverman M, Okun R. Curr Ther Res Clin Exp 1971; 13:648-53.
Summary	**Pregnancy Category: B** **Lactation Category: U** • There is no clinical indication for **diethylpropion** during pregnancy.

Diethylstilbestrol—(Stilphostrol)

International Brand Name—Honvol (Canada)

Drug Class	Antineoplastics; Estrogens; Hormones
Indications	Metastatic breast cancer
Mechanism	Binds and stimulates estrogen receptors
Dosage with Qualifiers	Metastatic breast cancer—15mg PO qd • **Contraindications**—hypersensitivity, male with breast carcinoma, estrogen-dependent carcinoma, pregnancy, active thrombophlebitis or thromboembolic disorders • **Caution**—CV disease, CAD, seizure disorder, hepatic adenoma, hypercalcemia, glucose intolerance
Maternal Considerations	**Diethylstilbestrol** was administered to approximately 3 million pregnant women in the US and in the Netherlands between 1947 and 1975. There was an increased risk of mammary carcinomas in exposed women. Pregnancy does not appear to influence adversely the tumor characteristics or prognosis of patients who have developed these malignancies. ***Side effects*** include depression, nervousness, dizziness, chest pain, shortness of breath, N/V, leg edema, erythema nodosum, decreased libido, fatigue, and increased coagulation factors II, VII, VIII, IX, and X.
Fetal Considerations	There are no adequate reports or well-controlled studies of **diethylstilbestrol** in human fetuses. It or a metabolite presumably crosses the human placenta. **Diethylstilbestrol**-exposed daughters frequently have developmental disorders of the cervix and corpus uteri (hypoplasia of the uterine cavity, uterine corpus, and cervix; T-shaped uterine cavity; constrictions of the uterine cavity; and bilateral hydrosalpinges). They have an increased risk of spontaneous abortion, ectopic pregnancy, infertility, possibly cervical incompetence and both cervical and vaginal carcinomas at a young age. Spontaneous uterine rupture at term has also been described. An increased risk of hypospadias in the sons exposed to DES *in utero* was reported. Rodent experiments reveal that **diethylstilbestrol** increases the incidence of genital tumors in not only 2nd-generation but also 3rd-generation animals. However, recent studies report no increased risk of lower genital tract abnormalities in 3rd-generation women.
Breastfeeding Safety	Estrogens are contraindicated for lactation suppression. **Diethylstilbestrol** does not effectively suppress lactation.
Drug Interactions	No clinically significant drug interactions were identified. However, estrogen is a potent inducer of a wide range of enzymes.
References	Adams DM, Druzin ML, Cederqvist LL. Obstet Gynecol 1989; 73:471-3. Althuisius SM, Dekker GA, Hummel P, et al. Am J Obstet Gynecol 2001; 185:1106-12. Brown DD. Br Med J 1969; 1:51. Hanselaar A, van Loosbroek M, Schuurbiers O, et al. Cancer 1997; 79:2229-36.

Hatch EE, Herbst AL, Hoover RN, et al. Cancer Causes Control 2001; 12:837-45.
Herbst AL, Anderson D. Semin Surg Oncol 1990; 6:343-6.
Hernandez-Diaz S. Lancet 2002; 359:1081-2.
Kaufman RH, Adam E. Obstet Gynecol 2002; 99:197-200.
Keller C, Nanda R, Shannon RL, et al. Int J Gynecol Cancer 2001; 11:247-50.
Klip H, Verloop J, van Gool JD, et al. Lancet 2002; 359:1102-7.
Palmer JR, Hatch EE, Rao RS, et al. Am J Epidemiol 2001; 154:316-21.
Treffers PE, Hanselaar AG, Helmerhorst TJ, et al. Ned Tijdschr Geneeskd 2001; 145:675-80.
van Gils AP, Tham RT, Falke TH, Peters AA. AJR Am J Roentgenol 1989; 153:1235-8.

Summary

Pregnancy Category: X
Lactation Category: NS

- **Diethylstilbestrol** is contraindicated during pregnancy and lactation.

Diflunisal—(Dolobid; Dopanone; Fluodonil; Noaldol)

International Brand Name—Adomal (Italy); Analeric (Greece); Ansal (New Zealand); Biartac (Belgium); Diflonid (Denmark, Norway, Sweden); Diflusal (Belgium); Dolobid (Australia, Bulgaria, Czech Republic, Ecuador, England, Hungary, Ireland, Italy, Japan, Mexico, Portugal, Russia, Spain, Taiwan, Thailand, Venezuela); Dolobis (France); Dolocid (Netherlands); Donobid (Denmark, Finland, Norway, Sweden); Dorbid (Brazil); Flovacil (Argentina); Flunidor (Portugal); Fluniget (Austria); Ilacen (Taiwan); Reuflos (Italy); Unisal (Switzerland)

Drug Class

Analgesics, non-narcotic; NSAIDs; Salicylates

Indications

Mild to moderate pain, osteoarthritis, rheumatoid arthritis

Mechanism

Inhibits cyclooxygenase and lipoxygenase, leading to reduced prostaglandin synthesis

Dosage with Qualifiers

Pain—begin 1000mg PO ×1; then 500mg PO q12h
Osteoarthritis—250-500mg PO q12h
Rheumatoid arthritis—250-500mg PO q12h

- **Contraindications**—hypersensitivity to drug or class, asthmatic attacks, urticaria, **aspirin**-precipitated rhinitis
- **Caution**—nasal polyps, GI bleeding, hypertension, cardiac failure, hepatic or renal dysfunction

Maternal Considerations

Diflunisal is an NSAID with anti-inflammatory, antipyretic, and analgesic properties. Similar to many NSAIDs, it inhibits platelet aggregation. There are no adequate reports of **diflunisal** in pregnant women. **Diflunisal** is superior to **aspirin** for the relief of postepisiotomy pain.
Side effects include peptic ulceration, GI bleeding, anaphylaxis, thrombocytopenia, Stevens-Johnson syndrome, nephritis, and hepatic or renal failure.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **diflunisal** crosses the human placenta. Treated *Cynomolgus* monkeys experience no increased rates of abortion, IUGR, or malformation. Rodent studies reveal embryotoxicity and teratogenicity (skeletal malformations) in doses 1-8× the MRHD. In the human fetus,

other NSAIDs can cause in the 3rd trimester constriction of the ductus arteriosus, followed by tricuspid incompetence and pulmonary hypertension. Platelet dysfunction, intracranial bleeding, or renal dysfunction may result in permanent renal failure, oligohydramnios, or necrotizing enterocolitis.

Breastfeeding Safety

There is no published experience in nursing women. **Diflunisal** is excreted into human milk, achieving an M:P ratio <0.07. Considering the indications and dosing, occasional **diflunisal** use is unlikely to pose a clinically significant risk to the breastfeeding neonate.

Drug Interactions

Competitively displaces **warfarin** from protein binding sites. In some normal volunteers, the concomitant administration of **diflunisal** and **warfarin, acenocoumarol,** or **phenprocoumon** resulted in prolongation of PT. Adjustment of dosage of oral anticoagulants may be required.
Concomitant use with **hydrochlorothiazide** increases the plasma **hydrochlorothiazide** levels.
Decreases the hyperuricemic effect of **hydrochlorothiazide** and **furosemide.**
Increases **acetaminophen** plasma levels by some 50%.
NSAIDs decrease the tubular secretion of **methotrexate** and potentiate its toxicity.
NSAIDs increase the risk of **cyclosporine**-induced toxicity, possibly due to decreased synthesis of renal prostacyclin.

References

Clark RL, Robertson RT, Minsker DH, et al. Teratology 1984; 30:319-32.
De Vroey P. Curr Med Res Opin 1978; 5:544-7.
Kollenberg LO, Hudyma EO, Robbins JM. J Am Podiatr Med Assoc 1985; 75:517-22.
Rowland JM, Robertson RT, Cukierski M, et al. Fundam Appl Toxicol 1987; 8:51-8.

Summary

Pregnancy Category: C
Lactation Category: S (likely)
- **Diflunisal** and other NSAIDs are probably safe if used occasionally for the noted indications during pregnancy and lactation.

Digitoxin—(Coramedan; Crystodigin)

International Brand Name—None identified.

Drug Class

Antiarrhythmics; Cardiac glycosides; Inotropes

Indications

Heart failure, atrial flutter, atrial fibrillation, SVT

Mechanism

Inhibits Na^+,K^+ transmembrane ATPase

Dosage with Qualifiers

Heart failure—0.2mg PO qd ×4d; maintenance dose varies between 0.05 and 0.3mg qd
Atrial flutter—0.2-0.3mg PO qd
Atrial fibrillation—0.2-0.3mg PO qd
SVT—0.3mg PO qd
Rapid digitalization—0.6mg, then 0.4mg in 4-6h, then 0.2mg q4-6h until drug level therapeutic

- **Contraindications**—hypersensitivity to drug or class, ventricular tachycardia, cardiac disease, and hypersensitive carotid sinus syndrome
- **Caution**—hypokalemia, hepatic and renal failure

Maternal Considerations

There are no adequate reports or well-controlled studies of **digitoxin** in pregnant women. **Digitoxin** is a crystalline-pure cardiac glycoside obtained from *Digitalis purpurea* and has pharmacologic action identical to that of digitalis. Excretion is slow (14-21d). Serum levels should be monitored periodically during pregnancy. Pregnant women receiving the usual dose of 0.25mg tend to have subnormal levels and may require a small increase during the 3rd trimester.
Side effects include digitalis intoxication that includes N/V, visual disturbance, electrolyte abnormalities (hypo/hyperkalemia), and bradycardia.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. **Digoxin** and presumably **digitoxin** cross the healthy human placenta, reaching F:M ratios approximating 0.8. However, the human placenta is rich in digoxin receptors, and placental binding increased and transfer decreased when there is hydrops. Fetal bradycardia is reported. Studies are compromised by tests that failed to differentiate between **digoxin** and endogenous digoxin-like substances. Rodent teratogenicity studies have not been performed.

Breastfeeding Safety

There is no published experience in nursing women. It is unknown whether **digitoxin** enters human breast milk. Endogenous digoxin-like substances are normal components of breast milk.

Drug Interactions

See **Digoxin.**

References

Soyka LF. Clin Perinatol 1975; 2:23-35.
Van Gundy JC, Bolam DL, Swigart SA, Nelson RM Jr. Nebr Med J 1986; 71:300-2.

Summary

Pregnancy Category: C
Lactation Category: U
- **Digitoxin** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.
- There are alternative digoxin-type agents with shorter elimination times.

Digoxin—(Digacin; Digitek; Lanicor; Lanoxicaps; Lanoxin)

International Brand Name—Cardigox (Belgium); Cardiogoxin (Argentina); Cardioxin (India); Digacin (Germany); Digomal (Italy); Digosin (Japan, Korea); Digoxina (Peru); Digoxine Navtivelle (France); Digoxin-Sandoz (Indonesia, Japan); Digoxin-Zori (Israel); Dilacor (Bulgaria); Dilanacin (Cyprus, Egypt, Iraq, Jordan, Sudan); Eudigox (Italy); Fargoxin (Indonesia); Grexin (Thailand); Lanacordin (Spain); Lanacrist (Sweden); Lanicor (Argentina, Austria, Czech Republic, Ecuador, Germany, Greece, Italy, Portugal, Venezuela); Lanikor (Russia); Lanitop (Ecuador); Lanoxin (Argentina, Belgium, Brazil, Canada, Denmark, England, Finland, Greece, Hong Kong, India, Indonesia, Ireland, Italy, Japan, Korea, Malaysia, Mexico, Netherlands, Norway, Paraguay, Philippines, Portugal, Russia, Sweden, Switzerland, Taiwan, Thailand, Uruguay); Lanoxin PG (New Zealand); Lenoxin (Germany); Mapluxin (Mexico); Purgoxin (South Africa); Sigmaxin (Australia); Toloxin (Thailand)

Drug Class

Antiarrhythmics; Cardiac glycosides; Inotropes

Indications

CHF, atrial fibrillation/flutter, paroxysmal atrial tachycardia, fetal arrhythmia

Mechanism

Inhibits Na^+,K^+ transmembrane ATPase

Dosage with Qualifiers

CHF—begin with a loading dose of 0.75-1.25mg PO, or 0.5-1mg IV/IM followed by a maintenance dose of 0.125-0.5mg PO qd

NOTE: digoxin levels should be maintained between 0.8 and 2ng/ml.
Atrial fibrillation/flutter—0.125-0.5mg PO qd
Paroxysmal atrial tachycardia—0.125-0.5mg PO qd
Fetal arrhythmia—1mg IV to load, 0.25-1mg PO bid
Rapid digitalization—0.4-0.6mg IV/PO, then 0.1-0.3mg q6-8h guided by the digoxin level

- **Contraindications**—hypersensitivity to drug or class, ventricular fibrillation, ventricular tachycardia, AV accessory pathway, sick sinus syndrome
- **Caution**—bradycardia, AV block, MI, cardiomyopathy, constrictive pericarditis, renal or hepatic dysfunction

Maternal Considerations

There is a long clinical experience with **digoxin** during pregnancy and the puerperium for the treatment of benign arrhythmias and cardiomyopathy. A full CV evaluation is recommended prior to its initiation. Potential stimulants, such as smoking, **caffeine,** and alcohol should be eliminated. Although no antiarrhythmic drug is completely safe during pregnancy, most are well tolerated and add relatively little risk. Drug therapy should be avoided during the 1st trimester and drugs with the best safety record used as first-line therapy. Women with peripartal cardiomyopathy who have persistently abnormal ventricular function must be continuously treated with **digoxin,** diuretics, and anticoagulation, and have the same relatively poor prognosis as patients with dilated cardiomyopathy. Heart transplantation may be necessary for survival.
Side effects include hallucinations, blurred vision, thrombocytopenia, arrhythmia, bradycardia, delirium, and electrolyte abnormalities (hypo/hyperkalemia).

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. **Digoxin** crosses the placenta, with a typical F:M ratio ranging from 0.6 to 0.8. There are, however, a high concentration of placental **digoxin** receptors and significant back-transport of digoxin by placental P-glycoprotein. **Digoxin** is generally considered first-line therapy for the treatment of fetal SVT in the absence of hydrops. Treatment is aimed initially at slowing the ventricular response rate and ultimately conversion to sinus rhythm. However, there are no trials confirming that conversion reflects therapeutic efficacy or disease natural history. After adequate maternal digitalization, conversion to normal sinus rhythm should occur within 72h; reported successes often occur after weeks. Certainly, the addition of a second agent would be desirable if there is no response. The fetal response is worse if tricuspid regurgitation is already present. Placental transport is dramatically reduced when there is hydrops, and this appears inversely proportional to the umbilical venous pressure. In this instance, many fetal medicine specialists consider **flecainide** a drug of choice. Direct fetal **digoxin** administration (IM) can be successful after more traditional intensive trials of transplacental therapy with **digoxin, verapamil,** and **procainamide,** either separately or in combination, fail. Transplacental **digoxin** therapy has also been used to improve ionotropy in fetuses with complete heart block. Despite adequate therapy and many times improvement in the fetal status *in utero,* many fetuses require postnatal pacemaker implantation or heart transplantation. Rodent teratogenicity studies have not been performed.

Breastfeeding Safety

There are no adequate reports or well-controlled studies in nursing women. **Digoxin** enters human breast milk in low concentration, achieving an M:P ratio approximating 0.7. As a result, the **digoxin** level of the breastfed neonate would be subtherapeutic. Endogenous digoxin-like substances are a normal component of breast milk.

Drug Interactions

Potassium-depleting diuretics are a major contributing factor to digitalis toxicity. *Calcium,* particularly if administered IV, may produce serious arrhythmias in digitalized patients.
Quinidine, verapamil, amiodarone, propafenone, indomethacin, itraconazole, alprazolam, and **spironolactone** each raise the serum **digoxin** level by reducing clearance and/or its volume of distribution.
Erythromycin and **clarithromycin** (and possibly other macrolides) and **tetracycline** may increase **digoxin** absorption in patients who inactivate **digoxin** by bacterial metabolism in the lower intestine.
Propantheline and **diphenoxylate** may increase **digoxin** absorption by decreasing gut motility.
Antacids, **kaolin, sulfasalazine, neomycin, cholestyramine,** certain anticancer drugs, and **metoclopramide** may interfere with intestinal **digoxin** absorption, resulting in low serum concentrations.
Rifampin may decrease serum **digoxin** concentration, especially in patients with renal dysfunction, by increasing the nonrenal clearance of **digoxin.**
Thyroid administration to a digitalized, hypothyroid patient may increase the dose of **digoxin** required.
Concomitant use of **digoxin** and sympathomimetics increases the risk of cardiac arrhythmias.
Succinylcholine may cause a sudden extrusion of potassium from muscle cells, and and trigger arrhythmias in digitalized patients.
Although β-adrenergic blockers or calcium channel blockers and **digoxin** may be useful in combination to control atrial fibrillation, their additive effects on AV node conduction can cause advanced or complete heart block.
Use caution combining **digoxin** with drugs that can cause significant renal function deterioration.
Due to considerable variability of the above interactions, the dosage of **digoxin** should be individualized.

References

Baughman KL. Curr Treat Options Cardiovasc Med 2001; 3:469-480.
Brackley KJ, Ismail KM, Wright JG, Kilby MD. Fetal Diagn Ther 2000; 15:355-8.
Cameron AD, Walker JJ, Nimrod CA. BMJ 1988; 297:623.
Chao RC, Ho ES, Hsieh KS. Am Heart J 1992; 124:1095-8.
Ebenroth ES, Cordes TM, Darragh RK. Pediatr Cardiol 2001; 22:483-7.
Facchini M, Bauersfeld U, Fasnacht M, Candinas R. Schweiz Med Wochenschr 2000; 130:1962-9.
Joglar JA, Page RL. Drug Saf 1999; 20:85-94.
Jones LM, Garmel SH. Obstet Gynecol 2001; 98:921-3.
Jouannic JM, Le Bidois J, Fermont L, et al. Fetal Diagn Ther 2002; 17:120-3.
Kleinman CS, Copel JA, Weinstein EM, et al. J Clin Ultrasound 1985; 13:265-73.
Krapp M, Baschat AA, Gembruch U, et al. Ultrasound Obstet Gynecol 2002; 19:158-64.
Lisowski LA, Verheijen PM, Benatar AA, et al. J Am Coll Cardiol 2000; 35:771-7.

Mozas J, Miranda JA, Barranco M. Int J Gynaecol Obstet 1995; 50:293-4.
Oudijk MA, Ambachtsheer EB, Stoutenbeek P, Meijboom EJ. Ned Tijdschr Geneeskd 2001; 145:1218-9.
Reinhardt D, Richter O, Genz T, Pottoff S. Eur J Pediatr 1982; 138:49-52.
Schmolling J, Renke K, Richter O, et al. Ther Drug Monit 2000; 22:582-8.
Weiner CP, Landas S, Persoon TJ. Am J Obstet Gynecol 1987; 157:368-71.
Weiner CP, Thompson MI. Am J Obstet Gynecol 1988; 158:570-3.

Summary

Pregnancy Category: C
Lactation Category: S

- **Digoxin** is indicated for the treatment of mild to moderate heart failure. Concomitant ACEIs should be discontinued during the 1st trimester if possible.
- **Digoxin** has a long clinical track record of treating both maternal and fetal arrhythmias; it is one of the safest antiarrhythmics to use during pregnancy.

Dihydroergotamine—(D.H.E. 45; Migranal)

International Brand Name—Adhaegon (Austria); Cervasal (Bulgaria); Detemes Retard (Austria); Diergospray (France); Dihydergot (Australia, Belgium, Czech Republic, Ecuador, Germany, Greece, India, Indonesia, Israel, Mexico, Netherlands, Norway, Peru, Spain, Switzerland, Turkey, Venezuela); Dihydroergotamine-Sandoz (Canada); Dihydergot Sandoz (Austria); Erganton (Germany); Ergont (Germany); Ergotamina (Paraguay); Ergovasan (Austria); Ikaran (Belgium, France, Italy, Portugal); Ikaran LP (France); Ikaran Retard (Switzerland); Migranal (Canada); Orstanorm (Finland, Sweden); Poligot (Thailand); Seglor (France, Italy, Taiwan); Seglor Retard (Portugal); Tamik (France, Hong Kong); Tenuatina (Spain); Verladyn (Germany); Verteblan (Greece)

Drug Class

Ergot alkaloids; Migraine agents

Indications

Migraine and cluster headache

Mechanism

Constricts cranial and peripheral vessels by activating multiple receptors, including H_1 and α_1

Dosage with Qualifiers

Migraine—1mg IM/IV, may repeat qh ×2; max 2mg IV, or 3mg/attack or 6mg/w; alternatively, 1 spray (0.5mg) NAS each nostril, may repeat in 15min; max 4 sprays/attack or 8 sprays/w
Cluster headache—1mg IM/IV, may repeat q1h ×2; max 2mg IV, or 3mg/attack or 6mg/w

NOTE: prime pump with 4 sprays, discard unused portion after 8h.

- **Contraindications**—hypersensitivity to drug or class, CAD, uncontrolled hypertension, basilar migraine, PVD, cerebrovascular disease, 5-HT_1 agonist within 24h, severe hepatic or renal dysfunction, concurrent vasoconstrictors, sepsis, potent CYP3A4 inhibitor use
- **Caution**—cardiac risk factors

Maternal Considerations

There are no adequate reports or well-controlled studies of **dihydroergotamine** in pregnant women. It possesses oxytocic properties and was used in several older trials to assist with the induction of labor. It was also used occasionally during pregnancy for the treatment of "low" BP. Neither of the last

two are indications. **Dihydroergotamine** is effective for the treatment of menstrual migraine.
Side effects include hypertension, peripheral or bowel ischemia, coronary spasm, MI, chest pain, tachycardia, bradycardia, N/V, numbness in fingers and toes, leg weakness, and itching.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **dihydroergotamine** crosses the human placenta. In one series, women with "low" BP were treated for 1w and the fetal umbilical artery S/D ratio increased 22%, thus suggesting placental transfer. In guinea pigs, chronic administration of **dihydroergotamine** is associated with IUGR suggesting decreased placental blood flow.

Breastfeeding Safety

There is no published experience in nursing women. It is unknown whether **dihydroergotamine** enters human breast milk. It is known that ergots inhibit prolactin, and that **ergotamine** is excreted into human breast milk and can have adverse effects on the breastfed neonate. It would be reasonable to stop breastfeeding until the headache has resolved.

Drug Interactions

Should not be used with peripheral vasoconstrictors as the combination may cause a synergistic elevation of BP.
Should not be taken within 24h of **sumatriptan**. **Sumatriptan** has been reported to cause coronary artery vasospasm, and its effect could be additive with **dihydroergotamine.**
There are reports that **propranolol** may potentiate the vasoconstrictive action of **ergotamine** by blocking the vasodilating property of **epinephrine.**
Nicotine may provoke vasoconstriction in some patients, predisposing to a greater ischemic response to **dihydroergotamine.**
Weakness, hyperreflexia, and incoordination have been reported after 5-HT_1 agonists were coadministered with SSRIs (e.g., **fluoxetine, fluvoxamine, paroxetine, sertraline**). There are no reports of drug interaction between SSRIs and **dihydroergotamine.**

References

Goeschen K, Behrens O, Muhlhaus K, et al. Z Geburtshilfe Perinatol 1989; 193:264-7.
Silberstein SD. J Womens Health Gend Based Med 1999; 8:919-31.

Summary

Pregnancy Category: X
Lactation Category: NS

- **Dihydroergotamine** is contraindicated during pregnancy and lactation.
- There are alternative agents for which there is more experience during pregnancy and lactation.

Dihydrotachysterol—(DHT; Hytakerol; Tachyrol)

International Brand Name—A.T.10 (Austria, Bulgaria, Germany, Hungary, Russia, Switzerland); AT 10 (England, Ireland, Italy, Japan); AT-10 (Australia); Dihydral (Belgium, Netherlands); Dygratyl (Denmark, Finland, Sweden); Hytakerol (Canada, Japan)

Drug Class	Vitamins/minerals
Indications	Osteoporosis, hypocalcemia, renal osteodystrophy
Mechanism	Stimulates bone mineralization as well as intestinal calcium and phosphorus absorption
Dosage with Qualifiers	Osteoporosis—0.6mg PO qd; give with calcium and fluoride Hypocalcemia—begin 0.8-2.4mg PO qd for several days, then 0.2-1mg PO qd Renal osteodystrophy—0.1-0.6mg PO qd • **Contraindications**—hypersensitivity to drug or class, hypercalcemia, hypervitaminosis D • **Caution**—renal stones, hyperphosphatemia, hypervitaminosis D
Maternal Considerations	There are no adequate reports or well-controlled studies of **dihydrotachysterol** (vitamin D) in pregnant women, though it is part of most prenatal vitamin preparations. **Dihydrotachysterol** and **calcitriol** are both effective for the management of hypoparathyroidism during pregnancy. The dose required typically needs to be readjusted up during the latter half of gestation. The dose of **calcitriol** should be reduced during lactation. ***Side effects*** include hypercalcemia, renal dysfunction, hypercalciuria, convulsion, polydipsia, N/V, anorexia, anemia, weakness, and metastatic calcifications.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **dihydrotachysterol** crosses the human placenta, nor is it known whether **dihydrotachysterol** increases fetal calcium. However, fetal supravalvular aortic stenosis may be associated with hypercalcemia secondarily to hypervitaminosis D, and hypercalcemia can occur during treatment with **dihydrotachysterol.** Rodent teratogenicity studies reveal similar abnormalities.
Breastfeeding Safety	There are no adequate reports or well-controlled studies in nursing women. While **dihydrotachysterol** increases the amount of calcium in breast milk, hypercalcemia is not seen in breastfed neonates. It is considered unlikely to have a clinically significant effect on the breastfeeding neonate.
Drug Interactions	Administration of thiazide diuretics to hypoparathyroid patients being treated with **dihydrotachysterol** may cause hypercalcemia.
References	Caplan RH, Beguin EA. Obstet Gynecol 1990; 76:485-9. Klotz HP. Sem Ther 1963; 39:559-60.
Summary	**Pregnancy Category: C** **Lactation Category: S** (likely) • **Dihydrotachysterol** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk. • Both mother and infant should be monitored to detect hypercalcemia during breastfeeding.

Diltiazem—(Cardizem; Clarute; Dilacor XR; Lacerol; Tiazac)

International Brand Name—Acalix (Argentina, Paraguay, Venezuela); Adizem-CD (Israel); Altiazem (Bulgaria, Hong Kong, Italy); Altiazem Retard (Italy); Altiazem RR (Russia); Angiotrofen (Costa Rica, Dominican Republic, El Salvador, Guatemala, Honduras, Nicaragua, Panama); Angiotrofin (Colombia, Costa Rica, Dominican Republic, El Salvador, Guatemala, Honduras, Mexico, Nicaragua, Panama); Angiotrofin Retard (Costa Rica, Dominican Republic, El Salvador, Guatemala, Honduras, Mexico, Nicaragua, Panama); Angiozem (Philippines); Angizem (Italy, Thailand); Angoral (Colombia); Anzem (South Africa); Apo-diltiazem (New Zealand); Auscard (Australia); Balcor (Brazil); Beatizem (Singapore); Bi-Tildiem (France); Calcicard (England); Calnurs (Japan); Cardcal (Australia); Cardiazem (Korea); Cardiben S.R. (Korea); Cardil (Bulgaria, Denmark, Malaysia, Russia, Taiwan); Cardil Retard (Greece); Cardiosta LP (France); Cardium (Hong Kong, Singapore); Cardizem (Australia, Brazil, Canada, Denmark, Finland, Indonesia, Norway, Sweden); Cardizem CD (Brazil, Canada); Cardizem Retard (Denmark, Finland, Sweden); Cardizem SR (Brazil, Canada); Carex (Argentina); Cartia XT (Taiwan); Cascor XL (Malaysia, Thailand); Cirilen (Ecuador); Cirilen AP (Ecuador); Cordizem (Indonesia, Malaysia); Deltazen (France); Diacor LP (France); Diatal (South Africa); Diladel (Italy); Dilatam (Israel, Philippines, Singapore, South Africa, Thailand); Dilatam 120 (Israel); Dilatame (Austria); Dilcard (Malaysia, New Zealand); Dilcardia (India); Dilcor (Denmark); Dilem (Thailand); Dilem SR (Thailand); Dilfar (Portugal); Dilgard (South Africa); Dilren (Russia); Dilrene (Czech Republic, France, Hungary); Dilso (Indonesia, Malaysia); Diltahexal (Australia, Germany); Diltam (Ireland); Diltelan (Korea, Taiwan); Diltiamax (Australia); Diltiasyn (Colombia); Dilzanton (Germany); Dilzem (Australia, Austria, Bulgaria, Czech Republic, Finland, Germany, Hungary, India, New Zealand, Philippines, Poland, Russia, Switzerland, Thailand); Dilzem CD (Australia); Dilzem Retard (Austria, Bulgaria, Czech Republic, Germany, Hungary); Dilzem RR (Switzerland); Dilzem SR (China, England, New Zealand); Dilzene (Italy); Dilzereal 90 Retard (Germany); Dilzicardin (Germany); Dinisor (Spain); Dinisor Retard (Spain); Dodexen (Peru); Dodexen A.P. (Peru); DTM (India); Dyalac (Philippines); Filazem (Philippines); Gadoserin (Japan); Grifodilzem (Peru); Hagen (Taiwan); Helsibon (Japan); Herben (Korea); Herbesser (Indonesia, Japan, Malaysia, Taiwan, Thailand); Herbesser 60 (Malaysia, Thailand); Herbesser 90 SR (Hong Kong, Malaysia, Thailand); Herbesser 180 SR (Hong Kong); Herbesser R100 (Hong Kong, Japan); Herbesser R200 (Hong Kong, Japan); Herbessor (China); Herbessor 30 (Malaysia); Hesor (Taiwan); Incoril AP (Dominican Republic, El Salvador, Honduras, Nicaragua); Iski (India); Iski-90 SR (India); Kaizem CD (India); Lacerol (Dominican Republic, El Salvador, Guatemala, Honduras, Nicaragua); Levodex (Israel); Levozem (Israel); Lytelsen (Japan); Masdil (Spain); Miocardie (Taiwan); Mono-Tildiem SR (Singapore); Myonil (Denmark); Myonil Retard (Denmark); Pazeadin (Japan); Presoken (Mexico); Tazem (Taiwan); Tiadil (Portugal); Tiazac (Canada); Tilazem (Argentina, Chile, Colombia, Ecuador, Mexico, Peru, South Africa, Uruguay); Tilazem 90 (South Africa); Tildiem (Belgium, Chile, England, France, Greece, Italy, Malaysia, Netherlands, Switzerland); Tildiem CR (Netherlands); Tildiem LA (England); Tildiem Retard (Greece); Vasmulax (Philippines); Vasocardol CD (Australia); Wentizem Retard (Hong Kong); Zandil (Philippines); Zemtrial (Philippines); Zildem (South Africa); Ziruvate (Japan)

Drug Class	Antiarrhythmics, class IV; Calcium-channel blockers
Indications	Angina, atrial fibrillation, atrial flutter
Mechanism	Calcium channel blocker
Dosage with Qualifiers	Angina—begin 30mg PO qid; max 360mg/d Atrial flutter/fibrillation—20mg (0.25 mg/kg) IV, over 2min; if inadequate response, 0.35mg/kg IV over 2min, then continue infusion with 10(5-15)mg/h for 24h *NOTE: may be packaged with* ***enalapril.*** • **Contraindications**—hypersensitivity to drug or class, AV block, hypotension, bradycardia, sick sinus syndrome, MI • **Caution**—hepatic or renal dysfunction
Maternal Considerations	There are no adequate reports or well-controlled studies of **diltiazem** in pregnant women. Clearance is unaltered during rabbit pregnancy. **Diltiazem** is used for the treatment of acute cardiac rhythm emergencies. *In vitro* and *in vivo* studies demonstrated effective inhibition of myometrial contractions and vasodilation of arteries collected from normal and preeclamptic women. Oral **diltiazem** has no advantage over **nifedipine** as a tocolytic agent. The CV alterations following either drug appear minimal in normotensive, pregnant women. Volume loading and a supine position further reduces the risk of an adverse CV reaction. Case reports document successful treatment of maternal angina secondary to coronary spasm. Recently, a relationship

between oral **erythromycin** and sudden cardiac death was reported in patients also receiving strong inhibitors of CYP3A such as nitroimidazole antifungal agents, **diltiazem, verapamil,** and **troleandomycin;** each doubles, at least, the AUC for a CYP3A substrate.
Side effects include edema, headache, N/V, dizziness, asthenia, rash, flushing, first-degree AV block, pulmonary congestion, photosensitivity, urticaria, dry mouth, dyspnea, hyperuricemia, osteoarticular pain, sexual difficulties, tinnitus, and erythema multiforme (Stevens-Johnson syndrome, toxic epidermal necrolysis).

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **diltiazem** crosses the human placenta. It does rapidly cross the rabbit placenta. Rodent studies suggest an increased incidence of skeletal and aortic arch malformations in some species at doses of **diltiazem** administered in multiples of the MRHD. Another study of rabbits concluded that chronic *in utero* exposure altered postnatal metabolism.

Breastfeeding Safety

There are no adequate reports or well-controlled studies in nursing women. **Diltiazem** enters human milk and may reach maternal serum levels. Though generally considered safe for breastfeeding women, it may be wise to consider another calcium channel blocker.

Drug Interactions

Diltiazem is both a substrate and an inhibitor of CYP3A4. Other drugs that are specific substrates, inhibitors, or inducers may alter the efficacy and side effect profile of **diltiazem.** Patients taking other drugs that are CYP3A4 substrates, especially those with renal and/or hepatic impairment, may require dose adjustments when starting or stopping **diltiazem.**
Patients taking **diltiazem** with agents known to affect cardiac contractility and/or conduction must be watched closely.
The depression of cardiac contractility, conductivity, and automaticity as well as the vascular dilation by anesthetics may be potentiated by calcium channel blockers.
Increases the AUC of **midazolam** and **triazolam** by 3-4 fold and the C_{max} by 2-fold. The t/2 is also increased (1.5-2.5 fold).
Increases **propranolol** levels and bioavailability by some 50%. If combination therapy is initiated or withdrawn, an adjustment to the **propranolol** dose may be necessary.
Increases the mean **buspirone** AUC 5.5-fold and C_{max} 4.1-fold. Enhanced effects and increased toxicity of **buspirone** are possible.
Increases serum **carbamazepine** levels (40-72% increase), resulting in toxicity in some cases.
Cimetidine increases peak **diltiazem** plasma levels (58%) and the AUC (53%). Patients using **diltiazem** should be carefully monitored when initiating and discontinuing **cimetidine.**
An interaction between **diltiazem** and **cyclosporine** is reported in renal and cardiac transplant patients where a reduction in the **cyclosporine** dose ranging from 15-48% was necessary to maintain trough levels achieved before the addition of **diltiazem.**
May increase plasma **digoxin** concentrations approximately 20%. Since the data are conflicting, it is recommended **digoxin** be monitored when initiating, adjusting, and discontinuing **diltiazem.**
May increase the mean **lovastatin** AUC and C_{max} by 3-4 times.
Increases the AUC of **quinidine** by 51% and t/2 by 36%.
Rifampin dramatically lowers the **diltiazem** plasma concentrations. Use of **diltiazem** with **rifampin** or any known CYP3A4 inducer should be avoided when possible.

References

Bregante MA, Aramayona JJ, Fraile LJ, et al. Xenobiotica 2000; 30:831-41.
El-Sayed YY, Holbrook RH Jr, Gibson R, et al. J Matern Fetal Med 1998; 7:217-21.
Fraile LJ, Bregante MA, Garcia MA, Solans C. Xenobiotica 2001; 31:177-85.
Ivorra MD, Chulia S, Noguera MA, D'Ocon MP. Pharmacology 1994; 49:33-41.
Kook H, Yoon YD, Baik YH. J Korean Med Sci 1996; 11:250-7.
Lubbe WF. N Z Med J 1987; 100:121.
Maekawa K, Ohnishi H, Hirase T, et al. J Intern Med 1994; 235:489-92.
Poli E, Merialdi A, Coruzzi G. Pharmacol Res 1990; 22:115-24.
Ray WA, Murray KT, Meredith S, et al. N Engl J Med 2004; 351:1089-96.
Reviriego J, Fernandez-Alfonso MS, Guerra P, Marin J. J Cardiovasc Pharmacol 1990; 16:128-38.
Scott WJ Jr, Resnick E, Hummler H, et al. Reprod Toxicol 1997; 11:207-14.

Summary

Pregnancy Category: C
Lactation Category: S (likely)

- **Diltiazem** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.
- Oral **erythromycin** should be avoided in women receiving **diltiazem. Ampicillin** plus **sulbactam** would be preferred in women with PPROM.

Dimenhydrinate—(Amosyt; Biodramina; Di-Men; Dimeno; Dimetabs; Dinate; Dommanate; Dramamine injection; Dramanate; Dramavance; Dramocen; Dramoject; Dymenate; Hydrate; Marmine; Or-Dram; Shodram; T-Circ; Travelgum; Wehamine)

International Brand Name—Anautin (Ecuador); Antimo (Indonesia); Apo-Dimenhydrinate (Canada); Biodramina (Costa Rica, El Salvador, Guatemala, Panama); Bonaling-A (Korea); Demodenal (Switzerland); Denim (Thailand); Dimate (Hong Kong); Dimen (Germany); Dimenate (Hong Kong, Malaysia); Dimin (Thailand); Divonal (Peru); Dramamine (Argentina, Bangladesh, Belgium, Costa Rica, Dominican Republic, El Salvador, England, France, Germany, Greece, Guatemala, Honduras, Ireland, Israel, Japan, Malaysia, Mexico, Netherlands, Nicaragua, Pakistan, Panama, Philippines, Portugal, Puerto Rico, South Africa, Switzerland, Turkey, Venezuela); Dramasan (Peru); Drimen (Greece); Gravamin (Peru); Gravol (Canada, Costa Rica, Dominican Republic, El Salvador, Guatemala, Hong Kong, India, Nicaragua, Panama, Peru, Philippines, Thailand); Lomarin (Italy); Mareol (Colombia); Menito (Taiwan); Motivan (Thailand); Nausex (Austria); Nausicalm (France); Novomin (Malaysia); Pasedol (Colombia); RubieMen (Germany); Travel Gum (China); Trimin (Taiwan); Vertirosan (Austria); Vomacur (Germany); Vomex (Philippines); Vomex A (Germany); Vomisin (Mexico); Votmine (Malaysia); Xamamina (Italy)

Drug Class

Anticholinergics; Antiemetics; Antivertigo

Indications

Motion sickness, migraine headache

Mechanism

Exact mechanism of action is unknown

Dosage with Qualifiers

Motion sickness—50-100mg PO/IM/IV q4-6h; begin at least 30min before anticipated activity, max 400mg/d
Migraine—50-100mg PO

- **Contraindications**—hypersensitivity to drug or class

- **Caution**—neonates, seizure disorder, glaucoma, concomitant use of ototoxic medication

Maternal Considerations

There are no adequate reports or well-controlled studies of **dimenhydrinate** in pregnant women. It is a popular agent in many locales for the relief of N/V during pregnancy, though the practice is unsupported by a single clinical trial. Both **dimenhydrinate** and **diphenhydramine** are considered treatment options for severe migraine headache during pregnancy. **Caution** is warranted since several investigators report an increase in uterine activity associated with **dimenhydrinate.**
Side effects include drowsiness, headache, fatigue, increase appetite, abdominal pain, N/V, diarrhea, increased bronchial secretion, anorexia, and nervousness.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **dimenhydrinate** crosses the human placenta. There is no indication that **dimenhydrinate** increases the risk of fetal abnormalities when given at any stage of pregnancy. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically. One recent epidemiologic study actually observed a lower prevalence of obstructive uropathy in exposed infants.

Breastfeeding Safety

There is no adequate published experience in nursing women. **Dimenhydrinate** is excreted in small quantities into human breast milk, though the kinetics remain to be elucidated. A long clinical experience is reassuring.

Drug Interactions

May increase the risk of CNS depression when used with **dexmedetomidine** or **azelastine.**
May delay gastric emptying when given with **pramlintide.**

References

Aube M. Neurology 1999; 53:S26-8.
Czeizel AE, Vargha P. Arch Gynecol Obstet 2005; 271:113-8.
Lemay M, Samaan M, St. Michel P, et al. Can Med Assoc J 1982; 127:606-7.

Summary

Pregnancy Category: B
Lactation Category: S (likely)
- **Dimenhydrinate** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Dinoprostone—(Cervidil; Prepidil; Prostin E2; Prostin E2 Vaginal Suppository)

International Brand Name—Cervidil (Canada, New Zealand); Cerviprime (India); Cerviprost (Austria, Czech Republic, Denmark, Finland, Germany, Italy, Norway, Russia, Switzerland); K-PE (Japan); Minprostin E(2) (Germany); Prandin E2 (South Africa); Prepidil (Austria, Belgium, Bulgaria, Canada, China, Colombia, Czech Republic, England, France, Hungary, Italy, Malaysia, Netherlands, Poland, South Africa, Spain); Primiprost (India); Propess (France, Hong Kong, Israel); Prostarmon E (Korea, Taiwan); Prostin 3 (Malaysia, Singapore); Prostine (France); Prostin E2 (Austria, Belgium, Bulgaria, Canada, China, Denmark, England, Hong Kong, Hungary, Indonesia, Ireland, Malaysia, Netherlands, Switzerland, Taiwan, Thailand); Prostin E2 Tab (New Zealand); Prostin E2 Vaginal Cream (Australia); Prostin E2 Vaginal Gel (New Zealand)

Drug Class ..... Oxytocics; Prostaglandins

Indications ..... Cervical ripening

Mechanism ..... Unknown

Dosage with Qualifiers .....

Cervical ripening—0.5mg gel PV endocervical, may repeat q6h ×2; alternatively, 10mg insert PV into the posterior fornix (remain supine 2h), remove with onset of labor or uterine tachysystole

NOTE: available in either gel or tablet-like insert formats.

- **Contraindications**—hypersensitivity to drug or class, other oxytocics, vaginal delivery itself contraindicated, undiagnosed vaginal bleeding, uterine hypertonicity, uterine tachysystole, fetal distress, imminent delivery, CPD, prior cesarean section or other major uterine surgery, grand multiparity
- **Caution**—ROM, asthma, glaucoma, increased intraocular pressure, hepatic or renal dysfunction

Maternal Considerations .....

Dinoprostone is the naturally occurring PGE_2. It is effective when administered by oral, vaginal, or intracervical routes for cervical ripening preceding either vaginal delivery or pregnancy termination. Efficacy is maintained after membrane rupture. Complications include tachysystole and uterine rupture. Outpatient use has been advocated, but there is no dose that assures the absence of tachysystole. The risk of the latter is especially great in women with a prior cesarean section. Two recent randomized trials compared **dinoprostone** to **misoprostol** for the induction of labor in women including those at high risk for fetal distress. **Misoprostol** and **dinoprostone** are equally safe for the induction of labor. However, **misoprostol** is more efficient, may be associated with a lower cesarean delivery rate, and is significantly cheaper. **Dinoprostone** reduces the risk of postpartum hemorrhage in high-risk patients. It has also been used to treat atony. Hypertension and anaphylaxis have been reported on occasion. The safety profile of **dinoprostone** is good; it has been used successfully in women with a wide range of medical complications.

Side effects include bronchospasm, bradycardia, hypertension, arrhythmias, uterine rupture, fetal acidosis, PROM, N/V, diarrhea, headache, uterine contractions, dizziness, flushing, fever, cough, chills, and dyspnea.

Fetal Considerations .....

There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **dinoprostone** crosses the human placenta. Any effect on the fetus appears to reflect complications of uterine activity, as cervical priming has no effect

on fetal blood flows. Rodent studies reveal embryotoxicity and an increased prevalence of skeletal anomalies when given during organogenesis.

Breastfeeding Safety

There is no published experience in nursing women. It is unknown whether **dinoprostone** enters human breast milk. However, considering the indication and dosing, **dinoprostone** use is unlikely to pose a clinically significant risk to the breastfeeding neonate. PGE_2 is naturally excreted into breast milk and has been reported as a cause of neonatal diarrhea.

Drug Interactions

Dinoprostone may augment the activity of other oxytocic agents and their concomitant use is not recommended. A dosing interval of 6-12h is recommended.

References

Biem SR, Turnell RW, Olatunbosun O, et al. J Obstet Gynaecol Can 2003; 25:23-31.

Denguezli W, Trimech A, Haddad A, et al. Arch Gynecol Obstet. 2007; 276:119-24.

Dodd JM, Crowther CA, Robinson JS. BMJ 2006; 332:509-13.

Fok WY, Leung TY, Tsui MH, et al. J Reprod Med 2005; 50:697-700.

Gregson S, Waterstone M, Norman I, Murrells T. BJOG 2005; 112:438-44.

Kelly AJ, Kavanagh J, Thomas J. Cochrane Database Syst Rev 2001; (2):CD003101.

Rozenberg P, Chevret S, Senat MV, et al. Am J Obstet Gynecol 2004; 191:247-53.

Stitely ML, Satin AJ. Clin Obstet Gynecol 2002; 45:114-24.

Van Selm M, Kanhai HH, Keirse MJ. Acta Obstet Gynecol Scand 1995; 74:270-4.

Voss DH, Cumminsky KC, Cook VD, et al. J Matern Fetal Med 1996; 5:186-93.

Wing DA; Misoprostol Vaginal Insert Consortium. Obstet Gynecol 2008; 112:801-12.

Summary

Pregnancy Category: C
Lactation Category: S

- **Dinoprostone** should be used during pregnancy only if the benefit justifies the potential perinatal risk.
- Other prostaglandin compounds, such as **misoprostol,** have similar efficacy, the same degree of safety, but lower cost.

Diphenhydramine—(Allerdryl 50; Allergia-C; Allergina; Amidryl; Banophen; Beldin; Belix; Ben-A-Vance; Bena-D10; Benadryl; Benadryl Steri-Dose; Benahist; Benapon; Bendramine; Benoject; Ben-Rex; Bydramine; Dibenil; Dimidril; Diphen; Diphenacen-50; Diphenhist; Dytuss; Fynex; Genahist; Hydramine; Hydril; Hyrexin; Noradryl; Norafed; Nordryl; Pharm-A-Dry; Restamin; Shodryl; Tega Dryl; Truxadryl; Tusstat; Uad Dryl; Wehdryl)

International Brand Name—Allermin (Japan); Benadryl N (Bulgaria, Czech Republic); Benocten (Switzerland); Broncho D (Israel); Cathejell (Israel); Dibrondrin (Austria); Difenhydramin (Denmark); Dimiril (India); Dormutil (Germany); Histergan (Israel, Puerto Rico, South Africa); Nytol (Canada, South Africa); Nytol Quickgels (Mexico); ratioAllerg (Germany); Resmin (Japan); Tzoali (Mexico); Unisom Sleepgels (Hong Kong); Vena (Japan); Venasmin (Japan)

Drug Class	Antihistamines
Indications	Antihistamine, anaphylaxis, dystonic reactions, sedation, insomnia, motion sickness
Mechanism	Nonselective central and peripheral H_1 receptor antagonist
Dosage with Qualifiers	Antihistaminic—25-50mg PO/IV/IM q6h prn Anaphylaxis—1-1.25mg/kg PO/IV/IM q4-6h; max 300mg/d Dystonic reactions—25-50mg PO tid or qid; max 300mg/d Sedation—25-50mg PO qid prn Insomnia—50mg PO qhs Motion sickness—25-50mg PO q4-6h prn; max 300mg/d • **Contraindications**—hypersensitivity to drug or class, concomitant use of alcohol • **Caution**—glaucoma, asthma, hyperthyroidism, CV disease, glaucoma, peptic ulcer
Maternal Considerations	There are no adequate reports or well-controlled studies of **diphenhydramine** in pregnant women. It has a long history of use in obstetrics. **Diphenhydramine** is a useful adjunct for women who have allergic reactions to local anesthesia, laminaria, and serum albumin, or for the treatment of severe migraine headaches. ***Side effects*** include drowsiness, somnolence, dry mouth, N/V, headache, abdominal pain, fever, and diarrhea.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. Though **diphenhydramine** crosses the human placenta, the kinetics remain to be elucidated. There is no evidence of increased fetal risk if administered during any stage of pregnancy. **Diphenhydramine** may cause neonatal depression if administered during labor. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically.
Breastfeeding Safety	There is no published experience in nursing women. It is unknown whether **diphenhydramine** enters human breast milk. Irritability is the most common adverse reaction reported in the newborns of women using antihistamines while breastfeeding.

Drug Interactions

Has additive effects with alcohol and other CNS depressants (hypnotics, sedatives, tranquilizers, etc.).
MAOIs prolong and intensify the anticholinergic (drying) effects.

References

Aube M. Neurology 1999; 53:S26-8.
Brost BC, Scardo JA, Newman RB. Am J Obstet Gynecol 1996; 175:1376-7.
Garfield RE, Bytautiene E, Vedernikov YP, et al. Am J Obstet Gynecol 2000; 183:118-25.
Ito S, Blajchman A, Stephenson M, et al. Am J Obstet Gynecol 1993; 168:1393-9.
Leathem AM. Clin Pharm 1986; 5:660-8.
Miller AA. J Perinatol 2000; 20:390-1.
Schardein JL, Hentz DL, Petrere JA, Kurtz SM. Toxicol Appl Pharmacol 1971; 18:971-6.
Woods JR Jr, Brinkman CR III, Assali NS. Obstet Gynecol 1976; 48:195-202.
Yoo SD, Rurak DW, Taylor SM, Axelson JE. J Pharm Sci 1993; 82:145-9.

Summary

Pregnancy Category: B
Lactation Category: S

- **Diphenhydramine** appears safe and effective for use during pregnancy.

Dipyridamole—(Persantine)

International Brand Name—Adezan (Greece); Agilease (Japan); Agremol (Thailand); Anginal (Japan, Taiwan); Anti-Plate 75 (South Africa); Apo-Dipyridamole FC (Canada); Atlantin (Japan); Atrombin (Finland); Cardoxin Forte (Israel); Chilcolan (Japan); Cleridium (France, Philippines); Coronair (Belgium); Coronamole (Japan); Corosan (Italy); Cortab (Indonesia); Dipyridan (Japan); Dipyrol (South Africa); Dirinol (Mexico); Efosin (Taiwan); Ethrine (Greece); Gulliostin (Japan); Isephanine (Japan); Justpertin (Japan); Lodimol (Mexico); Microbanzol (Japan); Miosen (Spain); Novodil (Italy); Parotin (Taiwan); Permiltin (Japan); Persantin (Argentina, Bangladesh, Belgium, France, Germany, Israel, Japan, Korea, Mexico, Pakistan, Peru, Poland, Puerto Rico, Slovenia, Turkey); Persantin 75 (Colombia, Mexico, Peru); Persantin 100 (Australia); Persantin Depot (Austria, Finland); Persantin Forte (Germany); Persantin PL (New Zealand); Persantin PL Prolonguetas (Mexico); Persantin Prolonguets (Portugal); Persantin Retard (Netherlands); Persantin Retardkapseln (Switzerland); Persantin SR (Australia); Piroan (Japan); Plato (South Africa); Posanin (Thailand); Prexin (Philippines); Pytazen SR (New Zealand); Ridamol (Philippines); Rupenol (Taiwan); Sandel (Taiwan); Solantin (Taiwan); Tovincocard (Italy); Trompersantin (Mexico); Vasokor (Indonesia)

Drug Class

Platelet inhibitors

Indications

Thrombus prophylaxis-DVT, angina, valvulopathy

Mechanism

A PDE inhibitor that blocks platelet adhesion and stimulates coronary artery dilation

Dosage with Qualifiers

Thromboembolism—150-400mg PO qd (usually given in combination with either **warfarin** or **aspirin**)
Angina—50mg PO tid
Valvulopathy—75-100mg PO qid

- **Contraindications**—hypersensitivity to drug or class
- **Caution**—hypotension

Maternal Considerations

Thromboembolus is a major complication of mechanical heart valves. The risk is greatly reduced but not eliminated by regimens of anticoagulation with **warfarin** or therapeutic **heparin** in addition to an antiplatelet agent. **Warfarin** is relatively contraindicated during pregnancy. The regimen of **dipyridamole,**

aspirin, and **ticlopidine** also appears to be effective prophylaxis. The effect on platelet function persists for about 72h after discontinuing therapy, but is not associated with a change in the bleeding time. Because preeclampsia is associated with a subclinical DIC state, and IUGR with placental thrombosis, a number of studies have examined the role of **dipyridamole** to reduce their incidence. For the most part, **dipyridamole** adds little to the beneficial effects of 81mg of **aspirin** for these indications. **Dipyridamole** has also been used for the treatment of essential thrombocythemia during pregnancy.
Side effects include hypotension, MI, arrhythmias, bronchospasm, rash, dyspnea, N/V, tachycardia, flushing, and diarrhea.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **dipyridamole** crosses the human placenta. The addition of **dipyridamole** to **aspirin** does not enhance the beneficial effect of **aspirin** on preventing IUGR. **Dipyridamole** use is associated with decreased Doppler measured flow resistance in the umbilical artery. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically.

Breastfeeding Safety

There is no adequate published experience in nursing women. **Dipyridamole** enters human milk, though the kinetics remain to be elucidated. There is no evidence to suggest a neonatal effect that would preclude breastfeeding. It has been used to treat respiratory difficulties in newborns with congenital diaphragmatic hernia.

Drug Interactions

Oral maintenance **theophylline** and other xanthine derivatives such as **caffeine** may abolish the coronary vasodilation induced by IV **dipyridamole.** This could lead to a false-negative **thallium** imaging result.
May increase the plasma levels and CV effects of **adenosine,** requiring a dose adjustment.
May counteract the anticholinesterase effect of cholinesterase inhibitors, thereby potentially aggravating myasthenia gravis.

References

Duley L, Henderson-Smart DJ, Knight M, King JF. Cochrane Database Syst Rev 2004; (1):CD004659.
Griesshammer M, Heimpel H, Pearson TC. Leuk Lymphoma 1996; 22(Suppl 1):57-63.
Hassouna A, Allam H. Cardiovasc Surg 2001; 9:478-81.
Hirose S, Yamada A, Kasugai M, et al. Asia Oceania J Obstet Gynaecol 1992; 18:187-93.
Kincaid-Smith P. Blood Press 1994; 3:18-23.
Kinouchi K, Fujita T, Narahara C, Kitamura S. J Anesth 2000; 14:115-8.
Menashe Y, Ben-Baruch G, Greenspoon JS, et al. J Reprod Med 1993; 38:625-9.
North RA, Ferrier C, Gamble G, et al. Aust N Z J Obstet Gynaecol 1995; 35:357-62.
Ueno M, Masuda H, Nakamura K, Sakata R. Surg Today 2001; 31:1002-4.
Uzan S, Beaufils M, Breart G, et al. Lancet 1991; 337:1427-31.
Wallenburg HC, Rotmans N. Am J Obstet Gynecol 1987; 157:1230-5.
Wallenburg HC, Rotmans N. Lancet 1988; 1:939.

Summary

Pregnancy Category: B
Lactation Category: S (likely)

- **Dipyridamole** appears safe for the noted indications during pregnancy and lactation.

Dirithromycin—(Dynabac; Norton)

International Brand Name—Dimac (Austria); Dynabac (Chile, France, Guatemala, Hong Kong, Hungary, Korea, Poland); Onzayt (Philippines); Unibac (Belgium)

Drug Class ..... Antibiotics; Macrolides

Indications ..... Bacterial infections (gram-positive aerobes: *S. aureus* (methicillin-susceptible only), *S. pneumoniae, S. pyogenes;* gram-negative aerobes: *Legionella pneumophila, Moraxella catarrhalis, Bordetella pertussis;* other bacteria: *Mycoplasma pneumoniae*)

Mechanism ..... Bactericidal— inhibits protein synthesis by binding to the P site of the 50S ribosomal subunit

Dosage with Qualifiers ..... Bacterial infection—500mg PO qd

- **Contraindications**—hypersensitivity to drug or class, bacteremia
- **Caution**—renal or hepatic dysfunction

Maternal Considerations ..... There is no published experience with **dirithromycin** during pregnancy. **Dirithromycin** is converted in the intestine to the microbiologically active **erythromycylamine. Dirithromycin** is comparable in efficacy to **erythromycin** for the treatment of skin and soft tissue infections with significantly less nausea. Once-daily dosing aids compliance.
Side effects include arrhythmias, pseudomembranous colitis, anorexia, anxiety, constipation, depression, dry mouth, dysmenorrhea, edema, epistaxis, fever, flu-like symptoms, gastritis, gastroenteritis, hemoptysis, hyperventilation, mouth ulceration, myalgia, nervousness, paresthesia, peripheral edema, somnolence, sweating, syncope, palpitation, taste perversion, tinnitus, tremor, dehydration, urinary frequency, vaginal moniliasis, vaginitis, vasodilation, and malaise.

Fetal Considerations ..... There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **dirithromycin** crosses the human placenta. Other macrolides cross the placenta. Rodent studies are reassuring, revealing no evidence of teratogenicity despite the use of doses higher than those used clinically. Very high doses were associated with IUGR.

Breastfeeding Safety ..... There is no published experience in nursing women. It is unknown whether **dirithromycin** enters human breast milk. It is excreted into rodent milk. Other macrolides are considered compatible with breastfeeding.

Drug Interactions ..... Absorption is slightly enhanced when taken immediately after antacids or H_2-receptor antagonists.
The following drug interactions have been reported with erythromycins. It is not known whether these same drug interactions will occur with **dirithromycin:**
May decrease **triazolam** clearance and potentially increase the pharmacologic effect of **triazolam.**
Increases serum **digoxin** levels.
Drug interactions have been reported between ***erythromycin*** and other medications, including **alfentanil, astemizole, bromocriptine, carbamazepine, cyclosporine, disopyramide, hexobarbital, lovastatin, phenytoin,** and **valproate.**

References ..... There is no published experience in pregnancy or during lactation.

Summary

Pregnancy Category: C
Lactation Category: U

- **Dirithromycin** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.
- There are alternative agents for which there is more experience during pregnancy and lactation.

Disopyramide—(Norpace)

International Brand Name—Dimodan (Mexico); Dirytmin (Belgium, Netherlands, Sweden); Disofarin (Mexico); Durbis (Denmark, Finland, Norway, Sweden, Switzerland); Durbis Retard (Finland, Norway, Sweden); Isorythm (France); Lispine (Japan); Norpace Retard (Czech Republic, Finland, Hong Kong, Indonesia, New Zealand, Philippines, South Africa); Norpaso (Argentina); Pyramide (New Zealand); Ritmodan (Italy, Portugal); Ritmoforine (Netherlands); Rythmical (Israel); Rythmodan (Austria, Belgium, Canada, China, Czech Republic, Ecuador, England, France, Greece, Indonesia, Ireland, Israel, Japan, Netherlands, Russia, South Africa); Rythmodan LA (Canada); Rythmodan Retard (New Zealand, South Africa); Rythmodul (Germany); Rytmilen (Bulgaria, Russia)

Drug Class

Antiarrhythmics, class IA

Indications

Ventricular arrhythmia

Mechanism

Stabilizes cell membrane by modifying the action potential in phase 0

Dosage with Qualifiers

Ventricular arrhythmia—load 300mg ×1, then 150mg PO q6h; adjust prn

- **Contraindications**—hypersensitivity to drug or class, cardiogenic shock, 2nd or 3rd AV block, CHF, prolongation of the QT interval, cardiomyopathy
- **Caution**—hypoglycemia, atrial tachyarrhythmias, renal or hepatic dysfunction

Maternal Considerations

There are no adequate reports or well-controlled studies of **disopyramide** in pregnant women. Pregnancy alters the percentage of free drug circulating in the plasma. Treatment of a cardiac arrhythmia with **disopyramide** during pregnancy is complicated by reported risks of hemorrhage or hypotension or uterine contractions leading to fetal distress. Patients should be monitored intensively to detect such complications.
Disopyramide is actually superior to placebo for the induction of labor.
Side effects include CHF, arrhythmia, thrombocytopenia, hypotension, dizziness, blurred vision, N/V, diarrhea, abdominal pain, dry mucous membranes, anxiety, urinary retention, pruritus, rash, and constipation.

Fetal Considerations

There are no adequate reports or well-controlled studies of **disopyramide** in human fetuses. It crosses the human placenta, achieving an F:M ratio approximating 0.26 for **disopyramide,** and 0.43 for its main metabolite, *N*-monodesalkyl disopyramide. Rodent studies are reassuring, revealing no evidence of teratogenicity despite doses higher than those used clinically. The highest doses were associated with embryotoxicity and IUGR.

Breastfeeding Safety

There are no adequate reports or well-controlled studies in nursing women. Though **disopyramide** is concentrated in human breast milk over maternal plasma after oral administration, the unsupplemented newborn would ingest <2mg/kg. Not

surprisingly, **disopyramide** is at or below the level of detection in the neonate.

Drug Interactions

Phenytoin and other hepatic enzyme inducers may lower the plasma levels of **disopyramide.** Monitoring of plasma levels is recommended to avoid ineffective therapy.
Other antiarrhythmic drugs (e.g., **quinidine, procainamide, lidocaine, propranolol**) may lead to excessive widening of the QRS complex and/or prolongation of the QT interval. **Quinidine** may increase slightly **disopyramide** levels.
Absent further research, **disopyramide** should not be administered 48h before or 24h after **verapamil.**
Cases of life-threatening interactions are reported when given with **clarithromycin** or **erythromycin,** indicating that inhibitors of CYP3A4 can cause a potentially fatal interaction.

References

Abbi M, Kriplani A, Singh B. J Reprod Med 1999; 44:653-5.
Barnett DB, Hudson SA, McBurney A. Br J Clin Pharmacol 1982; 14:310-2.
Ellsworth AJ, Horn JR, Raisys VA, et al. DICP 1989; 23:56-7.
Grand A. Ann Cardiol Angiol 1992; 41:549-64.
Hoppu K, Neuvonen PJ, Korte T. Br J Clin Pharmacol 1986; 21:553.
MacKintosh D, Buchanan N. Br J Clin Pharmacol 1985; 19:856-7.
Tadmor OP, Keren A, Rosenak D, et al. Am J Obstet Gynecol 1990; 162:482-6.

Summary

Pregnancy Category: C
Lactation Category: S (likely)
- **Disopyramide** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Disulfiram—(Antabuse; Antadict; Aversan; Disulfiram; Tetmosol)

International Brand Name—Antabus (Austria, Bulgaria, Denmark, Ecuador, Finland, Germany, Hungary, Norway, Spain, Sweden, Switzerland, Turkey); Busetal (Peru); Difiram (Thailand); Esperal (France, India, Russia); Nocbin (Japan); Refusal (Netherlands); Tetradin (Portugal)

Drug Class

Antialcoholics

Indications

Alcohol dependence

Mechanism

Inhibits acetaldehyde dehydrogenase

Dosage with Qualifiers

Alcohol dependence—begin 500mg PO qam ×1w; continue 500-125mg PO qam, tapering from high to low slowly

NOTE: must abstain from alcohol >12h before administration.

- **Contraindications**—hypersensitivity to drug or class, alcohol use <12 h, **metronidazole** use, CAD, psychosis
- **Caution**—diabetes mellitus, seizures, hepatic or renal dysfunction

Maternal Considerations

There are no adequate reports or well-controlled studies of **disulfiram** in pregnant women. **Disulfiram** is a deterrent to alcohol consumption in patients with a history of alcohol abuse. Its use is increasingly more common in reproductive-age women.

The safety of **disulfiram** during pregnancy is not established. The published literature consists mostly of case reports and small series. ***Side effects*** include CV collapse, arrhythmia, seizure, coma, psychosis, optic neuritis, hepatitis, rash, drowsiness, fatigability, headache, allergic dermatitis, and a metallic or garlic-like taste.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **disulfiram** crosses the human placenta. There are several case reports of limb abnormalities in alcoholic women treated with **disulfiram** during pregnancy. *In vitro,* **disulfiram** is embryotoxic, affecting both DNA synthesis and morphologic development.

Breastfeeding Safety

There is no published experience in nursing women. It is unknown whether **disulfiram** enters human breast milk.

Drug Interactions

Should be used cautiously with **phenytoin** and its congeners as it may cause **phenytoin** intoxication. Serum levels should be followed and the dose adjusted as necessary.
Since **disulfiram** may prolong PT, it may be necessary to adjust the dose of oral anticoagulants when beginning or stopping **disulfiram.**
Patients taking **isoniazid** with **disulfiram** may develop an unsteady gait or marked changes in mental status. **Disulfiram** should be discontinued if such signs appear.

References

Gardner RJ, Clarkson JE. N Z Med J 1981;93:184-6.
Helmbrecht GD, Hoskins IA. Am J Perinatol 1993; 10:5-7.
Nora AH, Nora JJ, Blu J. Lancet 1977; 2:664.
Reitnauer PJ, Callanan NP, Farber RA, Aylsworth AS. Teratology 1997; 56:358-62.
Thompson PA, Folb PI. J Appl Toxicol 1985; 5:1-10.

Summary

Pregnancy Category: C
Lactation Category: U

- **Disulfiram** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Divalproex—(Depakote)

International Brand Name—Depakote (France); Epival (Canada); Valcote (Colombia, Peru)

Drug Class

Anticonvulsants; Migraines

Indications

Seizures, mania, migraine prophylaxis

Mechanism

Acetaldehyde dehydrogenase inhibition

Dosage with Qualifiers

Seizures—10-15mg/kg/d PO in 1-3 divided doses, increase by 5-10mg/kg/d qw; max 60mg/kg/d; therapeutic trough = 50-100mcg/ml
Mania—250mg tid PO, increase by 5-10mg/kg/d every 2-3d; max 60mg/kg/d; therapeutic trough = 50-100mcg/ml
Migraine prophylaxis—250-500mg PO bid

NOTE: take with food.

- **Contraindications**—hypersensitivity to drug or class, hepatic dysfunction or disease

- **Caution**—renal dysfunction, bone marrow suppression, bleeding tendencies, congenital metabolic disorders

■ Maternal Considerations

There are no adequate reports or well-controlled studies of **divalproex** in pregnant women. **Divalproex** is a stabilized form of **valproic acid.** It disassociates into **valproate** in the GI tract. While the metabolism of **valproate** is unaltered by pregnancy, clearance is increased primarily because of decreased binding. It is suggested the drug be taken in divided doses to avoid high peaks (see **valproic acid**). Among patients treated for a bipolar disorder, the risk of suicide attempt is higher during treatment with **divalproex** than it is with **lithium.** However, **divalproex** for the prevention of postpartum episodes of bipolar disorder does not appear more effective than monitoring without drug. **Valproate** seems to reduce the induction of **lamotrigine** metabolism associated with pregnancy or use of contraceptives. Monitoring of anticonvulsant drug levels with appropriate dose adjustments is warranted throughout pregnancy, and vitamin K (10mg/d) should be given in the last month of gestation, particularly when CYP enzyme–inducing agents are being used. ***Side effects*** include congenital NTDs, N/V, diarrhea, abdominal pain, hepatotoxicity, pancreatitis, hyponatremia, SIADH, aplastic anemia, thrombocytopenia, pancytopenia, bleeding, hyperammonemia, psychosis, Stevens-Johnson syndrome, dyspepsia, alopecia, tremor, appetite changes, insomnia, peripheral edema, blurred vision, tinnitus, and respiratory disorders.

■ Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. **Valproate** and its metabolites cross the placenta, perhaps by a proton-linked transport system, and are concentrated in fetal plasma at least in part because of increased protein binding. The F:M ratio exceeds unity. **Valproate** is a human teratogen. **Valproic acid** has been associated with a variety of major and minor malformations, including a 20-fold increase in NTDs, cleft lip and palate, CV abnormalities, GU defects, developmental delay, endocrinologic disorders, limb defects, and autism. **Divalproex** monotherapy during the 1st trimester increases the risk of a fetal NTD by about 10×, or to a prevalence of 1-2%. This association likely reflects pharmacogenetics since preconception maternal folate supplementation does not necessarily reduce the risk of recurrence in subsequent pregnancies. Other associated malformations involve the CV system and the limbs. Its combination with other anticonvulsants increases the risks of malformation. In one small but population-based study, all children exposed to **valproate** had minor, and some of them major, cognitive or neurologic problems. The placenta is not a depot for **valproic acid.** It would appear that there are more adverse outcomes in pregnancies with in utero **valproate** exposure vs. the other antiepileptic drugs. Other agents should be used whenever possible. For women who fail other antiepileptic drug therapy and require **valproate,** the dose should be limited if possible. As for most psychotropic drugs, monotherapy and the lowest effective quantity given in divided doses to minimize the peaks can minimize the risks. (See **Valproic acid.**)

■ Breastfeeding Safety

There are no adequate reports or well-controlled studies in nursing women. Only small amounts of **valproate** (1-10%) enter human breast milk, and its serum concentration in breastfed neonates is subclinical. (See **Valproic acid.**)

Drug Interactions

New interactions are continuously being reported. The following is only a partial list.

Drugs that affect the expression of hepatic enzymes, particularly those that elevate glucuronosyltransferases, may alter the clearance of **valproate.** For example, **phenytoin, carbamazepine, phenobarbital,** and **primidone** may double the clearance of **valproate.** Patients on monotherapy will generally have longer t/2s and higher concentrations than those receiving polytherapy for antiepilepsy. Monitoring of **valproate** and concomitant drug concentrations should be increased whenever enzyme-inducing drugs are started or withdrawn.

Aspirin decreases **valproate** protein binding and inhibits the metabolism of **valproate.**

Felbamate may increase **valproate** peak concentration by as much as 35%.

Rifampin may increase the oral clearance of **valproate** by up to 40%.

May decrease plasma clearance of **amitriptyline** and its metabolite, **nortriptyline.** Consider reducing the dose of **amitriptyline/nortriptyline** in the presence of **valproate.**

Serum **carbamazepine** decreased 17% while that of its metabolite, carbamazepine-10,11-epoxide, increased by 45% when given with **valproate.**

Clonazepam may induce absence status in **valproate**-treated patients with a history of absence-type seizures.

Displaces **diazepam** from its albumin binding sites and inhibits its metabolism, almost doubling the free fraction of **diazepam.** Plasma clearance and volume of distribution for free **diazepam** are reduced by at least 20%.

Inhibits the metabolism of **ethosuximide,** increasing its elimination t/2 by some 25%. Patients receiving **valproate** and **ethosuximide,** especially along with other anticonvulsants, should be monitored closely for changes in serum concentrations of both drugs.

The dose of **lamotrigine** should be reduced when given with **valproate,** as **valproate** increases the elimination t/2 of **lamotrigine** from 26h to 70h. Serious skin reactions (such as Stevens-Johnson syndrome and toxic epidermal necrolysis) have been reported with concomitant **lamotrigine** and **valproate** administration.

May reduce the induction of **lamotrigine** metabolism associated with pregnancy or use of contraceptives.

Inhibits the metabolism of **phenobarbital,** increasing the t/2 by 50% and decreasing clearance by 30%. All patients receiving concomitant barbiturate therapy should be closely monitored for neurologic toxicity. **Primidone,** which is metabolized to a barbiturate, may be involved in a similar interaction with **valproate.**

There are reports of breakthrough seizures occurring with the combination of **valproate** and **phenytoin. Valproate** decreases **phenytoin** albumin binding sites and inhibits its hepatic metabolism, increasing the free concentration of **phenytoin** by 60%. Total plasma clearance and apparent volume of distribution (Vd) of **phenytoin** increases 30% in the presence of **valproate.** Both the clearance and apparent Vd of free **phenytoin** are reduced by 25%.

The clearance of **zidovudine** may be decreased by ⅓ when given with **valproate.**

References

Bailey DN, Briggs JR. Ther Drug Monit 2005; 27:375-7.
Duncan S, Mercho L, Lopes-Cendes I, et al. Epilepsia 2001; 42:750-3.

Goodwin FK, Fireman B, Simon GE, et al. JAMA 2003; 290:1467-73.
Kalviainen R. Epilepsy Behav 2006; 9:636-40.
Nakamura H, Ushigome F, Koyabu N, et al. Pharm Res 2002; 19:154-61.
Philbert A, Pedersen B, Dam M. Acta Neurol Scand 1985; 72:460-3.
Tomson T. Ther Drug Monit 2005; 27:718-21.
Tomson T, Luef G, Sabers A, et al. Neurology 2006; 67:1297-9.
Viinikainen K, Eriksson K, Monkkonen A, et al; NEAD Study Group. Neurology 2006; 67:407-12.
von Unruh GE, Froescher W, Hoffmann F, Niesen M. Ther Drug Monit 1984; 6:272-6.
Wisner KL, Hanusa BH, Peindl KS, Perel JM. Biol Psychiatry 2004; 56:592-6.

Summary

Pregnancy Category: D
Lactation Category: S

- **Divalproex** should be used during pregnancy only if the benefit justifies the potential perinatal risk.
- There are more adverse outcomes in pregnancies after *in utero* **valproate** exposure than with the other antiepileptic drugs. Alternative agents should be used whenever possible.
- As for most psychotropic drugs, using monotherapy and the lowest effective quantity given in divided doses to minimize the peaks can minimize the risks.
- There are alternatives for migraine prophylaxis during pregnancy.
- Exposed women should undergo a targeted ultrasound examination to search for fetal NTDs.

Dobutamine—(Dobutrex)

International Brand Name—Butamine (Israel); Cardiject (India); Cardiomin (Philippines); Dobuject (China, Czech Republic, Denmark, Finland, Indonesia, Israel, Korea, Mexico, Russia, Singapore, Sweden, Thailand); Dobumine (Korea); Dobutamina (Ecuador); Dobutamin Giulini (Germany); Dobutamin Hexal (Germany); Dobutamin-Ratiopharm (Germany); Inotrex (Greece, Portugal); Inotrop (Indonesia); Oxiken (Mexico)

Drug Class

Adrenergic agonists; Inotropes

Indications

Cardiac decompensation

Mechanism

Stimulates β_1-adrenergic receptors

Dosage with Qualifiers

Cardiac decompensation—2-10mcg/kg/min IV; max 40mcg/kg/min

- **Contraindications**—hypersensitivity to drug or class, IHSS, hypertension
- **Caution**—history of recent MI, arrhythmia or sulfite allergy

Maternal Considerations

There are no adequate reports or well-controlled studies of **dobutamine** in pregnant women. **Dobutamine** is a direct-acting β-adrenergic ionotropic agent producing a pressor effect with less chronotropy than the β-adrenergic agents, plus some degree of vasodilation (e.g., pulmonary vascular resistance) but no dopaminergic renal effects. **Dobutamine** is recommended for ionotropic support of women with cardiac decompensation during pregnancy. It is used to improve ventricular function in

women with idiopathic dilated cardiomyopathy. **Dobutamine** can also induce a modest but unsustained increase in cardiac output in patients with idiopathic pulmonary hypertension. The diagnosis of peripartal cardiomyopathy is limited to women with CHF and decreased LV systolic function during the last month of pregnancy or within 5mo of delivery. Women whose ventricular function is normal at rest and exercise may have their **dobutamine** tapered and ultimately discontinued after 6-12mo. The **dobutamine** challenge test is used to assess ventricular function in women with a history of peripartal cardiomyopathy who have regained normal resting LV size and performance. **Digoxin** is recommended prior to **dobutamine** when treatment is necessary for atrial fibrillation.
Side effects include tachycardia, arrhythmia, phlebitis, hypotension, N/V, headache, angina, palpitations, SOB, hypertension, myocardial ischemia, and VF.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. **Dobutamine** crosses the human placenta, though the kinetics remain to be elucidated. **Dobutamine** has been used in twin-twin transfusion syndrome with possible benefit. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically.

Breastfeeding Safety

There is no published experience in nursing women. It is unknown whether **dobutamine** enters human breast milk.

Drug Interactions

Preliminary studies suggest the use of **dobutamine** with **nitroprusside** results in a higher cardiac output and, usually, a lower pulmonary wedge pressure than when either drug is used alone.

References

Baughman KL. Curr Treat Options Cardiovasc Med 2001; 3:469-80.
Brown G, O'Leary M, Douglas I, Herkes R. Anaesth Intensive Care 1992; 20:80-3.
Fishburne JI, Meis PJ, Urban RB, et al. Am J Obstet Gynecol 1980; 137:944-52.
Hibbard JU, Lindheimer M, Lang RM. Obstet Gynecol 1999; 94:311-6.
Lampert MB, Weinert L, Hibbard J, et al. Am J Obstet Gynecol 1997; 176:189-95.
Mareschal-Desandes R, Hascoet JM, Bosser G, et al. Arch Pediatr 2002; 9:377-81.

Summary

Pregnancy Category: B
Lactation Category: U

- **Dobutamine** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Docetaxel—(Taxotere)

International Brand Name—Daxotel (Thailand); Dexotel (India); Oncodocel (Colombia); Taxoter (Russia); Taxotere (Egypt, Israel); Texot (Argentina)

Drug Class	Antineoplastics, antimitotics
Indications	Breast cancer, lung cancer, gestational choriocarcinoma
Mechanism	Mitotic inhibitor
Dosage with Qualifiers	Cancer—dose varies per protocol; most regimens recommend 60-100mg/m^2 • **Contraindications**—hypersensitivity to drug or class, agranulocytosis • **Caution**—renal or hepatic dysfunction
Maternal Considerations	There are no adequate reports or well-controlled studies of **docetaxel** in pregnant women. There are now several case reports of its use during pregnancy with reassuring results. ***Side effects*** include thrombocytopenia, leukopenia, anemia, agranulocytosis, myelosuppression, skin rash, edema, stomatitis.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **docetaxel** crosses the human placenta. While there is no evidence of teratogenicity, rodent studies reveal clear evidence of both embryo and fetal toxicity at doses far below those used in humans.
Breastfeeding Safety	There is no published experience in nursing women. It is unknown whether **docetaxel** enters human breast milk. However, it is generally considered incompatible with breastfeeding in light of its pharmacologic mechanism.
Drug Interactions	*In vitro* studies reveal the metabolism of **docetaxel** may be modified by compounds that induce, inhibit, or are metabolized by CYP3A4 (e.g., **cyclosporine, erythromycin, ketoconazole, terfenadine, troleandomycin**). Caution should be exercised.
References	De Santis M, Lucchese A, De Carolis S, et al. Eur J Cancer Care 2000; 9:235-7. Nieto Y, Santisteban M, Aramendia JM, et al. Clin Breast Cancer 2006; 6:533-4. Potluri V, Lewis D, Burton GV. Clin Breast Cancer 2006; 7:167-70. Winquist E, Carey M. Gynecol Oncol 2000; 79:523-4.
Summary	**Pregnancy Category: D** **Lactation Category: NS** (possibly) • **Docetaxel** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk. • Alternative agents should be sought for which there is more experience during pregnancy and lactation.

Docusate calcium—(Colace; Ediclone; Kasof; Laxagel; Prenate-90; Rapilax; Regulax; Surfak; Wasserlax)

International Brand Name—Colace (Canada, Ireland); Cusate (Thailand); Jamylene (France); Lambanol (Italy); Laxadine (Indonesia); Norgalax (Belgium, Israel, Russia); Regutol (Israel); Selax (Canada); Soflax (Canada); Softon (Hong Kong); Tirolaxo (Spain)

Drug Class	Laxatives
Indications	Constipation
Mechanism	Retains moisture and fat within the large bowel
Dosage with Qualifiers	Constipation—100mg PO qd or bid *NOTE: may be packaged with* ***casanthranol.*** • **Contraindications**—hypersensitivity to drug or class, fecal impaction, mineral oil use, acute abdomen, colitis, GI obstruction • **Caution**—N/V
Maternal Considerations	While there are no adequate reports or well-controlled studies of **docusate** in pregnant women, there is a long clinical experience with virtually no reported complications. **Docusate** is frequently used postpartum to avoid constipation in women who have had a repaired episiotomy. It may rarely potentiate the hepatotoxicity of other drugs. ***Side effects*** include bitter taste, nausea, rash, diarrhea, throat irritation, and intestinal obstruction.
Fetal Considerations	**Docusate** is not absorbed systemically and thus does not cross the placenta. A three-generational rodent study failed to identify any adverse effects on reproduction. There are reports of neonatal hypomagnesemia after maternal abuse of stool softeners.
Breastfeeding Safety	There are no adequate reports or well-controlled studies in nursing women. **Docusate** is not absorbed systemically and thus will not enter human breast milk.
Drug Interactions	No clinically relevant interactions identified.
References	Gattuso JM, Kamm MA. Drug Saf 1994; 10:47-65. MacKenzie K, Henwood S, Foster G, et al. Fundam Appl Toxicol 1990; 15:53-62. Schindler AM. Lancet 1984; 2:822.
Summary	**Pregnancy Category: C** **Lactation Category: S** • Most laxatives are relatively safe if used intermittently in the absence of contraindications.

Dofetilide—(Tikosyn)

International Brand Name—None identified.

Drug Class	Antiarrhythmics, class III
Indications	Atrial flutter/fibrillation
Mechanism	Prolongs the phase 3 action potential
Dosage with Qualifiers	Atrial flutter/fibrillation—500mcg PO q12h; adjust dose based on QTc and creatinine clearance *NOTE: renal dosing; restricted access in the US.* • **Contraindications**—hypersensitivity to drug or class, QT prolongation (>440-500msec), renal failure, hypokalemia • **Caution**—bradycardia, electrolyte abnormalities, renal dysfunction, CYP3A4 inhibitors
Maternal Considerations	There is no published experience with **dofetilide** during pregnancy. ***Side effects*** include ventricular arrhythmias, QT interval prolongation, chest pain, dizziness, headache, nausea, dyspepsia, diarrhea, flu-like symptoms, and rash.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **dofetilide** crosses the human placenta. Rodent studies reveal that **dofetilide** produces a spectrum of defects similar to **phenytoin,** including cardiac, digital, and oral facial clefting malformations, possibly by blocking potassium channels.
Breastfeeding Safety	There is no published experience in nursing women. It is unknown whether **dofetilide** enters human breast milk.
Drug Interactions	**Cimetidine** is contraindicated as it may increase **dofetilide** levels by more than 50%. If a patient requires **dofetilide** and antiulcer agent, either **omeprazole, ranitidine,** or antacids (aluminum and magnesium hydroxides) should be used. **Verapamil** is contraindicated as it can increase **dofetilide** by 40%, although overall exposure to **dofetilide** is not significantly increased. In one study, the use of **verapamil** with **dofetilide** increased the rate of torsades de pointes. **Ketoconazole** is contraindicated as it increases the **dofetilide** C_{max} by 100%, and the AUC by 70% in females. **Trimethoprim** is contraindicated, whether alone or in combination with **sulfamethoxazole,** as it almost doubles the **dofetilide** AUC and C_{max}. Inhibitors of renal cationic secretion are contraindicated. Drugs that are actively secreted by this route (e.g., **triamterene, metformin, amiloride**) should be used with care as they too might increase **dofetilide** levels. Metabolized in part by CYP3A4. Inhibitors of CYP3A4 (e.g., **amiodarone,** azole antifungal agents, cannabinoids, **diltiazem,** grapefruit juice, macrolides, **nefazodone, norfloxacin,** protease inhibitors, **quinine,** SSRIs, **zafirlukast**) may increase systemic **dofetilide.** The concomitant use of **digoxin** has been associated with a higher occurrence of torsades de pointes, but it is unclear whether this represents an interaction with **dofetilide** or the

presence of more severe structural heart disease, a known risk factor for arrhythmia, in patients on **digoxin.**

References

Danielsson BR, Skold AC, Azarbayjani F. Curr Pharm Des 2001; 7:787-802.

Summary

Pregnancy Category: C
Lactation Category: U

- **Dofetilide** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.
- There are alternative agents for which there is more experience during pregnancy and lactation.

Dolasetron mesylate—(Anzemet)

International Brand Name—Anemet (Germany); Anzemet (Argentina, Austria, Brazil, Canada, Costa Rica, Dominican Republic, Ecuador, El Salvador, England, France, Guatemala, Honduras, Ireland, Italy, Korea, Mexico, Nicaragua, Panama, Venezuela); Zamanon (South Africa)

Drug Class

Antiemetics; Serotonin receptor antagonists

Indications

Severe N/V secondary to either chemotherapy or anesthesia

Mechanism

Selective 5-HT_3 receptor antagonist

Dosage with Qualifiers

N/V, postoperative—typically 12.5mg IV ×1 15min before surgery ends
N/V, chemotherapy—100mg PO ×1 1h pre-chemo, or 1.8mg/kg IV ×1 15min pre-chemo

- **Contraindications**—hypersensitivity to drug or class
- **Caution**—hypomagnesemia, prolonged QT

Maternal Considerations

There is no published experience with **dolasetron** during pregnancy.
Side effects include arrhythmia, headache, diarrhea, abdominal pain, fever, fatigue, dizziness, increased LFTs, leukopenia, hypertension, pain, drowsiness, and urinary retention.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **dolasetron** crosses the placenta. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically.

Breastfeeding Safety

There is no published experience in nursing women. It is unknown whether **dolasetron** enters human breast milk.

Drug Interactions

The potential for clinically significant drug interactions appears low for drugs commonly used in chemotherapy or surgery, as **dolasetron** is eliminated by multiple routes.
Cimetidine, a nonselective inhibitor of CYP, can increase **dolasetron** by about 25%, whereas **rifampin,** a potent inducer of CYP, decreases it by about 30%.
Caution should be exercised using **dolasetron** with drugs that prolong ECG intervals, particularly the QTc.
Atenolol decreases the clearance of **dolasetron** by about 27%.

References

There is no published experience in pregnancy or during lactation.

Summary

Pregnancy Category: B
Lactation Category: U

- **Dolasetron** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.
- There are many alternative agents for which there is more experience during pregnancy and lactation.

Donepezil—(Aricept)

International Brand Name—Asenta (Israel); Eranz (Colombia, Mexico); Memorit (Israel)

Drug Class

Cholinesterase inhibitors

Indications

Alzheimer's disease

Mechanism

Reversibly binds and inactivates acetylcholinesterase

Dosage with Qualifiers

Alzheimer's dementia—begin 5mg PO qhs; increase gradually to 10mg PO qhs after 4-6w

- **Contraindications—**hypersensitivity to drug or class, sick sinus syndrome, SVT
- **Caution—**asthma, CAD, peptic ulcer

Maternal Considerations

Donepezil is believed to enhance cholinergic function by increasing ACh concentration in the intact cholinergic nerves, keeping them functionally intact. Further, **donepezil** potentiates activity of the NMDA system even at low therapeutic concentrations (0.01-1mcM). This action together with cholinesterase inhibition could contribute to the improvement of learning, memory, and cognition in patients with Alzheimer's disease. There is no evidence that **donepezil** alters the course of the underlying disease. It is metabolized by CYP isozymes 2D6 and 3A4 and undergoes glucuronidation. Neither gender nor race appears to alter clearance, though it is prolonged by cirrhosis. There is no published experience with **donepezil** during pregnancy.
Side effects include seizures, respiratory depression, diarrhea, pain, insomnia, N/V, ecchymosis, weight loss, depression, dream disturbances, syncope, urinary frequency, and arthritis.

Fetal Considerations

There is no published experience in human pregnancy. It is unknown whether **donepezil** crosses the human placenta. Rodent studies are for the most part reassuring, revealing no evidence of teratogenicity at up to 18× the MRHD. At 8× the MRHD, the stillbirth rate was slightly increased in rats.

Breastfeeding Safety

There is no published experience in nursing women. It is unknown whether **donepezil** enters human breast milk.

Drug Interactions

Ketoconazole and **quinidine,** inhibitors of CYP3A4 and 2D6, respectively, inhibit **donepezil** metabolism *in vitro.* **Ketoconazole** increased the mean **donepezil** AUC and C_{max} by about ⅓. Inducers of CYP2D6 and CYP3A4 (e.g., **carbamazepine, dexamthasone, phenobarbital, phenytoin, rifampin**) could increase the elimination rate of **donepezil.**
Cholinesterase inhibitors may interfere with the activity of anticholinergic medications. A synergistic effect can be expected when cholinesterase inhibitors are given concurrently with

succinylcholine, similar neuromuscular blocking agents, or cholinergic agonists such as **bethanechol.**

References ..... There is no published experience in pregnancy or during lactation.

Summary .....

Pregnancy Category: C
Lactation Category: S

- **Donepezil** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Dopamine—(Intropin)

International Brand Name—Cardiopal (Colombia); Cardiosteril (Germany); Catabon (Japan); Docard (Israel, Philippines); Dopamex (Thailand); Dopamin (Bulgaria, Norway); Dopamina (Spain); Dopamin AWD (Germany, Hungary); Dopamin Braun (Switzerland); Dopamine (France, Netherlands); Dopamine Injection (Australia); Dopaminex (Thailand); Dopamin Guilini (Austria, Germany, Indonesia); Dopamin Leopold (Austria); Dopamin Natterman (Austria, Bulgaria, Germany); Dopaminum (Poland); Dopinga (India); Dopmin (Bulgaria, Czech Republic, Denmark, Finland, Malaysia, Taiwan, Turkey); Dopmin E (Russia); Drynalken (Mexico); Dynatra (Belgium); Dynos (South Africa); Giludop (Denmark, Sweden, Turkey); Inopan (Korea); Inopin (Thailand); Inotropin (Mexico); Intropin IV (Hong Kong, Malaysia); Uramin (Taiwan)

Drug Class ..... Adrenergic agonists; Inotropes

Indications ..... Shock, refractory CHF

Mechanism ..... Stimulates α- and β_1-adrenergic and dopaminergic receptors

Dosage with Qualifiers .....

Adjunct for shock—1-50mcg/kg/min IV; max 20-50mcg/kg/min
2-5mcg/kg/min: primarily dopaminergic receptor effects, but may exhibit a pressor effect
5-10mcg/kg/min: primarily β-adrenergic effects with inotropy and chronotropy
>10mcg/kg/min: primarily α-adrenergic effects with peripheral vasoconstriction
Refractory CHF—1-3mcg/kg/min IV

- **Contraindications**—hypersensitivity to drug, class, or sulfites; VF; pheochromocytoma
- **Caution**—diabetes mellitus, occlusive vascular diseases, Raynaud's disease, usage of MAOIs

Maternal Considerations .....

There are no adequate reports or well-controlled studies of **dopamine** in pregnant women. **Dopamine** is a natural catecholamine that produces both positive chronotropic and inotropic effects. Several investigators have applied its vasodilating properties to the treatment of preeclamptic hypertension. A low-dose infusion of **dopamine** aids the management of acute renal failure caused by preeclampsia. A treatment program of IV fluids, **furosemide,** and/or **dopamine** has been suggested for preeclamptic women with anuria (output <100ml/24h). If unsuccessful, early dialysis should be considered. The evidence for the use of prophylactic medical interventions (e.g., the use of loop diuretics, **mannitol,** and low-dose **dopamine**), is poor. Studies in monkeys report both increased and decreased uterine blood flow depending on dose.
Side effects include anaphylaxis, asthma, gangrene, hypotension, tachycardia, ventricular arrhythmia, ectopic beats, angina, palpitation, widened QRS complex, bradycardia, hypertension,

vasoconstriction, dyspnea, azotemia, headache, anxiety, and piloerection.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. There are specific **dopamine** receptors on the human placenta. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically. Maternal toxicity occurred and was associated with decreased neonatal survival.

Breastfeeding Safety

There is no published experience in nursing women. It is unknown whether **dopamine** enters human breast milk.

Drug Interactions

Cyclopropane or halogenated hydrocarbon anesthetics increase cardiac autonomic irritability and may sensitize the myocardium to catecholamines such as **dopamine.** This interaction is related to both the pressor and the β-adrenergic stimulating activities of these catecholamines, and may produce ventricular arrhythmias and hypertension. Animal studies suggest that **dopamine**-induced ventricular arrythmias during anesthesia can be reversed by **propranolol.**

MAO inhibition prolongs and potentiates the effect of **dopamine.** Patients who have received a MAOI within 2-3w of requiring **dopamine** should begin at 1/10 of the initial dose.

Low-dose **dopamine** and diuretic agents may produce an additive effect on urine flow.

TCAs may potentiate the CV effects of adrenergic agents.

Cardiac effects are antagonized by β-adrenergic blocking agents, such as **propranolol** and **metoprolol.** The peripheral vasoconstriction caused by high doses of **dopamine** is antagonized by α-adrenergic blocking agents. **Dopamine**-induced renal and mesenteric vasodilation is not antagonized by either α- or β-adrenergic blocking agents.

Butyrophenones (such as **haloperidol**) and phenothiazines can suppress the dopaminergic renal and mesenteric vasodilation induced with low-dose **dopamine** infusion.

Use with vasoconstricting agents (such as **ergonovine**) and some oxytocic drugs may result in severe hypertension.

Use of **phenytoin** plus **dopamine** has been associated with hypotension and bradycardia.

References

Brown G, O'Leary M, Douglas I, Herkes R. Anaesth Intensive Care 1992; 20:80-3.

Keiseb J, Moodley J, Connolly CA. Hypertens Pregnancy 2002; 21:225-34.

Mantel GD. Best Pract Res Clin Obstet Gynaecol 2001; 15:563-81.

Martinez de Ita AL, Garcia Caceres E, Helguera Martinez AM, Cejudo Carranza E. Ginecol Obstet Mex 1998; 66:462-8.

Nasu K, Yoshimatsu J, Anai T, Miyakawa I. Gynecol Obstet Invest 1996; 42:140-1.

Summary

Pregnancy Category: C
Lactation Category: U

- **Dopamine** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Doxazosin—(Cardura)

International Brand Name—Alfadil (Sweden); Alfamedin (Germany); Cadex (Israel); Cadil (Korea); Cardenalin (Japan); Cardil (Korea); Cardoral (Israel); Cardoxan (New Zealand); Cardular (Germany); Cardular PP (Germany); Cardular Uro (Germany); Cardura (Argentina, Bulgaria, Chile, Czech Republic, Ecuador, England, Hong Kong, Hungary, Indonesia, Ireland, Malaysia, Mexico, Netherlands, Peru, Portugal, Russia, Singapore, South Africa, Thailand, Turkey, Uruguay, Venezuela, Zambia); Carduran (Colombia, Denmark, Norway, Philippines, Spain); Cardura XL (Hong Kong); Cardura-XL S.R. (Korea); Cazosin (Thailand); Dedralen (Italy); Diblocin (Germany); Diblocin PP (Germany); Diblocin Uro (Germany); Dophilin (Taiwan); Dosabin (Taiwan); Dosan (New Zealand); Doxaben (Taiwan); Doxacard (Hong Kong, India); Doxagamma (Germany); Doxaloc (Israel); Doxan (Taiwan); Doxasyn (Hong Kong); Doxolbran (Argentina); Genzosin (Taiwan); Jutalar (Germany); Kaltensif (Indonesia); Kinxasen (Taiwan); Pencor (Singapore, Thailand); Saxobin (Taiwan); Supressin (Austria); Uriduct (Germany); Xadosin (Taiwan); Zoxan LP (France)

Drug Class	Adrenergic antagonists; α-Blockers; Antihypertensives
Indications	Hypertension
Mechanism	Selective antagonist of peripheral α_1-adrenergic receptors
Dosage with Qualifiers	Hypertension—1mg PO qd, increase slowly (dose range 1-8mg qd); max 16mg qd • **Contraindications**—hypersensitivity to drug or class • **Caution**—hepatic or renal dysfunction
Maternal Considerations	There are no adequate reports or well-controlled studies of **doxazosin** in pregnant women. It is similar to **atenolol.** ***Side effects*** include arrhythmias, headache, N/V, somnolence, edema, dyspnea, asthenia, diarrhea, angina, fatigue, hypotension, back pain, flu-like syndrome, diarrhea, dry mouth, blurred vision, and dyspepsia.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **doxazosin** crosses the human placenta. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically.
Breastfeeding Safety	There are no adequate reports or well-controlled studies in nursing women. It is unknown whether **doxazosin** enters human breast milk. It is concentrated in rodent milk. Similar agents are generally considered compatible with breastfeeding.
Drug Interactions	*In vitro* studies suggest that **doxazosin** is a substrate for CYP3A4. Potent CYP3A4 inhibitors (e.g., atanazavir, **clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, voriconazole**) may increase **doxazosin** levels.
References	There is no published experience in pregnancy or during lactation.
Summary	**Pregnancy Category: B** **Lactation Category: U** • There are many alternatives for which there is greater experience during pregnancy and lactation.

Doxepin—(Sinequan; Zonalon)

International Brand Name—Anten (New Zealand); Aponal (Germany); Deptran (Australia); Doneurin (Germany); Doxal (Finland); Expan (Colombia); Gilex (Israel); Mareen (Germany); Quitaxon (Belgium, Denmark, France, Portugal, South Africa); Sinquan (Denmark, Germany, Switzerland); Zonalon Cream (Israel)

Drug Class	Antidepressants; Tricyclics
Indications	Depression, anxiety, pruritus (topical)
Mechanism	Exact mechanism unknown, but does inhibit NE and serotonin reuptake
Dosage with Qualifiers	Depression—begin 25-75mg PO qhs (alternatively 50mg PO tid), increase gradually based on response; max 300mg qd Anxiety—begin 25-75mg PO qhs (alternatively 25mg PO tid), increase gradually based on response; max 300mg qd Pruritus—apply cream (5% cream) qid to affected area; systemic absorption significant with widespread application • **Contraindications**—hypersensitivity to drug or class, glaucoma, urinary retention • **Caution**—advanced age
Maternal Considerations	There are no adequate reports or well-controlled studies of **doxepin** in pregnant women. ***Side effects*** include dry mouth, blurred vision, constipation, urinary retention, drowsiness, extrapyramidal symptoms, confusion, disorientation, hallucinations, numbness, paresthesias, ataxia, seizures, eosinophilia, leukopenia, thrombocytopenia, purpura, lowered libido, testicular swelling, gynecomastia, rash, and anorexia.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **doxepin** crosses the human placenta.
Breastfeeding Safety	There are no adequate reports or well-controlled studies in nursing women. While only small amounts of **doxepin** and its active metabolite enter breast milk, one report described apnea and drowsiness though the neonatal plasma **doxepin** was just into the detectable range. Caution is suggested.
Drug Interactions	Metabolized by CYP2D6 (and CYP3A4 as a minor pathway). CYP2D6 is reduced in 7-10% of Caucasians (''poor metaoblizers''), causing higher than expected plasma concentrations of TCAs. Depending on the fraction of drug metabolized by CYP2D6, the increase in plasma concentration may be small, or quite large (8-fold increase in plasma AUC of TCAs). Drugs that inhibit CYP2D6 render normal metabolizers poor metabolizers. An individual who is stable on a given dose of a TCA may become abruptly toxic when given one of these inhibiting drugs. Drugs that inhibit CYP2D6 include those not metabolized by the enzyme (e.g., **quinidine, cimetidine**) and those that are substrates (many other antidepressants, phenothiazines, and the class 1C antiarrhythmics **propafenone** and **flecainide**). While all SSRIs (e.g., **fluoxetine, sertraline, paroxetine**) inhibit CYP2D6, they vary in the extent of inhibition. Clinical problems depend on the degree of inhibition and the pharmacokinetics of the SSRI involved. Of particular

importance, sufficient time must be allowed before initiating a TCA in a patient being withdrawn from **fluoxetine,** given the long t/2 of the parent and active metabolite (at least 5w).
Use of TCAs with drugs that inhibit CYP2D6 may require lower doses than usually prescribed for either drug. The dose of TCA may need to be increased if the other drug is withdrawn. Thus, MAOIs should be discontinued at least 2w prior to the cautious initiation of therapy with **doxepin.** Serious side effects and even death have been reported following the concomitant use of certain drugs with MAOIs.
In patients who are well-controlled on TCAs also receiving **cimetidine,** discontinuation of the **cimetidine** may decrease established steady-state TCA levels and compromise their therapeutic effects.
Alcohol ingestion increases the danger inherent in any intentional or unintentional **doxepin** overdosage.

References

Frey OR, Scheidt P, von Brenndorff AI. Ann Pharmacother 1999; 33:690-3.
Wisner KL, Perel JM, Findling RL. Am J Psychiatry 1996; 153:1132-7.

Summary

Pregnancy Category: C
Lactation Category: NS (possibly)

- **Doxepin** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.
- There are other agents available for which there is greater experience during pregnancy and lactation.

Doxorubicin—(Adriamycin)

International Brand Name—A.D.Mycin (Korea); Adriablastin (Austria, Hungary, Switzerland); Adriablastina (Czech Republic, Greece, Portugal); Adriablastina R.D. (Thailand); Adriacin (Japan); Adriamicine (Russia); Adriamycin (China, Czech Republic, Denmark, England, Finland, Hong Kong, Ireland, Malaysia, Norway, Sweden, Thailand); Adriamycin P.F.S. (Korea); Adriamycin RD (Indonesia); Adriamycin R.D.F. (Korea); Adriblastin (Russia); Adriblastina (Belgium, Bulgaria, Costa Rica, Dominican Republic, El Salvador, Guatemala, Honduras, Israel, Italy, Netherlands, Nicaragua, Panama, Peru, Philippines, Taiwan, Turkey); Adriblastina CS (Colombia); Adriblastina PFS (Israel); Adriblastine (France); Adrim (India, Philippines); Adrimedac (Germany); Adrubicin (Korea); Amminac (Thailand); Caelyx (Australia, Canada, Hong Kong, Israel, Mexico, Peru, Philippines, Singapore, South Africa, Taiwan, Thailand); Carcinocin (Indonesia); Doxolem (Costa Rica, Dominican Republic, El Salvador, Guatemala, Honduras, Mexico, Nicaragua, Panama, Thailand); Doxor Lyo (Taiwan); Doxorubicin (India); Doxorubicin Meiji (India); Doxorubin (New Zealand, Thailand); Farmiblastina (Spain); Ifadox (Mexico); Rubidox (Philippines)

Drug Class

Antineoplastics, antibiotics

Indications

Cancer (bladder, breast, bronchogenic, gastric, ovary, thyroid, leukemia, lymphoma, Hodgkin's lymphoma, bone, Wilms' tumor, neuroblastoma)

Mechanism

Interferes with DNA synthesis by binding to it

Dosage with Qualifiers

Cancer—dose varies per protocol; most regimens recommend 60-75mg/m^2 IV q3w

NOTE: hepatic and renal dosing; use of a cardioprotectant agent (dexrazoxane) during treatment recommended. ***Doxorubicin*** *should not be administered IM since severe local tissue necrosis might occur.*

- **Contraindications**—hypersensitivity to drug or class, hyperbilirubinemia, cardiomyopathy, CHF, myelosuppression,

previous treatment with complete courses of **doxorubicin, idarubicin,** or **daunorubicin**
- **Caution**—hepatic dysfunction, concomitant radiation therapy

Maternal Considerations

There are no adequate reports or well-controlled studies of **doxorubicin** in pregnant women. Irreversible myocardial toxicity may occur during or months after therapy. ACEIs and dexrazoxane offer cardioprotection. Women with breast cancer diagnosed during pregnancy are frequently treated during the 1st trimester of pregnancy with a complex regimen including **fluorouracil, doxorubicin,** and **cyclophosphamide.** Women with Hodgkin's lymphoma who survived without recurrence ≥3y and who attempt pregnancy after combination chemotherapy including **doxorubicin** do not experience significant subfertility. ***Side effects*** include potentiation of **cyclophosphamide** toxicity, arrhythmia, pericarditis, alopecia, hyperpigmentation, N/V, stomatitis, cellulitis, tissue necrosis, AML, fever, chills, urticaria, and neurotoxicity.

Fetal Considerations

Though there are no adequate reports or well-controlled studies in human fetuses, there are numerous uncontrolled series and case reports whose interpretations are complicated by the fact that **doxorubicin** is often given with other agents. There is no firm evidence of teratogenicity or perinatal myocardial dysfunction in fetuses of women treated with **doxorubicin.** Women treated during the 2nd and 3rd trimesters of pregnancy experience little increase in the rate of complication during labor and delivery, and their neonates do well. There is essentially no long-term follow-up of exposed fetuses. **Doxorubicin** is associated with a series of anomalies in rats similar to VATER—esophageal atresia, tracheoesophageal fistula, and cloacal and urogenital anomalies.

Breastfeeding Safety

There are no adequate reports or well-controlled studies in nursing women. **Doxorubicin** is concentrated in human breast milk, achieving maximum M:P ratios approximating 4.4. However, the maximum concentration of active drug approximates 0.24mg/L. Thus, the amount ingested by the breastfeeding neonate would be insignificant.

Drug Interactions

Extensively metabolized by the liver. Toxicities associated with **doxorubicin** may be increased when used in combination with other cytotoxic drugs.

There are reports that **paclitaxel** infused over 24h followed by **doxorubicin** administered over 48h resulted in a significant decrease in **doxorubicin** clearance with more profound neutropenic and stomatitis episodes than the reverse sequence.

In one study where **progesterone** was given to patients with advanced malignancies at high doses coupled with a fixed **doxorubicin** dose, the authors noted enhanced **doxorubicin**-induced neutropenia and thrombocytopenia.

Cyclosporine may increase the AUC for both **doxorubicin** and doxorubicinol, possibly due to a decrease in clearance of parent drug and a decrease in metabolism of doxorubicinol causing more profound and prolonged hematologic toxicity. Coma and/or seizures have also been described.

In a clinical study of women with metastatic breast cancer, the concurrent use of the cardioprotectant dexrazoxane and a regimen of **fluorouracil, doxorubicin,** and **cyclophosphamide** was associated with a lower tumor response rate.

Necrotizing colitis manifested by cecal inflammation, bloody stools, and severe and sometimes fatal infections has been associated with a combination of **doxorubicin** and **cytarabine.**
Cyclophosphamide may increase the level of doxorubicinol, which has only 5% of the cytotoxic activity of **doxorubicin.**
Concurrent treatment with **doxorubicin** has been reported to exacerbate **cyclophosphamide**-induced hemorrhagic cystitis. AML has been reported as a second malignancy after treatment with **doxorubicin** and **cyclophosphamide.**
Phenobarbital increases the elimination of **doxorubicin.**
Phenytoin levels may be decreased by **doxorubicin.**
Streptozocin may inhibit the hepatic metabolism of **doxorubicin.**
Saquinavir increased mucosal toxicity when combined with **cyclophosphamide, doxorubicin,** and **etoposide** in patients with HIV-associated non-Hodgkin's lymphoma.

References

Berry DL, Theriault RL, Holmes FA, et al. J Clin Oncol 1999; 17:855-61.
d'Incalci M, Broggini M, Buscaglia M, Pardi G. Lancet 1983; 1:75.
Egan PC, Costanza ME, Dodion P, et al. Cancer Treat Rep 1985; 69:1387-9.
Gwyn KM, Theriault RL. Curr Treat Options Oncol 2000; 1:239-43.
Hahn KM, Johnson PH, Gordon N, et al. Cancer 2006; 107:1219-26.
Hodgson DC, Pintilie M, Gitterman L, et al. Hematol Oncol 2006; 25:11-5.
Liu MI, Hutson JM. BJU Int 2000; 86:107-12.
Menegola E, Broccia ML, Renzo FD. Teratog Carcinog Mutagen 2001; 21:283-93.
Merei JM. Pediatr Surg Int 2002; 18:36-9.
Merei JM, Hasthorpe S, Hutson JM. Eur J Pediatr Surg 2002; 12:3-7.
Meyer-Wittkopf M, Barth H, Emons G, Schmidt S. Ultrasound Obstet Gynecol 2001; 18:62-6.

Summary

Pregnancy Category: D
Lactation Category: S (likely)

- **Doxorubicin** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.
- Successful pregnancies are the norm despite chemotherapy.

Doxycycline—(Doxy; Doxy-100; Doxychel; Doxycycline Hyclate; Monodox; Vibramycin; Vibra-Tabs)

International Brand Name—Amermycin (Thailand); Atrax (Philippines); Azudoxat (Germany); Bactidox (Germany); Banndoclin (Indonesia); Basedillin (Japan); Bassado (Italy); Biocolyn (Philippines); Biodoxi (India); Bronmycin (Malaysia); Cloran (Korea); Cyclidox (South Africa); Dagracycline (Netherlands); Dentistar (Korea); Deoxymykoin (Czech Republic); Doinmycin (Taiwan); Doryx (China, New Zealand, Singapore); Dosil (Spain); Dotur (Costa Rica, Dominican Republic, El Salvador, Guatemala, Honduras, Nicaragua, Panama); Doxaciclin (Japan); Doxibiotic (Israel); Doxilin (Singapore); Doximed (Finland); Doximycin (Czech Republic, Finland); Doxin (Indonesia, Philippines, Thailand); Doxine (New Zealand, Singapore); Doxi-Sergo (Spain); Doxsig (Australia); Doxy-1 (India); Doxycin (Canada); Doxycline (Thailand); Doxycycline (Belgium); Doxylin (Israel, Norway, Thailand); Doxymycin (Netherlands, South Africa, Taiwan); Doxytec (Canada); Doxytrim (Israel); Dumoxin (Denmark, Finland, Indonesia, Netherlands, Norway, Thailand); Esdoxin (Japan); Etidoxina (Colombia); Gewacyclin (Austria); Granudoxy (France); Ibralene (Philippines); Idocyklin (Sweden); Interdoxin (Indonesia); Lydox (India); Magdrin (Japan); Medomycin (Hong Kong, Malaysia, Taiwan, Thailand); Miraclin (Italy); Monocin (Korea); Monodox (Colombia); Paldomycin (Japan); Periostat (England, Ireland, Israel); Remycin (Taiwan); Roximycin (Japan); Serodoxy (Korea); Servidoxine (Ecuador); Servidoxyne (Malaysia, Philippines, Thailand); Siadocin (Thailand); Siclidon (Indonesia); Sigadoxin (Austria, Portugal, Switzerland); Supracyclin (Austria, Switzerland); Supramycina (Ecuador); Tolexine (France); Tolexine Ge (France); Torymycin (Thailand); Tsurupioxin (Japan); Veemycin (Thailand); Viadoxin (Indonesia); Vibrabiotic (Greece); Vibracina (Spain); Vibradox (Denmark, Portugal); Vibramicina (Argentina, Colombia, Costa Rica, Dominican Republic, Ecuador, El Salvador, Guatemala, Honduras, Mexico, Nicaragua, Panama, Peru, Portugal); Vibramycine (Belgium, France); Vibramycin-N (Korea); Vibra-S (Netherlands); Vibratab (Hungary); Vibra-Tabs (Australia, Canada, Finland); Vibraveineuse (France); Vibravenos (Germany); Vibravenos SF (Israel); Viradoxyl-N (Korea); Wanmycin (Hong Kong, Malaysia); Zadorin (Costa Rica, Dominican Republic, Ecuador, El Salvador, Guatemala, Honduras, Hong Kong, Nicaragua, Panama)

Drug Class	Antibiotics; Tetracyclines
Indications	Gonorrhea, *Chlamydia*, PID, malaria, Lyme disease, anthrax
Mechanism	Bacteriostatic—inhibits protein synthesis
Dosage with Qualifiers	Gonorrhea, uncomplicated—100mg PO bid ×7d; for complicated, use in combination with another agent such as **ceftriaxone, cefixime,** or **ciprofloxacin** (if not pregnant or breastfeeding) *Chlamydia*—100mg PO bid ×7d PID—100mg PO bid ×10-14d with another agent such as **ceftriaxone** 250mg IM Malaria—100mg PO qd beginning 1-2d before departure and continuing through 4w after exposure Lyme disease—100mg PO bid ×14-21d (28d if associated with arthritis) Anthrax—100mg IV/PO q12h; postexposure, 100mg PO q12h for 60d or until disease excluded *NOTE: **doxycycline** is the first choice for pregnant women infected with anthrax.* • **Contraindications**—hypersensitivity to drug or class, pregnancy (see **Tetracycline**) • **Caution**—hepatic or renal dysfunction (see **Tetracycline**)
Maternal Considerations	**Doxycycline** is synthetically derived from oxytetracycline (see **Tetracycline**). ***Side effects*** include neutropenia, thrombocytopenia, hepatotoxicity, pseudomembranous colitis, anorexia, epigastric distress, N/V, diarrhea, stomatitis, glossitis, black hairy tongue, dysphagia, hoarseness, renal toxicity, dizziness, headache, and teeth discoloration (see **Tetracycline**).
Fetal Considerations	Use of tetracyclines during tooth development (3rd trimester, infancy, and in children <8y) may cause permanent discoloration of the teeth (see **Tetracycline**).

Breastfeeding Safety	See **Tetracycline**.
Drug Interactions	Patients on anticoagulant therapy may require downward adjustment of their anticoagulant dose as other tetracyclines can depress plasma prothrombin activity. It is advisable to avoid tetracyclines in conjunction with penicillin as bacteriostatic drugs may interfere with the bactericidal action of penicillin. Absorption of tetracyclines is impaired by antacids containing aluminum, calcium, or magnesium, and iron-containing preparations. Absorption of **tetracycline** is impaired by **bismuth.** Barbiturates, **carbamazepine,** and **phenytoin** decrease the half-life of **doxycycline.** The concurrent use of **tetracycline** and **methoxyflurane** is reported to cause fatal renal toxicity. Concurrent use of **tetracycline** may render oral contraceptives less effective.
References	See **Tetracycline**.
Summary	**Pregnancy Category: D** **Lactation Category: NS** • See **Tetracycline.**

Dronabinol—(Marinol)

International Brand Name—Marinol (Canada)

Drug Class	Antiemetics
Indications	N/V associated with chemotherapy, AIDS-related anorexia
Mechanism	Activates cannabinoid receptors
Dosage with Qualifiers	N/V (post-chemo)—5mg/m^2 PO ×1 1-3h before first dose of chemo; max 4-6×/d Anorexia (AIDS)—2.5mg PO bid; max 20mg qd • **Contraindications**—hypersensitivity to drug or class • **Caution**—schizophrenia
Maternal Considerations	There are no adequate reports or well-controlled studies of **dronabinol** in pregnant women. Several publications suggest a relationship between cannabis use and head and neck cancers in a dose-response manner for frequency and duration of use. Interaction was observed with cigarette smoking and alcohol use. ***Side effects*** include anxiety, euphoria, dizziness, dry mouth, mood disturbances, ataxia, paranoia, orthostatic hypotension, tachycardia, hallucinations, palpitations, tachycardia, facial flush, and conjunctivitis.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **dronabinol** crosses the human placenta. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically.

Breastfeeding Safety

There is no published experience in nursing women. It is unknown whether **dronabinol** enters human breast milk. Breastfeeding is contraindicated in HIV-infected nursing women where formula is available to reduce the risk of neonatal transmission.

Drug Interactions

Cannabinoids may interact with other medications through both metabolic and pharmacodynamic mechanisms. **Dronabinol** is highly protein bound and therefore might displace other protein-bound drugs. Practitioners should monitor patients for a change in dose requirements when administering **dronabinol** to patients receiving other, highly protein-bound drugs.
Amphetamines, **cocaine,** and other sympathomimetic agents may produce an additive hypertension, tachycardia, and possibly cardiotoxicity.
Atropine, scopolamine, antihistamines, and other anticholinergic agents may result in additive or super-additive tachycardia, and drowsiness.
Amitriptyline, amoxapine, desipramine, and other TCAs may cause additive tachycardia, hypertension, and drowsiness.
Barbiturates, benzodiazepines, ethanol, **lithium,** opioids, **buspirone,** antihistamines, muscle relaxants, and other CNS depressants may cause additive drowsiness and CNS depression.

References

Carriot F, Sasco AJ. Rev Epidemiol Sante Publique 2000; 48:473-83.
Doyle E, Spence AA. Br J Anaesth 1995; 74:359-61.
Lee MJ. Obstet Gynecol Clin North Am 1998; 25:65-83.
Reiter GS. AIDS Clin Care 1996; 8:89-91, 93, 96.

Summary

Pregnancy Category: B
Lactation Category: U

- **Dronabinol** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.
- There are alternative agents for which there is more experience during pregnancy and lactation.

Droperidol—(Inapsine)

International Brand Name—Dehidrobenzoperidol (Portugal, Spain); Dehydrobenzperidol (Austria, Belgium, Czech Republic, Denmark, Finland, Germany, Israel, Mexico, Netherlands, Switzerland, Taiwan, Thailand, Turkey); Droleptan (England, France, Israel); Droperol (India); Inapsin (South Africa); Sintodian (Italy)

Drug Class

Anesthetics, adjunct; Antivertigo; Anxiolytics; Sedatives

Indications

Perioperative N/V

Mechanism

Unknown; antagonizes dopamine and α-adrenergic receptors

Dosage with Qualifiers

N/V (perioperative)—0.625-1.25mg IM/IV q3-4h prn

- **Contraindications**—hypersensitivity to drug or class, prolonged QT interval
- **Caution**—history of reaction to other drugs causing tardive dyskinesia, hypotension, CNS depression, CHF, bradycardia, diuretics, hypokalemia, hypomagnesemia, hepatic or renal dysfunction, and alcohol abuse

Maternal Considerations

There are no adequate reports or well-controlled studies of **droperidol** in pregnant women. It has been used in emergency

rooms for the acute management of migraine headache with success similar to **meperidine. Droperidol, propofol,** and **alizapride,** in decreasing order of effectiveness for the doses used in this study, reduced the incidence of pruritus induced by the use of intrathecal **morphine.** In addition, **droperidol** reduces N/V after epidural **morphine** similar in efficacy to **dexamethasone.** The addition of **metoclopramide** appears to enhance its efficacy. In one study, it was inferior to **granisetron** after cesarean section. There is a black box warning currently issued by the FDA based on reports of prolonged QT–associated dysrhythmia. However, the dozens of cases reported to the FDA were in fact multiple reports of 3 cases. ***Side effects*** include tardive dyskinesia (treat with **diphenhydramine** or **benztropine**), arrhythmia, hypotension, prolonged QT interval, bronchospasm, laryngospasm, delirium, drowsiness, chills, anxiety, nightmares, fever, and hypertension.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **droperidol** crosses the human placenta. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically. Neonatal mortality was increased perhaps because of maternal neglect.

Breastfeeding Safety

There is no published experience in nursing women. It is unknown whether **droperidol** enters human breast milk. However, considering the indications, its short-term use is unlikely to pose a significant risk to the breastfeeding neonate.

Drug Interactions

Any drug with the potential to prolong the QT interval should not be used with **droperidol.** Possible pharmacodynamic interactions can occur between **droperidol** and class I or III antiarrhythmics, antihistamines that prolong the QT interval, antimalarials, calcium channel blockers, neuroleptics that prolong the QT interval, and antidepressants.

Caution is indicated using drugs known to induce hypokalemia or hypomagnesemia as they may precipitate QT prolongation. These include diuretics, laxatives, and supraphysiologic use of steroid hormones with mineralocorticoid potential.

Other CNS-depressant drugs (e.g., barbiturates, tranquilizers, opioids, and general anesthetics) have additive or potentiating effects. When patients have received such drugs, the dose of **droperidol** must be reduced. After the administration of **droperidol,** the dose of other CNS-depressant drugs should also be reduced.

References

Bailey P, Norton R, Karan S. Anesthesiology 2002; 97:288-9.

Fujii Y, Tanaka H, Toyooka H. Acta Anaesthesiol Scand 1998; 42:921-5.

Gan TJ, White PF, Scuderi PE, et al. Anesthesiology 2002; 97:287.

Horta ML, Morejon LC, da Cruz AW, et al. Br J Anaesth 2006; 96:796-800.

Richman PB, Allegra J, Eskin B, et al. Am J Emerg Med 2002; 20:39-42.

Tzeng JI, Wang JJ, Ho ST, et al. Br J Anaesth 2000; 85:865-8.

Summary

Pregnancy Category: C
Lactation Category: S (likely)

- **Droperidol** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.
- **Droperidol** has long been a cheap and effective antiemetic used for prophylaxis at cesarean section, though rescue therapy may not be as effective as the 5-HT_3 blockers such as **ondansetron** or **granisetron.**

Econazole nitrate—(Spectazole)

International Brand Name—Amicel (Italy); Bismultin (Greece); Derma-Coryl (Israel); Dermazole (Australia, Hong Kong, Singapore); Ecanol (India); Econ (Thailand); Econite (Hong Kong); Ecosone (Hong Kong); Ecostatin (Canada, England, Ireland, New Zealand); Ecotam (Spain); Ecreme (New Zealand); Epi-Pevaryl (Germany); Fongeryl (France); Fungazol (Korea); Gyno-Coryl (Israel); Micolak (Mexico); Micolis (Argentina, Chile, Ecuador, Paraguay, Peru, Uruguay); Micos (Italy); Micostyl (Brazil, Mexico); Palavale (Japan); Penicomb (Greece); Pevaryl (Bahrain, Cyprus, Egypt, Germany, Greece, Hong Kong, Ireland, Jordan, Malaysia, New Zealand, Philippines, Poland, Slovenia, Sudan, Turkey, Venezuela)

Drug Class ..... Antifungals; Dermatologics

Indications ..... Tinea and cutaneous candidiasis

Mechanism ..... An imidazole derivative that changes fungal cell wall permeability.

Dosage with Qualifiers .....

Tinea—apply cream to affected area qd
Cutaneous candidiasis—apply cream to affected area bid

- **Contraindications**—hypersensitivity
- **Caution**—unknown

Maternal Considerations .....

Econazole has been used for the treatment of *Candida* vaginitis with success somewhat inferior to **clotrimazole.** Systemic absorption of **econazole** is extremely low. There are no adequate reports or well-controlled studies of **econazole** in pregnant women. However, it was effective *in vitro* using samples obtained from pregnant women. **Econazole** prolongs pregnancy in rats when given orally.
Side effects include burning, itching, redness, and rash.

Fetal Considerations .....

There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **econazole** crosses the human placenta. One epidemiologic study of women using vaginally administered **econazole** is reassuring. Considering the dose and route, it is unlikely the maternal systemic concentration will reach a clinically relevant level. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically. Embryotoxic effects were noted in rodents after oral administration of 10-40× the MRHD.

Breastfeeding Safety .....

There is no published experience in nursing women. It is unknown whether **econazole** enters human breast milk. It is present in rodent breast milk after high oral doses. Considering the indication, dosing, and route, it seems unlikely to pose a clinically significant risk to the breastfeeding neonate.

Drug Interactions ..... No clinically significant interactions identified.

References .....

Czeizel AE, Kazy Z, Vargha P. Eur J Obstet Gynecol Reprod Biol 2003; 111:135-40.
Guaschino S, Michelone G, Stola E, et al. Biol Res Pregnancy Perinatol 1986; 7:20-2.

Summary .....

Pregnancy Category: C
Lactation Category: S (likely)

- There are other antifungal agents with higher clinical efficacy and more experience during pregnancy.

Edrophonium—(Enlon; Reversol; Tensilon)

International Brand Name—Enlon (Canada)

Drug Class	Cholinesterase inhibitors; Musculoskeletal agents
Indications	Diagnosis of myasthenia gravis, anesthesia adjunct
Mechanism	Parasympathetic, cholinesterase inhibitor
Dosage with Qualifiers	Myasthenia gravis, diagnosis—2mg IV test dose over 15-30sec; if no response after 1min, repeat with 8mg. If a reaction, halt infusion and administer atropine 0.5mg IV Anesthesia, adjunct—reversal of nondepolarizing neuromuscular blockade: 500mcg/kg IV given 1min after atropine 0.02mg/kg IV push • **Contraindications**—hypersensitivity, intestinal obstruction • **Caution**—asthma, arrhythmia
Maternal Considerations	**Edrophonium** is a short- and rapid-acting cholinergic drug. There are no adequate reports or well-controlled studies of **edrophonium** in pregnant women. Older literature suggests anticholinesterases may trigger preterm labor. ***Side effects*** include severe cholinergic reaction, arrhythmias, respiratory paralysis, diplopia, tearing, seizures, dysphagia, dysarthria, dysphonia, hypotension, diarrhea, and abdominal pain.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **edrophonium** crosses the human placenta; the chemical structure suggests it will not. There are no reports of either fetal toxicity or teratogenicity. Rodent teratogenicity studies apparently have not been performed.
Breastfeeding Safety	There is no published experience in nursing women. It is unknown whether **edrophonium** enters human breast milk. The chemical structure suggests it will not be excreted into the breast milk. Considering the indication, one-time **edrophonium** use is unlikely to pose a clinically significant risk to the breastfeeding neonate.
Drug Interactions	May trigger a cholinergic crisis if combined with cholinergic drugs. **Aspirin** and or **dipyridamole** may decrease cholinesterase inhibitory activity. β-Blockers may increase the risk of an arrhythmia (heart block). Will prolong the duration of neuromuscular blockade from **succinylcholine.** Avoid **atropine**-like agents if there is a prolongation of the QT time. Aminoglycosides may decrease muscle stimulating efficacy.
References	Drachman DB. N Engl J Med 1978; 298:186-93.
Summary	**Pregnancy Category: C** **Lactation Category: S** (likely) • **Edrophonium** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Efavirenz—(Sustiva)

International Brand Name—Efavir (India); Filginase (Argentina); Stocrin (Colombia, Hong Kong, Israel, Mexico, Peru, Singapore, South Africa, Taiwan, Thailand); Sustiva (Canada); Virorrever (Argentina)

Drug Class	Antivirals; Non-nucleoside reverse transcriptase inhibitors
Indications	HIV infection
Mechanism	NNRTI
Dosage with Qualifiers	HIV—600mg PO qd • **Contraindications**—hypersensitivity • **Caution**—hepatic dysfunction, **cisapride** use, **triazolam** use, **midazolam** use, **astemizole** use
Maternal Considerations	There are no adequate reports or well-controlled studies of **efavirenz** in pregnant women. However, there are several case series of HIV-infected women who have conceived while taking **efavirenz.** It is common practice to switch women on **efavirenz** to another NNRTI. The vast majority of these pregnancies are unintended, stressing the importance of contraceptive counseling. Hepatotoxicity may be more common during pregnancy. Perhaps the most relevant consideration when initiating a pregnant woman on an NNRTI is whether normally tolerated side effects will be magnified by pregnancy. ***Side effects*** include Stevens-Johnson syndrome, dermatitis, erythema multiforme, rash, drowsiness, insomnia, abnormal dreams, hyperlipidemia, diarrhea, N/V, fever, and hepatic dysfunction.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. **Efavirenz** crosses the placenta, achieving an F:M ratio approximating unity. Its use has been associated with CNS malformations in monkey fetuses at doses that approximate those in humans, and with NTDs in exposed human fetuses. These studies led to a reclassification of the drug to category D. Rodent studies reveal an increased frequency of reabsorptions.
Breastfeeding Safety	**Efavirenz** enters human breast milk. In one study with a mean **efavirenz** maternal plasma concentration of 6.6 mg/L, the milk concentration was 3.5 mg/L and the infant plasma level was 0.9 mg/L. Breastfeeding is generally contraindicated in HIV-infected women where formula is available to reduce the risk of neonatal transmission. However, none of the children studied became infected while breastfeeding. **Efavirenz** is excreted in the breast milk of rats.
Drug Interactions	**Efavirenz** is a CYP3A4 inducer. Thus, substrates of CYP3A4 may have lower than normal plasma concentrations when used in tandem. It also inhibits CYP2C9, 2C19, and 3A4. Co-administration of drugs primarily metabolized by these isozymes may result in altered plasma concentrations of the co-administered drug, necessitating dose adjustments. Drugs inducers of CYP3A4 (e.g., **phenobarbital, rifampin, rifabutin**) may increase **efavirenz** clearance and lower plasma concentrations. **Astemizole, midazolam, triazolam, cisapride,** ergot deriviatives, and **voriconazole** should not be administered with **efavirenz.** **Efavirenz** may decrease concentrations of atazanavir, **clarithromycin, indinavir, lopinavir, methadone, saquinavir,** and **sertraline.**

Saquinavir should not be used as sole protease inhibitor in combination with **efavirenz.**
Ritonavir increases the **efavirenz** concentration. The combination results in a higher frequency of adverse clinical affects (e.g., dizziness, nausea, paresthesia) and laboratory abnormalities (elevated liver enzymes).

References

Bussmann H, Wester CW, Wester CN, et al. J Acquir Immune Defic Syndr 2007; 45:269-73.
Cadman J. GMHC Treat Issues 1998; 12:12.
De Santis M, Carducci B, De Santis L, et al. Arch Intern Med 2002; 162:355.
Floridia M, Tamburrini E, Ravizza M, et al; The Italian Group on Surveillance on Antiretroviral Treatment in Pregnancy. Antivir Ther 2006; 11:941-6.
Fundaro C, Genovese O, Rendeli C, et al. AIDS 2002; 16:299-300.
Hill JB, Sheffield JS, Zeeman GG, Wendel GD Jr. Obstet Gynecol 2001; 98:909-11.
Schneider S, Peltier A, Gras A, et al. J Acquir Immune Defic Syndr 2008; 48:450-4.
Taylor GP, Low-Beer N. Drug Saf 2001; 24:683-702.

Summary

Pregnancy Category: D (reclassified from category C in 2004)
Lactation Category: S (possibly)

- The goal of HIV treatment during pregnancy is achievement and maintenance of a zero viral load.
- The early experience with **efavirenz** during pregnancy is concerning; it is likely a human teratogen.
- **Efavirenz** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.
- There are alternative agents for which there is more experience during pregnancy and lactation.
- Physicians are encouraged to register pregnant women under the Antiretroviral Pregnancy Registry (1-800-258-4263) for a better follow-up of the outcome while under treatment with **efavirenz.**

Eletriptan—(Relpax)

International Brand Name—Relert (Costa Rica, Dominican Republic, El Salvador, Guatemala, Honduras, Israel, Nicaragua, Panama); Relpax (England, France, Ireland, Mexico)

Drug Class

Serotonin receptor agonists

Indications

Migraine headache, acute

Mechanism

Binds with high affinity to 5-HT_{1B}, 5-HT_{1D}, and 5-HT_{1F} receptors, causing cranial vessel constriction

Dosage with Qualifiers

Migraine headache, acute—20-40mg PO ×1; may repeat q2h ×1 if recurs; max 80mg/24h

- **Contraindications**—hypersensitivity to drug or class, uncontrolled hypertension, cerebrovascular disease, ischemic heart disease, coronary spasm, basilar or hemiplegic migraines, PVD, ischemic bowel, 5-HT_1 agonist or ergot use <24h, CYP3A4 inhibitor use <7d
- **Caution**—cardiac risk factors

Maternal Considerations

Migraine is a paroxysmal disorder with attacks of headache, N/V, photo- and phonophobia, and malaise. There is no published experience with **eletriptan** during pregnancy.
Side effects include hypertensive crisis, MI, coronary spasm, ventricular arrhythmias, CVA, peripheral vascular ischemia, bowel ischemia, N/V, cramping, dyspepsia, dysphagia, somnolence, headache, paresthesias, and chest or jaw or neck pain or pressure.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **eletriptan** crosses the human placenta. In mice and rabbits, **eletriptan** at 6-12× the MRHD during organogenesis is associated with IUGR and skeletal abnormalities.

Breastfeeding Safety

According to the manufacturer, **eletriptan** is excreted in human breast milk. The mean total amount of **eletriptan** in breast milk after a single 80mg dose over 24h approximated 0.02% of the administered dose. The M:P ratio was 1:4, but showed great variability. The resulting **eletriptan** concentration-time profile is similar to plasma, with very low concentrations of drug present in the milk 18-24h after ingestion (mean, 1.7 ng/ml).

Drug Interactions

Eletriptan is metabolized primarily by CYP3A4.
Ergot-containing drugs (e.g., **dihydroergotamine, methysergide**) are reported to cause prolonged vasospastic reactions that may be additive. Use of ergot-type medications within 24h of **eletriptan** is not recommended
Propranolol increases both the C_{max} and AUC by 10% and 33%, respectively.
Use of other 5-HT_1 agonists within 24h of **eletriptan** is not recommended.

References

There is no published experience in pregnancy or during lactation.

Summary

Pregnancy Category: C
Lactation Category: S (likely)

- **Eletriptan** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.
- There are alternative agents with a more reassuring safety profile.

Enalapril—(Vasotec)

International Brand Name—Acetec (Malaysia); Acetensil (Spain); Alapren (South Africa); Alphapril (Australia); Alphrin (Korea); Analept (Bulgaria, Greece); Anapril (Hong Kong, Singapore); Antens (Korea); Auspril (Australia); Bajaten (Chile); Beartec (Korea); Benalipril (Germany); Biocronil (Colombia); BQL (India, South Africa); Cardiopril (Peru); Controlvas (Spain); Converten (India); Convertin (Israel); Corprilor (Singapore); Elfonal (Korea); EnaABZ (Germany); Enahexal (New Zealand); Enaladil (Mexico); Enalagamma (Germany); Enalapril (Germany, Spain); Enaldun (Hong Kong); Enalin (Korea); Enaloc (Finland); Enalpapril (Israel); Enam (China); Enap (Singapore); Enapren (Italy); Enapril (Thailand); Enaprin (Korea); Enaril (Korea, Thailand); Enetil (Colombia); Enpril (Korea); Envas (India); Erotec (Korea); Etron (Korea); Glioten (Brazil, Chile, Colombia, Costa Rica, Dominican Republic, Ecuador, El Salvador, Guatemala, Honduras, Mexico, Nicaragua, Panama, Paraguay, Peru); Hipertal (Philippines); Hypace (Philippines, South Africa); Hytrol (India); Innovace (England, Ireland); Inoprilat (Indonesia); Invoril (China, India, Malaysia, Singapore, South Africa, Thailand); Kenopril (Mexico); Lapril (Thailand); Lenipril (Korea); Lepril (Korea); Lotrial (Argentina, Costa Rica, Dominican Republic, Ecuador, El Salvador, Guatemala, Honduras, Nicaragua, Panama, Peru); Lowtril (Korea); Malepril (Korea); Meipril (Indonesia); Naprilene (Italy); Naritec (Korea, Thailand); Nuril (India); Pharmapress (Hong Kong); Pres (Germany); Presil (Colombia); Renallapin (Korea); Renaton (Korea); Renavace (Japan); Renitec (Argentina, Austria, Belgium, Brazil, Bulgaria, China, Colombia, Czech Republic, Denmark, Ecuador, Egypt, Finland, France, Greece, Hong Kong, Hungary, Malaysia, Mexico, Netherlands, New Zealand, Norway, Peru, Philippines, Poland, Portugal, South Africa, Spain, Sweden, Taiwan, Thailand, Turkey, Venezuela); Renitek (Russia); Reniten (Switzerland); Renivace (Indonesia); Repantril (Indonesia); Sintec (Taiwan); Tenace (Indonesia); Unaril (Taiwan); Unipril (Colombia); Vasopress (Philippines); Vasotec (Canada); Xanef (Germany)

Drug Class	ACEI/A2R-antagonists
Indications	Hypertension, CHF, MI, nephropathy
Mechanism	ACEI
Dosage with Qualifiers	Hypertension—begin 5mg PO qd (max 40mg qd); alternatively 0.625-1.25mg IV, then up to 5mg IV q6h CHF—begin 2.5mg PO qd (max 40mg qd) MI—begin 2.5mg PO qd (max 40mg qd), quickly titrate dose up Nephropathy—5-20mg PO qd *NOTE: also combined with either **hydrochlorothiazide** or **felodipine.*** • **Contraindications**—hypersensitivity, renal artery stenosis • **Caution**—renal dysfunction, hypovolemia, severe CHF, collagen vascular disease
Maternal Considerations	There are no adequate reports or well-controlled studies of **enalapril** in pregnant women. It is generally well tolerated, and pregnancy does not alter dosing. However, **enalapril** should be discontinued immediately when discovered during pregnancy and replaced with another suitable hypotensive agent to prevent or minimize the fetal risks. ***Side effects*** include angioedema, hypotension, renal failure, hyperkalemia, hepatotoxicity, neutropenia, pancreatitis, dizziness, N/V, fatigue, dyspepsia, rash, urticaria, and myalgia.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. **Enalapril** crosses the human placenta, but does not equilibrate, even after 6h, at least in the isolated perfused model. Relative to laboratory-tested species, the human fetus has higher vulnerability to **enalapril** and other ACEIs, exhibiting a syndrome not seen in experimental animals because humans develop these systems prior to calvarial ossification at the end of 1st trimester. Exposure to agents that interfere with angiotensin actions are associated with cranial hypoplasia, anuria, reversible or irreversible renal failure, death, oligohydramnios, prematurity, IUGR, and patent ductus arteriosus, even in the 1st trimester. Longterm renal disease is reported in survivors. **Enalapril** produces fetal hypotension in rhesus macaques.

Breastfeeding Safety

There are no adequate reports or well-controlled studies in nursing women. Trace amounts of **enalapril** are detected in breast milk, though the kinetics remain to be elucidated. Until further study, the infant should be monitored for possible adverse effects, the drug given at the lowest effective dose, and breastfeeding avoided at times of peak drug levels if breastfeeding continues.

Drug Interactions

Diuretics, especially if recently begun, may be associated with hypotension after initiation of **enalapril**. The possibility can be minimized by volume loading, discontinuing the diuretic, or increasing salt intake before **enalapril**.

The antihypertensive effect appears augmented by agents that release renin (e.g., diuretics).

NSAIDs may in patients with preexisting renal disease cause a further decline that is usually reversible if **enalapril** is discontinued.

Attenuates potassium loss caused by thiazide-type diuretics when given IV. Potassium-sparing diuretics (e.g., **spironolactone, triamterene, amiloride**), potassium supplements, or potassium-containing salt substitutes may cause significant increases in the serum potassium, and should be used with caution.

Lithium toxicity has been reported in patients receiving ACEIs, including **enalapril.** Serum **lithium** levels be monitored frequently.

References

Burrows RF, Burrows EA. Aust N Z J Obstet Gynaecol 1998; 38:306-11.

Ducsay CA, Umezaki H, Kaushal KM, et al. Am J Obstet Gynecol 1996; 175:50-5.

Miller RK, Jessee L, Barrish A, et al. Teratology 1998; 58:76-81.

Redman CW, Kelly JG, Cooper WD. Eur J Clin Pharmacol 1990; 38:99.

Tabacova S. Crit Rev Toxicol 2005; 35:747-55.

Tabacova S, Little R, Tsong Y, et al. Pharmacoepidemiol Drug Saf 2003; 12:633-46.

Summary

Pregnancy Category: C (1st trimester), **D** (2nd and 3rd trimesters)

Lactation Category: S (likely)

- **Enalapril** and other inhibitors of angiotensin's actions should be avoided during pregnancy if possible.
- There are alternative agents for which there is more experience during pregnancy and lactation.
- When the mother's disease requires treatment with **enalapril,** the lowest doses should be used followed by close monitoring of the fetus.

Encainide

International Brand Name—None identified.

Drug Class	Antiarrhythmics, class I
Indications	Ventricular arrhythmias
Mechanism	Stabilizes membrane charge by depressing the phase 0 action potential
Dosage with Qualifiers	Ventricular arrhythmia (maternal or fetal)—10-50mg PO qid • **Contraindications**—hypersensitivity, cardiogenic shock, AV block (partial or complete) • **Caution**—heart failure, hepatic or renal dysfunction, prolonged QT interval
Maternal Considerations	**Encainide** was voluntarily removed from the market in 1991 but remains available for patients with certain life-threatening arrhythmias. There are no adequate reports or well-controlled studies of **encainide** in pregnant women. There is only a single case report of **encainide** use for a maternal arrhythmia. ***Side effects*** include cardiac arrest, CHF, arrhythmia, dizziness, blurred vision, headache, tremor, fatigue, palpitations, asthenia, tremor, constipation, edema, and abdominal pain.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **encainide** crosses the human placenta. A related drug, **flecainide,** does cross the human placenta and reaches therapeutic levels in the fetus. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically.
Breastfeeding Safety	There is no published experience in nursing women. **Encainide** enters human breast milk, though its kinetics remains to be detailed. **Flecainide** is excreted at low levels and is generally considered safe during breastfeeding.
Drug Interactions	See **Flecainide.**
References	Fagih B, Sami M. Can J Cardiol 1999; 15:113-7.
Summary	**Pregnancy Category: C** **Lactation Category: U** • **Encainide** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk. • There are other, similar agents for which there is greater experience regarding use during pregnancy

Enoxacin—(Penetrex)

International Brand Name—None identified.

Drug Class	Antibiotics; Quinolones
Indications	UTI, uncomplicated gonorrhea
Mechanism	Bactericidal by inhibition of DNA gyrase
Dosage with Qualifiers	UTI, uncomplicated—200mg PO bid ×7d (avoid meals) UTI, complicated—400mg PO bid ×14d (avoid meals) Gonorrhea, uncomplicated—400mg PO ×1 • **Contraindications**—hypersensitivity • **Caution**—pregnancy, lactation, renal or hepatic dysfunction, seizure disorder, diabetes mellitus, sun exposure
Maternal Considerations	There are no published reports of **enoxacin** use during pregnancy. It is a broad-spectrum agent with high oral absorption. It is not effective for the treatment of syphilis. ***Side effects*** include anaphylaxis, phototoxicity, pseudomembranous colitis, seizures, psychoses, N/V, diarrhea, dyspepsia, light-headedness, pruritus, rash, arthralgia, and tendon rupture.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **enoxacin** crosses the human placenta. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically. Adverse effects were associated with maternal toxicity. As a class, the new quinolones do not appear associated with an increased risk of malformation or musculoskeletal problems in humans. Longer follow-up and MRI of the joints may be warranted to exclude subtle cartilage and bone damage. There are no clinically significant musculoskeletal dysfunctions reported in children exposed to other fluoroquinolones *in utero.*
Breastfeeding Safety	There is no published experience in nursing women. It is unknown whether **enoxacin** enters human breast milk. It does enter rodent milk, and other quinolone-type drugs are excreted into human breast milk. In some animals, slow elimination of a related agent, **ciprofloxacin,** results in blood levels out of proportion to the dose ingested. Because of the potential for some quinolones to cause arthropathy in juvenile animals, they should be avoided in pregnant and lactating women until more information is available.
Drug Interactions	See **Ciprofloxacin.**
References	There is no published experience in pregnancy or during lactation.
Summary	**Pregnancy Category: C** **Lactation Category: NS** (possibly) • **Enoxacin** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk. • There are alternative agents for which there is more experience during pregnancy and lactation.

Enoxaparin—(Lovenox)

International Brand Name—Aerotina (Argentina); Clexane (Belgium, Bulgaria, China, Czech Republic, England, Germany, Greece, Hong Kong, Hungary, India, Ireland, Israel, Italy, Korea, Malaysia, Netherlands, Paraguay, Philippines, Poland, Russia, Spain, Switzerland, Turkey, Uruguay, Venezuela); Clexane 40 (South Africa); Clexane Forte (Israel); Klexane (Canada, Denmark, Finland, Norway, Sweden); Lovenox (Austria, Canada, France, Indonesia, Portugal)

Drug Class ..... Anticoagulants; Low-molecular-weight heparins

Indications ..... Prevention and treatment of venous thrombosis in the maternal or placental circulations

Mechanism ..... Binds ATIII, accelerates inhibition of factor Xa

Dosage with Qualifiers .....

DVT prophylaxis (episode within 12mo of pregnancy, no thrombophilia)—begin at 20-40mg SC qd
DVT prophylaxis (associated with thrombophilia)—depends on the thrombophilia and medical history. Consult a specialty text such as *High Risk Pregnancy: Management Options.*
Antiphospholipid syndrome—begin at 20-40mg SC qd
Cesarean section—at least 40mg SC qd until patient is active
Treatment of acute thrombosis—1-1.5mg/kg SC q12h

NOTE: target for anti-Xa activity depends on indication and laboratory test used.
NOTE: does not significantly influence bleeding time, PT, or PTT.
NOTE: manufacturer has specifically sought to discourage its use during pregnancy.

- **Contraindications**—hypersensitivity, active bleeding, thrombocytopenia
- **Caution**—diabetic retinopathy, renal dysfunction

Maternal Considerations .....

The incidence of PE and DVT is higher in pregnant compared to nonpregnant patients, reaching a rate of 0.05-1% in all pregnancies, and as high as 3% after cesarean section. Pregnancy increases the clearance of both **heparin** and low-MW heparinoids such as **enoxaparin** requiring periodic monitoring throughout pregnancy (anti-Xa activity of 0.20-0.40U/ml for prophylaxis, and 0.4-0.7U/ml for full anticoagulation). The mean maximum dose required to achieve a therapeutic anti-Xa level at 5-6h after injection in one study was 38.1mg every 12h (range 30-75mg every 12h). The mean anti-Xa level was 0.28IU/ml (median 0.3, range 0.05-0.8IU/ml). The risk of osteoporosis is similar to unfractionated **heparin,** though the risk of thrombocytopenia may be lower. Acute thrombosis should be treated with therapeutic anticoagulation for the remainder of pregnancy and for at least 6w postpartum (a minimum of 3mo total).
One as-yet unconfirmed report suggests the addition of **enoxaparin** to the therapy of women with gestational hypertension may have a beneficial effect on uterine blood flow. **Enoxaparin** has also been used for prophylaxis during pregnancy in women with thrombophilia or mechanical heart valve or antiphospholipid syndrome. There have been multiple deaths of treated pregnant women with a mechanical heart valve, and the manufacturer specifically discourages its use for this indication. Women treated with LMWHs for prevention of thromboembolic complications are at risk of developing an epidural or spinal hematoma after neuraxial anesthesia. Unlike unfractionated **heparin, enoxaparin** is not predictably reversed with **protamine.** Preferably, LMWHs are replaced with unfractionated **heparin** at

36w. Otherwise, patients should be instructed to withhold their next injection once contractions begin, or 12h prior to a planned induction of labor. **Enoxaparin** should be discontinued 12-24h (depending on daily dose) before placement of neuraxial (epidural or spinal) anesthesia. **Enoxaparin** should not be (re)instituted until at least 12h after removal of an indwelling epidural catheter.
Side effects include epidural/spinal hematoma, thrombocytopenia, paralysis, CHF, pneumonia, anemia, hemorrhage, fever, injection site hematoma or bruising, hematuria, and elevated transaminases.

Fetal Considerations

Neither unfractionated nor fractionated **heparin** crosses the human placenta, and thus **enoxaparin** does not pose a direct risk to the human fetus. Epidemiologic studies are reassuring. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically.

Breastfeeding Safety

There are no adequate reports or well-controlled studies in nursing women. One investigation found no anti-Xa activity in the breast milk from a single patient. **Enoxaparin** is unlikely to cross in light of its high MW, and if it does cross and is ingested by the nursing newborn, it is likely to be degraded.

Drug Interactions

Agents that can enhance the risk of bleeding (e.g., anticoagulants; platelet inhibitors including **aspirin;** salicylates; NSAIDs, including **ketorolac; dipyridamole; sulfinpyrazone**) should be discontinued prior to beginning **enoxaparin.**

References

Backos M, Rai R, Baxter N, et al. Br J Obstet Gynaecol 1999; 106:102-7.
Bar J, Mashiah R, Cohen-Sacher B, et al. Thromb Res 2001; 101:235-41.
Carlin AJ, Farquharson RG, Quenby SM, et al. Hum Reprod 2004; 19:1211-4.
Casele H, Haney EI, James A, et al. Am J Obstet Gynecol 2006; 195:1109-13.
Casele HL, Laifer SA, Woelkers DA, Venkataramanan R. Am J Obstet Gynecol 1999; 181:1113-7.
Dimitrakakis C, Papageorgiou P, Papageorgiou I, et al. Haemostasis 2000; 30:243-8.
Huxtable LM, Tafreshi MJ, Ondreyco SM. Clin Appl Thromb Hemost. 2005;11:171-81.
James D, Steer P, Weiner CP, Gonik B (Eds.) High Risk Pregnancy: Management Options, 2nd ed. Philadelphia: WB Saunders, 2006.
Laurent P, Dussarat GV, Bonal J, et al. Drugs 2002; 62:463-77.
Lepercq J, Conard J, Borel-Derlon A, et al. BJOG 2001; 108:1134-40.
Rowan JA, McCowan LM, Raudkivi PJ, North RA. Am J Obstet Gynecol 2001; 185:633-7.
Torricelli M, Reis FM, Florio P, et al. Ultrasound Med Biol 2006; 32:1431-5.

Summary

Pregnancy Category: B
Lactation Category: S (likely)

- **Enoxaparin** is a more costly alternative to unfractionated **heparin** with likely equal efficacy and a similar risk of osteoporosis complicating long-term therapy.
- The dose of **enoxaparin** administered *must* be monitored periodically throughout pregnancy and puerperium by the measurement of anti-Xa activity to assure appropriate levels.

Ephedrine

International Brand Name—None identified.

Drug Class	Adrenergic agonists; Bronchodilators; Decongestants, nasal
Indications	Nasal decongestant, pressor support after epidural analgesia
Mechanism	Causes release of epinephrine and NE from nerve endings, resulting in mainly β-adrenergic stimulation; also a weak direct-acting vasopressor
Dosage with Qualifiers	Decongestant—25-50mg PO q6h (max 150mg/d) *NOTE: may be combined with* ***theophylline, pentobarbital,*** *or* ***potassium iodide.*** • **Contraindications**—hypersensitivity, thyroid toxicosis, porphyria, CAD, hypertension, use of an MAOI within 14d • **Caution**—glaucoma, arrhythmia, hyperthyroidism
Maternal Considerations	There are no adequate reports or well-controlled studies of **ephedrine** in pregnant women. When abused as a decongestant, **ephedrine** may exacerbate the hypertension associated with preeclampsia. There is a long clinical experience with the use of **ephedrine** during labor to treat hypotension associated with neuraxial anesthesia. It is considered the vasopressor of choice unless contraindicated by maternal condition (e.g., coexisting valvular stenosis) and is protective of the uterine circulation, perhaps through release of NO in the placental vessels. But while interventions such as colloids, **ephedrine, phenylephrine,** or lower leg compression reduce the incidence of hypotension, none has been shown to eliminate the need to treat maternal hypotension during spinal anesthesia for cesarean section. Women with preeclampsia are less likely to experience hypotension at the time of spinal anesthesia, and require significantly less **ephedrine** when they do. ***Side effects*** include arrhythmias, insomnia, nervousness, dizziness, and tachycardia.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. **Ephedrine** apparently crosses the placenta, though the kinetics remain to be elucidated. Rodent teratogenicity studies have not been conducted. The long clinical experience with the drug, both in OTC preparations and in the labor suite, is reassuring.
Breastfeeding Safety	There are no adequate reports or well-controlled studies in nursing women. **Ephedrine** is excreted and concentrated into breast milk, but <1% of the ingested dose is excreted. Thus, it is generally considered safe for breastfeeding women. However, a single dose of **pseudoephedrine** reduces 24h milk production by as much as 25%.
Drug Interactions	**Bromocriptine** may increase the risk of hypertension, stroke, and MI. **Cyclobenazaprine** may decrease the pressor effect. **Atomoxetine** may increase the pressor response. May decrease the hypoglycemic effect of insulin.
References	Aljazaf K, Hale TW, Ilett KF, et al. Br J Clin Pharmacol 2003; 56:18-24.

Aya AG, Vialles N, Tanoubi I, et al. Anesth Analg 2005; 101:869-75.
Cooper DW, Carpenter M, Mowbray P, et al. Anesthesiology 2002; 97:1582-90.
Cyna AM, Andrew M, Emmett RS, et al. Cochrane Database Syst Rev 2006; (4):CD002251.
Ducros L, Bonnin P, Cholley BP, et al. Anesthesiology 2002; 96:612-6.
Findlay JW, Butz RF, Sailstad JM, et al. Br J Clin Pharmacol 1984; 18:901-6.
Li P, Tong C, Eisenach JC. Anesth Analg 1996; 82:288-93.

Summary

Pregnancy Category: C
Lactation Category: S

- **Ephedrine** is commonly found in many OTC preparations.
- It is a popular agent for the treatment of hypotension associated with neuraxial anesthesia.

Epinephrine—(Adrenalin Chloride; Ana-Guard; Epifrin; EpiPen; Glaucon; Philip; Racepinephrine; Sus-Phrine)

International Brand Name—Adrenalin (Bulgaria, Canada, Finland, Norway, Sweden, Turkey); Adrenalina (Italy); Adrenalina Sintetica (Switzerland); Adrenaline (Greece, Russia); Adrenaline Aguettant (France); Adrenalini Bitarticas (Indonesia); Adrenalin Medihaler (Denmark, Finland); Ana-Guard (South Africa); Anapen (France); Bosmin (Taiwan); Epifrin (New Zealand); Epinefrina (Chile); Epipen (Canada, Israel, South Africa); Epipen Jr. 0.15mg Adrenaline Auto-Injector (Australia); Epipen Junior (Israel); Eppy (Bulgaria, Ireland, Italy, South Africa, Sweden); Eppy ''N'' (Israel); Eppystabil (Austria); Glaucon (Czech Republic); Glaufrin (Sweden); Isopto Epinal (Spain); L-Adrenalin (Austria); Medihaler-Iso (South Africa); Posumin (Taiwan); Simplene (England, Ireland, South Africa); Suprarenin (Austria); Weimer Adrenaline (Hong Kong, Philippines); Weradren (Philippines)

Drug Class

Adrenergic agonists; Bronchodilators; Inotropes; Ophthalmics; Pressors

Indications

Severe asthma, anaphylaxis, cardiac arrest

Mechanism

Potent activator of α- and β-adrenoceptors

Dosage with Qualifiers

Severe asthma—0.1-0.5mg SC q10-15min
Anaphylaxis—0.1-0.5mg SC q10-15min (or 0.1-0.25mg IV over 5-10min)
Cardiac arrest—0.5-1mg IV q3-5min prn (or 1mg via ET tube, 0.1-1mg intracardiac); may follow with 1-4mcg/min constant infusion

NOTE: usually a 1:10,000 solution; may be combined with a local anesthetic.

- **Contraindications**—hypersensitivity, narrow-angle glaucoma, CAD, CV disease, sulfite allergy
- **Caution**—asthma, hyperthyroidism

Maternal Considerations

Epinephrine is commonly used for the relief of severe bronchospasm secondary to allergy. There are no adequate reports or well-controlled studies of **epinephrine** in pregnant women. Theoretically, it could lead to a decrease in uterine blood flow. **Epinephrine** in solution with local anesthetic decreases vascular absorption of local anesthetic, intensifying neural blockade and in some cases prolonging the duration of the block. The maternal response may be potentiated by a variety of drugs and by preeclampsia.

	Side effects include stroke, cerebral hemorrhage, arrhythmias, hypertension, tachycardia, tremor, N/V, and headache.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. **Epinephrine** apparently rapidly crosses the human placenta, which is rich in catecholamine receptors. It is teratogenic in mice at 25× the MRHD.
Breastfeeding Safety	There is no published experience in nursing women. It is unknown whether **epinephrine** enters human breast milk. However, considering the indication, dosing, and its rapid destruction when orally ingested, **epinephrine** use is unlikely to pose a clinically significant risk to the breastfeeding neonate.
Drug Interactions	Use with excessive **digitalis,** mercurial diuretics, or other drugs that sensitize the heart to arrhythmias is not recommended. May be potentiated by TCAs, certain antihistamines (e.g., **chlorpheniramine, diphenhydramine, tripelennamine**), and **levothyroxine.**
References	Nguyen TT, Tseng YT, McGonnigal B, et al. Placenta 1999; 20:3-11.
Summary	**Pregnancy Category: C** **Lactation Category: S** • **Epinephrine** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Epoetin alfa—(EPO; Epogen; Eprex; Erythropoietin; Procrit)

International Brand Name—Epoade (Japan); Epokine (Philippines); Epoxitin (Italy); Eprex (Belgium, Bulgaria, Czech Republic, Denmark, England, Finland, France, Greece, Hungary, Italy, Netherlands, Norway, Portugal, Russia, South Africa, Spain, Sweden, Switzerland, Turkey); Erypo (Austria, Germany, Switzerland); Espo (Japan); Hemapo (Indonesia)

Drug Class	Hematopoietic agents; Hormones
Indications	Transfusion reduction or severe hyporegenerative anemia secondary to AZT therapy, chronic renal failure, or chemotherapy
Mechanism	Stimulates RBC production
Dosage with Qualifiers	Transfusion reduction—300U/kg SC 3×/w beginning 10d preoperative AZT-related anemia—150U/kg SC/IV 3×/w beginning for 8w; may increase to 300U/kg for 3w if poor response Renal failure–related anemia—50-100U/kg IV/SC 3×/w Chemotherapy-related anemia—150U/kg SC/IV 3×/w beginning for 8w; may increase to 300U/kg for 3w if poor response • **Contraindications**—hypersensitivity • **Caution**—hypertension; iron, folate or vitamin B_{12} deficiency; CHF; CAD; seizure disorder; sickle cell anemia
Maternal Considerations	There are no adequate reports or well-controlled studies of **epoetin** in pregnant women. Case series suggest hypertension may complicate as many as 20% of cases. It is often prescribed for pregnant women under going chronic renal dialysis. Adjuvant **epoetin** safely enhances the efficacy of iron sucrose in the treatment of gestational iron deficiency anemia resistant to orally

administered iron alone. In one case report, it was used successfully to treat a pregnant Jehovah's Witness with sickle cell disease.
Side effects include severe hypertension, CHF, MI, stroke, DVT, seizures, headache, arthralgia, tachycardia, fever, diarrhea, N/V, dyspnea, dizziness, rash, and paresthesias.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **epoetin** crosses the human placenta. It does not cross the isolated placental cotyledon. In the offspring of rats treated with 500U/kg, a diverse group of abnormalities was observed, including delayed ossification. There were no effects below that dose.

Breastfeeding Safety

There is no published experience in nursing women. It is unknown whether synthetic **epoetin** enters human breast milk, though erythropoietin is a normal component of breast milk.

Drug Interactions

No clinically significant interactions identified.

References

Breymann C, Visca E, Huch R, Huch A. Am J Obstet Gynecol 2001; 184:662-7.
Danko J, Huch R, Huch A. Lancet 1990; 335:737-8.
Reisenberger K, Egarter C, Kapiotis S, et al. Obstet Gynecol 1997; 89:738-42.
Sifakis S, Angelakis E, Vardaki E, et al. Gynecol Obstet Invest 2001; 51:150-6.
Tan TL, Ahmad H, Jhavar R, et al. J Obstet Gynaecol 2007; 27:82-3.

Summary

Pregnancy Category: C
Lactation Category: S (likely)
- **Epoetin** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.
- A growing body of evidence suggests it is advantageous for certain women with iron deficiency.

Epoprostenol—(Flolan)

International Brand Name—Flolan (Australia, Austria, Belgium, Canada, Denmark, England, France, Ireland, Israel, Italy, Netherlands, Singapore, Spain)

Drug Class

Antihypertensives; Platelet inhibitors; Prostaglandins; Vasodilators

Indications

Pulmonary hypertension

Mechanism

Prostacyclin is a direct vasodilator.

Dosage with Qualifiers

Pulmonary hypertension—2ng/kg/min IV, increase 1-2ng/min q15min; infuse through a central line

- **Contraindications**—hypersensitivity, CHF, pulmonary edema
- **Caution**—unknown

Maternal Considerations

Epoprostenol is prostacyclin. PPH is a rare, progressive condition aggravated by the physiologic changes of pregnancy.
Epoprostenol has been used to treat women during pregnancy and in the immediate postpartum period with apparent success. The maternal mortality rate ranges from 30% to 50%.
Side effects include pulmonary edema, rebound pulmonary hypertension, thrombocytopenia, headache, N/V, anxiety,

	tachycardia, hypotension, chest pain, diarrhea, paresthesias, and dyspnea.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **epoprostenol** crosses the human placenta. A small amount of carbacyclin is transferred across isolated cotyledons from normal placentas. The placenta and fetus synthesize large quantities of prostacyclin. There is no reason to suspect toxicity. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically.
Breastfeeding Safety	There is no published experience in nursing women. It is unknown whether **epoprostenol** is excreted into breast milk. However, prostacyclin is a normal component of human breast milk.
Drug Interactions	Hypotension may occur when given with diuretics, antihypertensive agents, or other vasodilators. May decrease the clearance of **furosemide** and **digoxin** by about 15%.
References	Badalian SS, Silverman RK, Aubry RH, Longo J. J Reprod Med 2000; 45:149-52. Kuhn DC, Walenga RW, Stuart MJ. Am J Perinatol 1991; 8:179-84. Stewart R, Tuazon D, Olson G, Duarte AG. Chest 2001; 119:973-5.
Summary	**Pregnancy Category: B** **Lactation Category: S** (likely) • **Epoprostenol** has been successfully employed in several women with life-threatening pulmonary hypertension.

Eprosartan mesylate—(Teveten)

International Brand Name—Epratenz (Belgium); Teveten (Australia, Austria, Canada, Denmark, England, France, Germany, Hong Kong, Ireland, Korea, Netherlands, Philippines, Sweden)

Drug Class	Antihypertensives; AT-1 antagonists
Indications	Hypertension
Mechanism	Highly specific AT-1 receptor antagonist
Dosage with Qualifiers	Hypertension—600-800mg PO qd • **Contraindications**—hypersensitivity, pregnancy • **Caution**—renal artery stenosis, volume depletion, CHF
Maternal Considerations	There is no published human experience with **eprosartan** during pregnancy. However, extensive experience with other compounds that inhibit aspects of the angiotensin-renin system indicate it should be avoided during pregnancy. ***Side effects*** include severe hypertension, CHF, MI, stroke, DVT, seizures, headache, arthralgia, tachycardia, fever, diarrhea, N/V, dyspnea, dizziness, rash, and paresthesias.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **eprosartan** crosses the

human placenta. Similar class drugs are known teratogens. While no adverse fetal effects are reported after 1st trimester exposure, later exposure to agents that interfere with angiotensin action is associated with cranial hypoplasia, anuria, reversible or irreversible renal failure, death, oligohydramnios, prematurity, IUGR, and patent ductus arteriosus. This "ACEI fetopathy" does not have a counterpart in experimental animals because humans develop these systems prior to calvarial ossification at the end of 1st trimester.

Breastfeeding Safety ..... There is no published experience in nursing women. It is unknown whether **eprosartan** enters human breast milk. **Eprosartan** is excreted into rodent breast milk. Until further study, the infant should be monitored for possible adverse effects, the drug given at the lowest effective dose, and breastfeeding avoided at times of peak drug levels if breastfeeding continues.

Drug Interactions ..... No clinically significant interactions identified.

References ..... There is no published experience in pregnancy or during lactation.

Summary .....

Pregnancy Category: C (1st trimester), **D** (2nd and 3rd trimesters)
Lactation Category: U

- **Eprosartan** and other inhibitors of angiotensin's actions should be avoided during pregnancy if possible.
- There are alternative agents for which there is more experience during pregnancy and lactation.
- When the mother's disease requires treatment with **eprosartan,** the lowest doses should be used followed by close monitoring of the fetus.

Ergocalciferol—(Biocatines D2 masiva; Deltalin; Drisdol; Radiostol; Vitamin D)

International Brand Name—Chocola D (Japan); Drisdol (Canada); Etalpha (Ecuador); One-Alpha (Israel, Puerto Rico); Ostelin (Australia); Ostoforte (Canada); Raquiferol (Argentina, Ecuador); Raquiferol D3 (Peru); Sterogyl (Greece); Sterogyl 15 (Belgium); Sterogyl-15 (France); Uvesterol D (France); Vigantol (Bulgaria, Germany, Hungary, Portugal, Russia, Spain); Vitaminol (Greece)

Drug Class ..... Vitamins/minerals

Indications ..... Rickets, hypoparathyroidism, familial hypophosphatemia

Mechanism ..... Vitamin D_2 stimulates intestinal absorption of calcium and phosphorus, and mineralization. Ergocalciferol is converted in the liver to 25-hydroxyergocalciferol and then in the kidney to the active 1,25-dihydroxyergocalciferol.

Dosage with Qualifiers .....

Rickets, osteomalacia—12,000-500,000U PO qd or 250mcg IM qd
Hypoparathyroidism—50,000-200,000U PO qd (supplement with 500mg elemental calcium 6×/d)
Familial hypophosphatemia—12,000-80,000U PO qd (supplement with 1-2g elemental phosphorus/d)

NOTE: 1mcg = 40U.

- **Contraindications**—hypersensitivity, renal osteodystrophy, hypercalcemia, hypervitaminosis A
- **Caution**—renal dysfunction or stones, CVD

Maternal Considerations

The recommended minimal daily requirement of vitamin D is 400U. The safety of larger doses is unknown. **Ergocalciferol** is a synthetic regulator of calcium. There are few well-controlled studies of **ergocalciferol** in pregnant women. Oral supplementation of vitamin D deficient women does raise serum 25-hydroxy vitamin D concentrations. There is a long clinical experience of **ergocalciferol** supplementation during pregnancy and lactation without complications. Meta-analysis suggests supplementation with **ergocalciferol** reduces the risk of a fall in the elderly by more than 20%.
Side effects include hypercalcemia, N/V, anorexia, anemia, weakness, and renal dysfunction.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **ergocalciferol** crosses the human placenta. Maternal vitamin D supplementation does not significantly increase the neonatal level. **Ergocalciferol** or a metabolite crosses the rodent placenta. Hypervitaminosis D has been associated with a syndrome characterized by supravalvular aortic stenosis, elfin facies, and mental retardation. Rare reports in fetal rats suggesting anomalous bone development when administered in high doses with **cortisone.** Neonates with low vitamin D have low levels of IL-10, a marker for future allergies.

Breastfeeding Safety

There are no adequate reports or well-controlled studies in nursing women. It is unknown whether **ergocalciferol** enters human breast milk. Vitamin D is a normal component of breast milk, and **ergocalciferol** has little effect on vitamin D metabolites in human breast milk. It is likely simple supplementation is safe during lactation. However, there is a single case report of a woman given large doses of vitamin D where 25-hydroxycholecalciferol was identified in her breast milk and the neonate developed hypercalcemia.

Drug Interactions

Mineral oil interferes with the absorption of fat-soluble vitamins. Thiazide diuretic use in hypoparathyroid patients being treated with **ergocalciferol** may cause hypercalcemia.

References

Bischoff-Ferrari HA, Dawson-Hughes B, Willett WC, et al. JAMA 2004; 291:1999-2006.
Clements MR, Fraser DR. J Clin Invest 1988; 81:1768-73.
Di Gregorio S, Danilowicz K, Rubin Z, Mautalen C. Nutrition 2000; 16:1052-5.
Saad HF, Dawodu A, Afandi BO, et al. Am J Clin Nutr 2007; 85:1565-71.
Takeuchi A, Okano T, Tsugawa N, et al. J Nutr 1989; 119:1639-46.
Zittermann A, Dembinski J, Stehle P. Pediatr Allergy Immunol 2004; 15:242-6.

Summary

Pregnancy Category: C
Lactation Category: S (likely)
- **Ergocalciferol** is considered safe and effective during pregnancy and lactation when used in therapeutic amounts.

Ergotamine—(Ergomar; Ergostat; Medihaler-Ergotamine; Wigrettes)

International Brand Name—Avamigran (Philippines); Ergodryl Mono (Australia); Ergo Sanol (Germany); Ergotamin Medihaler (Denmark); Lingraine (England); Medihaler Ergotamine (Canada, England, New Zealand)

Drug Class	Ergot alkaloids
Indications	Abort or prevent migraine headache
Mechanism	Complex and multiple; partial agonist-antagonist against tryptaminergic, dopaminergic, and α-adrenergic receptors depending upon site
Dosage with Qualifiers	Abort or prevent migraine headache—1 tab SL q30min prn at first sign of attack; max 3 tabs qd, or 5 tabs qw *NOTE: 2mg tablets.* • **Contraindications**—hypersensitivity to drug or class, PVD, CAD, hypertension, hepatic or renal dysfunction, severe pruritus, sepsis, pregnancy • **Caution**—breastfeeding
Maternal Considerations	There are no adequate reports or well-controlled studies in pregnant women. **Ergotamine** is a highly active uterine contractile agonist. Inadvertent use may lead to abortion. Epidemiologic study reveals an increased prevalence of preterm birth and IUGR in **ergotamine** users. **Ergotamine** produces constriction of both arteries and veins. It causes constriction of peripheral and cranial blood vessels and depresses the central vasomotor centers. The pain of a migraine attack is believed secondary to greatly increased amplitude of pulsations in the cranial arteries, especially the meningeal branches of the external carotid artery. **Ergotamine** reduces extracranial blood flow, decreases the amplitude of pulsation in the cranial arteries, and decreases hyperperfusion of the territory of the basilar artery. It is effective in controlling up to 70% of acute migraine attacks and is considered specific for the treatment of this headache syndrome. **Atropine** or antiemetic compounds of the phenothiazine group may relieve the associated N/V. There is a case report of its association with maternal MI following an **ergotamine**-associated abortion. ***Side effects*** include nausea, vomiting (up to 10%), leg weakness, myalgia, numbness and paresthesias of the fingers and toes, precordial pain, transient changes in heart rate, edema, and pruritus.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **ergotamine** crosses the human placenta. While there is no clear evidence it is a teratogen, the severe vasoconstriction associated with toxicity could lead to profound fetal hypoxia and death. It has also been associated with Möbius' syndrome.
Breastfeeding Safety	There are no adequate reports or well-controlled studies in nursing women. **Ergotamine** is excreted into human breast milk. Theoretically, excessive dosing or prolonged administration of **ergotamine** might inhibit lactation. Though generally considered incompatible with breastfeeding, the only published study found no effect on milk production or infant weight gain.

Drug Interactions

The pressor effects of **ergotamine** and other vasoconstrictor drugs can cause dangerous hypertension when combined.

References

Au KL, Woo JS, Wong VC. Eur J Obstet Gynecol Reprod Biol 1985; 19:313-5.
Banhidy F, Acs N, Puho E, Czeizel AE. Br J Clin Pharmacol 2007; 64:510-6.
de Groot AN, van Dongen PW, van Roosmalen J, Eskes TK. Eur J Obstet Gynecol Reprod Biol 1993; 51:73-7.
Graf WD, Shepard TH. J Child Neurol 1997; 12:225-7.
Jolivet A, Robyn C, Huraux-Rendu C, Gautray JP. J Gynecol Obstet Biol Reprod (Paris) 1978; 7:129-34.
Marti V, Salas E, Torner P, Dominguez de las Rozas JM. Med Clin (Barc) 1999; 113:758-9.
Moretti ME, Lee A, Ito S. Can Fam Physician 2000; 46:1753-7.
Raymond GV. Teratology 1995; 51:344-7.

Summary

Pregnancy Category: X
Lactation Category: NS (possibly)

- **Ergotamine** should be avoided during pregnancy and lactation and used only if the benefit justifies the potential perinatal risk.
- There are alternative agents for which there is a higher safety profile and more experience during pregnancy and lactation.

Erythromycin—(Akne-Mycin; A/T/S; C-Solve-2; Del-Mycin; Dumotrycin; E-Base; Emgel; Endoeritrin; Erisone; Eritomicina; Erycette; Erygel; Erythra-Derm; ETS; Ilotycin; Mercina; PCE; Proterytrin; Retcin; Romycin; Sansac; Staticin; T-Stat)

International Brand Name—Abboticin (Denmark, Finland, Norway, Sweden); Abboticine (Denmark, Finland, Norway, Sweden); Abomacetin (Japan); Acneryne (Belgium); Acnesol (India); Aknederm Ery Gel (Germany); Aknemycin (Austria, Belgium, Germany); Akne-Mycin (Indonesia, Malaysia, Netherlands, Singapore); Bonac Gel (Peru); Cliniderm (Uruguay); Deripil (Spain); Emu-V (New Zealand, South Africa); Emu-Ve (Argentina); Emuvin (Austria); Emycin (Korea); E-Mycin (Hong Kong, India, Israel, Malaysia); Eriecu (Ecuador); Erimycin-T (Thailand); Eritimix (Venezuela); Eritrocina (Italy); Eritromicina (Colombia); Erixyl (Dominican Republic); Ermycin (Paraguay); Eros (Indonesia); Eryacne (France, Hong Kong, Singapore, Thailand); Eryacnen (Brazil, Ecuador); Ery-B (Taiwan); Eryc (Australia, Bulgaria, China, Czech Republic, Hungary, Israel, Korea, Netherlands, Russia); Eryc-125 (Canada); Eryc-250 (Canada); Erycen (England, Ireland); Erycin (Denmark, Philippines); Erycinum (Austria); Eryc LD (Australia); Eryderm (Belgium, Israel, Malaysia, Netherlands, Russia, South Africa, Switzerland); Erydermec (Germany); Erydermer (Germany); Eryhexal (Germany, Russia); Erymax (Belgium, Finland, Norway, Philippines, Sweden); Ery-maxin (Austria); Erymed (Indonesia); Erysafe (India); Erytab (Israel); Ery-Tab (Thailand); Erythrocin (Hong Kong, India, Turkey); Erythromid (Canada, Ireland, South Africa); Erythromycin (Denmark, Hungary, India); Erythro-Teva (Israel); Erytop (Germany); Erytrarco (Switzerland); Erytrociclin (Italy); Etinycine (China); Etrolate (Thailand); Iloticina (Argentina); Ilotycin T.S. (South Africa); Inderm Gel (Germany); Labocne (Chile); Latotryd (Mexico); Lederpax (Mexico, Paraguay); Monomycin (Germany); Monomycina (Ecuador); Oftalmolosa Cusi Eritromicina (Spain); Oftalmolosa Cusi Erythromycin (Poland); Oftamolets (Argentina); Paediathrocin (Germany); Pantodrin (Spain); Pantomicina (Ecuador); Primacine (Indonesia); Rythocin (Thailand); Sans-acne (Canada, Mexico); Skid Gel E (Germany); Stiemycin (Colombia, Costa Rica, Dominican Republic, England, Guatemala, Hong Kong, Ireland, Korea, Malaysia, New Zealand, Nicaragua, Panama, Philippines, Taiwan, Thailand); Stimycine (France)

Drug Class

Antibiotics; Dermatologics; Macrolides; Ophthalmics

Indications

Bacterial infection; PPROM; certain STDs; prophylaxis for rheumatic heart disease, bacterial endocarditis, and GBS

Mechanism

Inhibits protein synthesis by binding the P site of the 50S ribosomal subunit

Dosage with Qualifiers

Bacterial infection—250-500mg PO q6-12h
PPROM—250mg PO qid ×10d

NOTE: may be combined with a sulfa agent to improve coverage of H. influenzae.

- **Contraindications**—hypersensitivity, **cisapride** use, **astemizole** use
- **Caution**—myasthenia gravis, hepatic dysfunction

Maternal Considerations

The routine use of macrolide antibiotics prolongs the latency interval and reduces infectious morbidity in women with PPROM, but offers no such prolongation in women with preterm labor and intact membranes, and may even increase the risk of neurodevelopmental compromise. Prolongation of the latency interval is not synonymous with irradication of inflammation. In one study, the administration of both **erythromycin** and **ampicillin** rarely eradicated intra-amniotic infection in patients with PPROM. In addition, intra-amniotic inflammation developed in ⅓ of women who did not have inflammation on admission despite antibiotic therapy. However, there was a subgroup of women with documented inflammation who demonstrated a decrease in the intensity of the inflammatory process after antibiotic administration. This group likely accounts for the beneficial effects of **erythromycin** on the latency interval.
Erythromycin reduces the frequency of preterm delivery in women with either asymptomatic bacteriuria or symptomatic lower genital tract infections. However, the practice of routine screening for BV in asymptomatic women who are at low risk for preterm delivery cannot be supported based on evidence from the literature. The frequency of GBS resistance renders it a poor selection for prophylaxis. **Erythromycin** is an effective alternative therapy for the treatment of chlamydial infection. Partner treatment is, overall, cost-effective among women ages 15-29. Though an alternative for the treatment of syphilis in penicillin-allergic patients, placental transport is low (<5%). Thus, **erythromycin** is not recommended for the treatment of syphilis during pregnancy. Penicillin-allergic women should be desensitized.
Recently, a relationship between oral **erythromycin** and sudden cardiac death was reported in patients also receiving strong inhibitors of CYP3A such as nitroimidazole antifungal agents, **diltiazem, verapamil,** and **troleandomycin;** each doubles, at least, the AUC for a CYP3A substrate. The potential implication for obstetrics is real with the growing use of **nifedipine** as a tocolytic agent in women who may also be treated with antibiotics for preterm PROM. Although not included in the referenced study, **nifedipine** is also a substrate for CYP3A, suggesting the likelihood for some interaction is high.
Side effects include anaphylaxis, hepatotoxicity, thrombophlebitis, ventricular arrhythmia, bradycardia, hypotension, N/V, diarrhea, pruritus, anorexia, abdominal pain, jaundice, eosinophilia, and elevated hepatic transaminases.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. **Erythromycin** crosses the human placenta, achieving an F:M concentration ratio of 0.3.

Breastfeeding Safety

There are no adequate reports or well-controlled studies in nursing women. **Erythromycin** is excreted into human breast milk, achieving an M:P ratio approximating unity. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically.

Drug Interactions

May increase **theophylline** levels, causing toxicity.
May increase serum **digoxin** levels.
May increase the anticoagulant effects of oral agents when used together.
Use with **ergotamine** or **dihydroergotamine** may trigger with acute ergot toxicity characterized by severe peripheral vasospasm and dysesthesia.
May decrease the clearance of **triazolam** and **midazolam.**
Other drug interactions include **alfentanil, astemizole, bromocriptine, carbamazepine, cisapride, cyclosporine, disopyramide, hexobarbital, lovastatin, phenytoin, tacrolimus, terfenadine,** and **valproate.** Each is metabolized by the CYP system and should be monitored closely in patients receiving **erythromycin.**

References

Gomez R, Nien JK, Medina L, et al. J Matern Fetal Neonatal Med 2007; 20:167-73.
Gray RH, Wabwire-Mangen F, Kigozi G, et al. Am J Obstet Gynecol 2001; 185:1209-17.
Heikkinen T, Laine K, Neuvonen PJ, Ekblad U. BJOG 2000; 107:770-5.
Kenyon S, Boulvain M, Neilson J. Cochrane Database Syst Rev 2001; (4):CD001058.
Kenyon SL, Taylor DJ, Tarnow-Mordi W; ORACLE Collaborative Group. Lancet 2001; 357:979-94.
Kenyon S, Pike K, Jones DR, et al. Lancet 2008; 372:1319-27.
Kenyon S, Pike K, Jones DR, et al. Lancet 2008; 372:1310-8.
Louik C, Werler MM, Mitchell AA. Am J Obstet Gynecol 2002; 186:288-90.
Manning SD, Foxman B, Pierson CL, et al. Obstet Gynecol 2003; 101:74-9.
Mercer BM, Miodovnik M, Thurnau GR, et al. JAMA 1997; 278:989-95.
Postma MJ, Welte R, van den Hoek JA, et al. Value Health 2001; 4:266-75.
Ray WA, Murray KT, Meredith S, et al. N Engl J Med 2004; 351:1089-96.
Sheffield JS, Sanchez PJ, Morris G, et al. Am J Obstet Gynecol 2002; 186:569-73.
Zhang Y, Zhang Q, Xu Z. Zhonghua Fu Chan Ke Za Zhi 1997; 32:288-92.

Summary

Pregnancy Category: B
Lactation Category: S

- **Erythromycin** is one option for the treatment of PPROM to prolong the latency period. It should, however, probably be avoided in women receiving a calcium channel blocker as a tocolytic agent and in women in preterm labor with intact membranes.
- **Erythromycin** reduces the frequency of preterm delivery in women with either asymptomatic bacteriuria or symptomatic lower genital tract infections.
- **Erythromycin** is an effective alternative therapy for the treatment of *Chlamydia* infection; partner treatment is cost-effective.
- Poor placental transport renders it a poor choice for the treatment of fetal infection.

Escitalopram—(Lexapro)

International Brand Name—Cipralex (England, India, Ireland, Israel, Sweden); Ipran (Chile); Lexapro (Argentina, Brazil, Colombia, Hong Kong, Peru, Philippines, Singapore, Thailand); Seroplex (France)

Drug Class	Antidepressants; SSRIs
Indications	Depression, anxiety (generalized)
Mechanism	Selectively inhibits serotonin reuptake
Dosage with Qualifiers	Depression—begin 10mg PO qd; max 20mg/d; taper slowly Anxiety, generalized—begin 10mg PO qd; max 20mg/d; taper slowly *NOTE: hepatic dosing.* • **Contraindications—**hypersensitivity to drug or class, citalopram hypersensitivity or use, MAOI <14d • **Caution—**hepatic or renal dysfunction, history of mania, seizure disorder, suicide risk
Maternal Considerations	Depression is common during and after pregnancy but often goes unrecognized. Pregnancy is not a reason *a priori* to discontinue psychotropic drugs. **Escitalopram** is the pure (*S*-) enantiomer (single isomer) of the racemic citalopram. The published experience with **escitalopram** during pregnancy consists mostly of inadequately documented case reports. Limited study suggests increased metabolism during the second half of pregnancy. As for most psychotropic drugs, using monotherapy and the lowest effective quantity given in divided doses to minimize the peaks can minimize the risks. ***Side effects*** include serotonin syndrome, withdrawal syndrome, mania, hyponatremia, insomnia, somnolence, sweating, fatigue, dizziness, dry mouth, decreased libido, anorgasmia, decreased appetite, constipation, diarrhea, dyspepsia, cholestasis, and abdominal pain.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **escitalopram** crosses the human placenta. **Citalopram** does cross the isolated, perfused human placenta with a mean steady-state transfer rate of 9%. The transfer is significantly lower compared with **fluoxetine,** which suggests lower fetal exposure will occur with **citalopram.** In contrast, umbilical cord serum measurements reveal that the highest cord:maternal ratios were seen with **citalopram** and **fluoxetine** compared to **sertraline** and **paroxetine.** Rodent studies are reassuring, revealing no evidence of teratogenicity despite the use of doses higher than those used clinically. Maternal toxicity, observed at most tested doses, was associated with IUGR. In contrast, the administration of **citalopram** was associated with CV and skeletal defects.
Breastfeeding Safety	There is no published experience in nursing women. It is unknown whether **escitalopram** enters human breast milk. Racemic **citalopram** enters human breast milk, and in one study **citalopram** and its metabolite M:P ratios were 2:3, but infant **citalopram** and metabolite plasma concentrations were very low or undetectable. However, there are two reports of infants experiencing somnolence, decreased feeding, and weight loss when breastfed by a **citalopram**-treated mother. Caution is advised.

Drug Interactions

In vitro studies indicated that CYP3A4 and CYP2C19 are the primary enzymes involved in the metabolism of **escitalopram.** However, because **escitalopram** is metabolized by multiple enzyme systems, inhibition of a single enzyme may not appreciably decrease **escitalopram** clearance.
Use with **ketoconazole,** a potent CYP3A4 inhibitor, is associated with a decrease in the **ketoconazole** C_{max} and AUC by 21% and 10%, respectively.
May increase the C_{max} and double the AUC of **desipramine,** suggesting a CYP2D6 inhibitory effect.
Cimetidine increases the **citalopram** AUC and C_{max} 43% and 39%, respectively.
There are rare post-marketing reports describing patients with weakness, hyperreflexia, and incoordination following the use of an SSRI and **sumatriptan.**
Increases the C_{max} and AUC of **metroprolol** by 50% and 82%, respectively. However, co-administration reportedly has no clinically significant effects on BP or heart rate.
Platelet release of serotonin has an important role in hemostasis. Epidemiologic studies suggest an association between serotonin reuptake inhibitors and upper GI bleeding, especially with NSAIDs or **aspirin.**

References

Heikkinen T, Ekblad U, Kero P, et al. Clin Pharmacol Ther 2002; 72:184-91.
Heikkinen T, Ekblad U, Laine K. BJOG 2002; 109:1003-8.
Hendrick V, Stowe ZN, Altshuler LL, et al. Am J Psychiatry 2003; 160:993-6.
Sit DK, Perel JM, Helsel JC, Wisner KL. J Clin Psychiatry 2008; 69:652-8.

Summary

Pregnancy Category: C
Lactation Category: NS (possibly)

- **Escitalopram** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.
- Maternal therapeutic drug monitoring of **citalopram** is recommended to minimize fetal exposure.
- There are alternative agents for which there is more experience during pregnancy (with lower placental transfer) and lactation.

Esmolol—(Brevibloc)

International Brand Name—Brevibloc (Argentina, Austria, Belgium, Brazil, Canada, Czech Republic, Denmark, England, Hungary, Israel, Italy, Korea, Mexico, Netherlands, Philippines, Poland, South Africa, Switzerland, Taiwan, Uruguay); Miniblock (India)

Drug Class

Adrenergic antagonists; Antiarrhythmics, class II; Antihypertensives; β-Blockers

Indications

Hypertension (perioperative), SVT

Mechanism

β_1-Receptor antagonist

Dosage with Qualifiers

Perioperative hypertension/tachycardia—begin 150mcg/kg/min IV; titrate up by 50mcg/kg/min for a max of 300mcg/kg/min
SVT—begin 500mcg/kg/min ×1min, then 50mcg/kg/min ×4min; repeat cycle if no effect, titrating infusion up by 50mcg/kg/min after each loading dose

- **Contraindications**—hypersensitivity, sinus bradycardia, AV heart block, cardiogenic shock
- **Caution**—asthma

Maternal Considerations

Esmolol is a short-acting β_1-blocker employed for the rapid but short-term (9min t/2) control of either hypertension or supraventricular arrhythmia. There are no adequate reports or well-controlled studies of **esmolol** in pregnant women. The published experience is limited to case reports and small series. It has been used successfully for BP control in women with preeclampsia or pheochromocytoma before induction of general anesthesia, and in women with terbutaline overdose or hypertrophic obstructive cardiomyopathy.
Side effects include bronchospasm, hypotension, cardiac failure, dizziness, N/V, somnolence, fatigue, and phlebitis.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. **Esmolol** crosses the human placenta, and fetal bradycardia may continue days after delivery despite the short effect in adults. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically. Maternal toxicity is associated with embryo lethality.

Breastfeeding Safety

There is no published experience in nursing women. It is unknown whether **esmolol** is excreted into breast milk.

Drug Interactions

Catecholamine-depleting drugs (e.g., **reserpine**) may have an additive effect when given with β-blocking agents.
May increase **digoxin** concentration.
Morphine increases plasma levels of **esmolol** by almost 50%.
May prolong the duration of neuromuscular blockade of **succinylcholine.**
Patients with a history of anaphylactic reaction may be more reactive to repeat challenge, either accidental, diagnostic, or therapeutic, while taking β-blockers. Such patients may be unresponsive to the usual doses of **epinephrine** used to treat allergic reaction.
Fatal cardiac arrest has occurred in patients with depressed myocardial function taking **esmolol** and **verapamil.**
Should not be used to control SVT in the presence vasoconstrictors or ionotropes such as **dopamine, epinephrine,** and **norepinephrine** because of the danger of blocking cardiac contractility when systemic vascular resistance is high.

References

Gilson GJ, Knieriem KJ, Smith JF, et al. J Reprod Med 1992; 37:277-9.
Ostman PL, Chestnut DH, Robillard JE, et al. Anesthesiology 1988; 69:738-41.

Summary

Pregnancy Category: C
Lactation Category: U
- **Esmolol** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Esomeprazole—(Nexium)

International Brand Name—Esoprax (Colombia); Inexium (France); Nexium (Australia, England, Germany, Hong Kong, Indonesia, Ireland, Israel, Korea, Malaysia, Singapore); Nexium-MUPS (Mexico); Sompraz (India)

Drug Class ····· Antiulcer; Gastrointestinals; Proton pump inhibitors

Indications ····· GERD, erosive esophagitis, *H. pylori* infection treatment

Mechanism ····· A proton pump inhibitor reducing gastric parietal cell release of hydrogen

Dosage with Qualifiers ····· GERD—20-40mg PO qd ×4-8w; max 80mg qd
Erosive esophagitis—20-40mg PO qd ×4-8w; max 80mg qd
H. pylori—40mg PO qd ×10d taken with **amoxicillin** and **clarithromycin**

- **Contraindications**—hypersensitivity
- **Caution**—hepatic dysfunction, long-term use

Maternal Considerations ····· **Esomeprazole** is the L-isomer of **omeprazole**. There are no adequate reports or well-controlled studies in pregnant women. **Esomeprazole** is cost-effective compared with **omeprazole** in the acute treatment of reflux esophagitis and GERD without esophagitis. These drugs are being used with increasing frequency during pregnancy, and there is a great need for additional study.
Side effects include hepatic dysfunction, diarrhea, and headache.

Fetal Considerations ····· It is unknown whether **esomeprazole** crosses the human placenta. The F:M ratio of **omeprazole** at steady state in sheep is about 0.5. The findings of an epidemiologic study including 600 pregnancies is reassuring. In another study run by the European Network of Teratology Information Services, the rates of major anomalies was compared among pregnant women exposed to **omeprazole, lanzoprazole,** or **pantoprazole** and a control group. They followed 295 pregnancies exposed to **omeprazole** (233 in the 1st trimester [T1]), 62 to **lansoprazole** (55 in T1) and 53 to **pantoprazole** (47 in T1), along with 868 controls. The rates of major congenital anomalies did not differ between the exposed and control groups and there were no differences when exposure was limited to the 1st trimester after exclusion of genetic, cytogenetic, or infectious anomalies. Rodent studies are likewise reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically.

Breastfeeding Safety ····· There is no published experience in nursing women. It is unknown whether **esomeprazole** is excreted into breast milk. As **esomeprazole** is the L-isomer of **omeprazole,** the risks should be similar.

Drug Interactions ····· Extensively metabolized in the liver by CYP2C19 and CYP3A4. Post-marketing reports describe changes in the PT of patients on **warfarin** and **esomeprazole.** Increases in INR and PT may lead to abnormal bleeding and even death. Patients treated with proton pump inhibitors and **warfarin** should be monitored frequently. Decreases the clearance of **diazepam,** a CYP2C19 substrate, by almost half, causing increased plasma levels 12h after dosing and onward. However, interaction is unlikely to be of clinical relevance at that time since the plasma levels are subtherapeutic. May reduce the plasma levels of atazanavir.

Inhibits gastric acid secretion and may interfere with the absorption of drugs whose bioavailability is affected by gastric pH (e.g., **ketoconazole,** iron salts, **digoxin**).
Use with **clarithromycin** and **amoxicillin** increases the plasma levels of both **esomeprazole** and 14-hydroxyclarithromycin.

References

Diav-Citrin O, Arnon J, Shechtman S, et al. Aliment Pharmacol Ther 2005; 21:269-75.
Nikfar S, Abdollahi M, Moretti ME, et al. Dig Dis Sci 2002; 47:1526-9.
Wahlqvist P, Junghard O, Higgins A, Green J. Pharmacoeconomics 2002; 20:279-87.

Summary

Pregnancy Category: B
Lactation Category: S (likely)
- **Esomeprazole** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.
- A growing body of work suggests proton-pump inhibitors are likely safe during pregnancy.

Estazolam—(Eurodin; Nuctalon; ProSom; Sedarest)

International Brand Name—Domnamid (Denmark); Esilgan (Indonesia, Italy, Korea, Philippines); Eszo 2 (Taiwan); Eurodin (Japan, Taiwan); Kainever (Portugal); Noctal (Brazil); Nuctalon (France); Tasedan (Mexico)

Drug Class

Benzodiazepines; Hypnotics; Sedatives

Indications

Insomnia

Mechanism

Binds to the benzodiazepine receptor, enhancing GABA effects

Dosage with Qualifiers

Insomnia—1-2mg PO qhs prn

- **Contraindications**—hypersensitivity, pregnancy, depressed respiratory function, and sleep apnea
- **Caution**—hepatic or renal dysfunction, suicidal ideation, history of substance abuse

Maternal Considerations

There is no published experience with **estazolam** during pregnancy. Other drugs of this class such as **diazepam** are considered to be relatively contraindicated during pregnancy. ***Side effects*** include somnolence, headache, asthenia, dizziness, and disorientation.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **estazolam** crosses the human placenta. Transplacental movement of similar drugs is known to occur, and neonatal depression is reported. (See **Diazepam**.)

Breastfeeding Safety

There is no published experience in nursing women. It is unknown whether **estazolam** enters human breast milk. (See **Diazepam**.)

Drug Interactions

The action of the benzodiazepines may be potentiated by anticonvulsants, antihistamines, alcohol, barbiturates, MAOIs, narcotics, phenothiazines, psychotropic medications, or other drugs that produce CNS depression.

Smokers have increased clearance of benzodiazepines compared to nonsmokers.

References ..... There is no published experience in pregnancy or during lactation.

Summary .....

Pregnancy Category: X
Lactation Category: U

- Benzodiazepines such as **estazolam** are generally contraindicated during pregnancy.
- There are alternative agents for which there is more experience during pregnancy and lactation.

Estradiol—(Alora; Climara; Estrace; Estraderm; Estring; Fempatch; Vivelle)

International Brand Name—Aerodiol (Australia, France, Germany, Hong Kong, Korea, Sweden); Bisteron (Taiwan); Climaderm (Brazil, Colombia, Mexico); Climara (Canada, China, France, Philippines, South Africa, Taiwan, Thailand); Climara Forte (New Zealand); Climara Low Dose (Philippines); Delidose (France); Dermestril (China, Germany, Israel, Italy); Dermestril Septem (France); Divigel (Korea, Malaysia, Singapore, Thailand); Estrace (Canada); Estracomb TTS (Hong Kong); Estraderm (Australia, Canada, Colombia, Denmark, Finland, Ireland, Norway, Sweden); Estraderm MX (Argentina, Australia, Peru); Estraderm TTS (Austria, Belgium, Brazil, Bulgaria, Colombia, Czech Republic, Ecuador, England, France, Germany, Greece, Hong Kong, Hungary, Indonesia, Israel, Italy, Japan, Korea, Malaysia, Netherlands, New Zealand, Paraguay, Peru, Philippines, Poland, Portugal, Russia, South Africa, Spain, Switzerland, Taiwan, Turkey, Uruguay, Venezuela); Estradot (Canada, England, Germany, Ireland); Estran (Korea); Estrapak 50 (Ecuador); Estrapatch (France); Estreva (Germany, Hong Kong, Indonesia, Italy); Estreva Comprimidosa (Peru); Estreva Gel (Peru); Estrifam (Germany); Estring (Austria, Canada, Denmark, Finland, Germany, Netherlands, Norway, South Africa, Switzerland); Estrofem (Argentina, Austria, Belgium, Brazil, Bulgaria, China, Czech Republic, Denmark, Finland, France, Hong Kong, Israel, Korea, Malaysia, Netherlands, New Zealand, Philippines, Singapore, South Africa, Switzerland, Taiwan, Thailand); Estrofem 2 (Thailand); Evafilm (France); Evepia (Korea); Evorel (Colombia, Israel, Mexico); Fem 7 (Costa Rica, Dominican Republic, El Salvador, Guatemala, Honduras, Hong Kong, Indonesia, Nicaragua, Panama, Peru, Singapore); Fematrix (China, England, Ireland); Femsept (France); Femseven (England, Indonesia, Ireland); Femtran (New Zealand); Ginedisc (Colombia, Mexico, Peru); Gynokadin (Germany); GynPolar (Germany); Kliovance (Australia); Lindisc (Colombia, Peru); Menodin TTS (Colombia); Meno-MPA (Israel); Menorest (Colombia, Germany, Italy, South Africa); Menoring (England, Ireland); Mestrace (Brazil); Oesclim (China, France); Oestring (Sweden); Oestrodose (Israel); Oestrogel (China, Mexico); Progynon (Sweden); Progynova (Norway); Sandrena (Mexico); Sandrena Gel (Australia, Germany); Sisare Gel (Germany); Systen (Mexico); Thais (France); Tradelia (Germany); Vagifem (Austria, Belgium, Bulgaria, Denmark, England, Hong Kong, Ireland, Italy, Philippines, Poland, Singapore, Sweden, Switzerland, Thailand, Uruguay); Vivelle (Canada); Vivelledot (France); Zumenon (Australia, Austria, Belgium, England, Ireland, Netherlands)

Drug Class ..... Estrogens; Hormones

Indications ..... Contraception (when used in combination with a progestational agent), vasomotor symptoms of menopause, osteoporosis prevention, atrophic vaginitis, primary ovarian failure, breast cancer palliation

Mechanism ..... A natural estrogen that binds to estrogen receptors, developing and maintaining female sex characteristics; has both receptor- and non–receptor-mediated activities

Dosage with Qualifiers .....

Vasomotor symptoms—1-2mg PO qd, cycle 21d on and 7d off, add a progestin days 14-21 if uterus present
Osteoporosis prevention—0.5mg PO qd, cycle 21d on and 7d off, add a progestin days 14-21 if uterus present
Atrophic vaginitis—1-2mg PO qd, cycle 21d on and 7d off, add a progestin days 14-21 if uterus present
Primary ovarian failure—1-2mg PO qd
Breast cancer palliation—10mg PO tid ×3mo

*NOTE: available in a variety of preparations as **ethinyl estradiol,** a more potent synthetic. Delivery systems include oral tablets, vaginal tablets, creams, rings, and SC and transdermal formulations produced by various manufacturers.*

- **Contraindications**—hypersensitivity, undiagnosed vaginal bleeding, thromboembolic disease, estrogen-dependent breast cancer, pregnancy
- **Caution**—hepatic dysfunction

Maternal Considerations

Estradiol is a naturally occurring estrogen, and as such may have a different risk profile than synthetic or phytoestrogens. It is commonly used for the short-term management of climacteric/postmenopausal symptoms. **Conjugated estrogens** and **estradiol** have comparable effects on hot flashes and may have similar short-term adverse effects. Recent studies suggest estrogen plus **medroxyprogesterone** for the treatment of menopausal symptoms increases the risk of breast cancer and CV disease. There are no indications for **estradiol** during pregnancy. The effect of **estradiol** on CV disease remains controversial.
Side effects include thromboembolism, stroke, MI, endometrial and breast cancer, gallbladder disease, pancreatitis, hypertension, breast tenderness, hepatic adenoma, bloating, N/V, headache, dizziness, depression, weight gain, libido changes, intolerance to contact lenses, migraine, and rash.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. While **diethylstilbestrol** and other synthetic/environmental estrogens are recognized teratogens with the potential for transgenerational effects, few studies support this effect for naturally occurring substances like **estradiol.** There is no clear evidence of fetal harm after inadvertent exposure during the 1st trimester. Some studies have suggested prenatal exposure to **estradiol** might alter immune programming.

Breastfeeding Safety

Though **estradiol** is excreted into breast milk and has been reported to reduce the amount of milk produced, it is not effective as an inhibitor of lactation. All pharmacokinetic studies have shown that the transfer to breast milk of both **progesterone** and estrogen when taking a contraceptive pill is of the same order as natural hormones. Estrogen-containing contraceptives should be initiated after the 6th week of lactation when the lipid profile has returned to normal and the risk of thrombosis is identical to that of the general population.

Drug Interactions

Estrogens are partially metabolized by CYP3A4. Thus, CYP3A4 inducers (e.g., St. John's wort, **phenobarbital, carbamazepine, rifampin**) may reduce plasma estrogen, possibly decreasing therapeutic effects and/or changing the uterine bleeding profile, and inhibitors (e.g., **erythromycin, clarithromycin, ketoconazole, itraconazole, ritonavir,** grapefruit juice) may increase plasma estrogens and result in side effects
The following interactions should be considered in any patient treated with any estrogen: accelerated PT, PTT, and platelet aggregation time; increased platelet count; increased factors II, VII antigen, VIII antigen, VIII coagulant activity, IX, X, XII, VII-X complex, II-VII-X complex, and β-thromboglobulin; decreased levels of anti-factor Xa and ATIII, and decreased ATIII activity; increased levels of fibrinogen and fibrinogen activity; increased plasminogen antigen and activity; increased plasma HDL and HDL-2 subfraction concentrations, reduced LDL-C concentration, and increased triglyceride levels.

■ **References**

Barlow S, Kavlock RJ, Moore JA, et al. Teratology 1999; 60:365-75.
Herbst AL. Gynecol Oncol 2000; 76:147-56.
Hook EB. Teratology 1994; 49:162-6.
Karpuzoglu-Sahin E, Hissong BD, Ansar Ahmed S. J Reprod Immunol 2001; 52:113-27.
Nelson HD. JAMA 2004; 291:1610-20.

■ **Summary**

Pregnancy Category: X
Lactation Category: S

- There is no indication for **estradiol** during pregnancy.
- There is no clear evidence of fetal harm after inadvertent exposure during the 1st trimester.

Estrogens, conjugated—(Azumon; Conjugen; Emopremarin; Mannest; Menopak-E; Ovest; Premarin; Trepova)

International Brand Name—Ayerogen (Venezuela); Ayerogen Crema Vaginal (Ecuador); Belestar (Argentina); C.E.S. (Canada); Climarest (Germany); Conpremin (Chile); Dagynil (Netherlands, Taiwan); Equin (Hong Kong, Spain); Estranova (Peru); Estrarona (Peru); Estromal (Indonesia); Estromon FC (Thailand); Eyzu (Taiwan); Femavit (Germany); Hyphorin (Japan); Menpoz (Philippines); Neo-Menovar (Argentina); Oestro-Feminal (Czech Republic, Ecuador, Germany); Premarin (Austria, Belgium, Brazil, Bulgaria, Canada, China, Colombia, Costa Rica, Denmark, Dominican Republic, Ecuador, El Salvador, England, Finland, France, Greece, Guatemala, Honduras, Hong Kong, Hungary, India, Ireland, Italy, Japan, Korea, Malaysia, Mexico, Netherlands, Nicaragua, Panama, Peru, Philippines, Portugal, Russia, Switzerland, Taiwan, Thailand, Turkey, Uruguay, Venezuela); Premarina (Sweden); Premarin Crema V (Mexico); Premarin Crema Vaginal (Colombia); Premarin Creme (New Zealand, South Africa); Premarin Vaginal Creme (Hong Kong, Korea, Malaysia, Philippines, Taiwan, Thailand); Presomen (Czech Republic, Germany); Prevagin-Premaril (Israel); Profemina (Paraguay); Romeda (Japan); Sefac (Japan); Srogen (Korea); Sukingpo (Taiwan); Sultrona (Mexico); Transannon (Switzerland); Trepova (Mexico)

■ **Drug Class**

Estrogens; Hormones

■ **Indications**

Primary ovarian failure, vasomotor symptoms of menopause, osteoporosis

■ **Mechanism**

Bind to estrogen receptors; has both receptor- and non–receptor-mediated activities

■ **Dosage with Qualifiers**

Vasomotor symptoms—0.3-1.25mg PO qd for 21d, and then 7d off; add a progestin days 14-21 if uterus present
Osteoporosis—0.625mg PO qd for 21d, and then 7d off; add a progestin days 14-21 if uterus present
Primary ovarian failure—1.25mg PO qd for 21d, and then 7d off; add a progestin days 14-21 if uterus present

NOTE: may be combined with ***medroxyprogesterone, meprobamate,*** *or* ***methyltestosterone.***

- **Contraindications**—hypersensitivity, pregnancy, undiagnosed vaginal bleeding, thromboembolic disease, estrogen-dependent breast cancer
- **Caution**—lactation, hepatic dysfunction

■ **Maternal Considerations**

Conjugated estrogens are a mixture of estrogens extracted from natural sources, most commonly pregnant mares' urine. They are widely used for the treatment of hot flashes in climacteric and postmenopausal women. **Conjugated estrogens** and **estradiol** have comparable effects on hot flashes and may have similar short-term adverse effects. Unopposed **conjugated estrogens** have been long known to increase the risk of endometrial cancer. Recent studies demonstrate that estrogen plus

medroxyprogesterone for the treatment of menopausal symptoms does not increase the risk of endometrial cancer compared to placebo, but it does increase the risk of breast cancer and CV disease and may increase the risk of ovarian cancer. Although **conjugated estrogens** plus **medroxyprogesterone** increases bone density and reduce the risk of fracture in healthy postmenopausal women, there is no net health benefit when the effects of hormone therapy on other important disease outcomes are included in a global model, even in women at high risk of fracture. Many women use **conjugated estrogens** alone after hysterectomy. The findings of the Women's Health Initiative Randomized Trial reveal that the use of **conjugated estrogens** alone increases the risk of stroke by 30%, reduces the risk of hip fracture by 40%, and does not alter the risk of CV disease. There are no indications for **conjugated estrogens** during pregnancy. (See **Estradiol.**)

Side effects include thromboembolism, stroke, MI, endometrial and breast cancer, gallbladder disease, pancreatitis, hypertension, breast tenderness, hepatic adenoma, bloating, N/V, headache, dizziness, depression, weight gain, libido changes, intolerance to contact lenses, migraine, and rash.

Fetal Considerations

Estrogen has myriad effects on the developing embryo/fetus; many are poorly understood (see **Estradiol**).

Breastfeeding Safety

See **Estradiol.**

Drug Interactions

Estrogens are partially metabolized by CYP3A4. Thus, CYP3A4 inducers (e.g., St. John's wort, **phenobarbital, carbamazepine, rifampin**) may reduce plasma estrogen, possibly decreasing therapeutic effects and/or changing the uterine bleeding profile, and inhibitors (e.g., **erythromycin, clarithromycin, ketoconazole, itraconazole, ritonavir,** grapefruit juice) may increase plasma estrogens and result in side effects

The following interactions should be considered in any patient treated with any estrogen: accelerated PT, PTT, and platelet aggregation time; increased platelet count; increased factors II, VII antigen, VIII antigen, VIII coagulant activity, IX, X, XII, VII-X complex, II-VII-X complex, and β-thromboglobulin; decreased levels of anti-factor Xa and ATIII, and decreased ATIII activity; increased levels of fibrinogen and fibrinogen activity; increased plasminogen antigen and activity; increased plasma HDL and HDL-2 subfraction concentrations, reduced LDL-C concentration, and increased triglyceride levels.

References

See **Estradiol.**

Anderson GL, Judd HL, Kaunitz AM, et al. JAMA 2003; 290:1739-48.

Cauley JA, Robbins J, Chen Z, et al. JAMA 2003; 290:1729-38.

Nelson HD. JAMA 2004; 291:1610-20.

The Women's Health Initiative Steering Committee. JAMA 2004; 249:1701-12.

Summary

Pregnancy Category: X

Lactation Category: S

- There is no indication for **conjugated estrogens** during pregnancy.
- There is no clear evidence of fetal harm after inadvertent exposure during the 1st trimester.

Estrogens, esterified—(Amnestrogen; Estratab; Evex; Femogen; Menest)

International Brand Name—Menest (Argentina, Indonesia); Neo-Estrone (Canada)

Drug Class

Estrogens; Hormones

Indications

Hormone replacement, vasomotor symptoms of menopause, osteoporosis prevention, atrophic vaginitis, primary ovarian failure, breast cancer palliation

Mechanism

Bind to estrogen receptors; has both receptor- and non–receptor-mediated activities

Dosage with Qualifiers

Vasomotor symptoms—1.25mg PO qd, cycle 21d on and 7d off, add a progestin days 14-21 if uterus present
Osteoporosis prevention—0.3mg PO qd, cycle 21d on and 7d off, add a progestin days 14-21 if uterus present
Atrophic vaginitis—0.3-1.25mg PO qd, cycle 21d on and 7d off, add a progestin days 14-21 if uterus present
Primary ovarian failure—1-25mg PO qd
Breast cancer palliation—10mg PO tid ×3mo

NOTE: may be combined with ***methyltestosterone.***

- **Contraindications**—hypersensitivity, pregnancy, undiagnosed vaginal bleeding, thromboembolic disease, estrogen-dependent breast cancer
- **Caution**—lactation, hepatic dysfunction

Maternal Considerations

Esterified estrogens are prepared synthetically from plant sources. There are no indications for **esterified estrogens** during pregnancy. Recent studies suggest estrogen plus **medroxyprogesterone** for the treatment of menopausal symptoms increases the risk of breast cancer and CV disease. It has been long known to increase the risk of endometrial cancer. (See **Estradiol.**)
Side effects include thromboembolism, stroke, MI, endometrial and breast cancer, gallbladder disease, pancreatitis, hypertension, breast tenderness, hepatic adenoma, bloating, N/V, headache, dizziness, depression, weight gain, libido changes, intolerance to contact lenses, migraine, and rash.

Fetal Considerations

Estrogen has myriad effects on the developing embryo/fetus; many are poorly understood (see **Estradiol**).

Breastfeeding Safety

See **Estradiol.**

Drug Interactions

Estrogens are partially metabolized by CYP3A4. Thus, CYP3A4 inducers (e.g., St. John's wort, **phenobarbital, carbamazepine, rifampin**) may reduce plasma estrogen, possibly decreasing therapeutic effects and/or changing the uterine bleeding profile, and inhibitors (e.g., **erythromycin, clarithromycin, ketoconazole, itraconazole, ritonavir,** grapefruit juice) may increase plasma estrogens and result in side effects
The following interactions should be considered in any patient treated with any estrogen: accelerated PT, PTT, and platelet aggregation time; increased platelet count; increased factors II, VII antigen, VIII antigen, VIII coagulant activity, IX, X, XII, VII-X complex, II-VII-X complex, and β-thromboglobulin; decreased

levels of anti-factor Xa and ATIII, and decreased ATIII activity; increased levels of fibrinogen and fibrinogen activity; increased plasminogen antigen and activity; increased plasma HDL and HDL-2 subfraction concentrations, reduced LDL-C concentration, and increased triglyceride levels.

References ..... See **Estradiol.**

Summary .....

Pregnancy Category: X
Lactation Category: S

- There is no indication for **esterified estrogens** during pregnancy.
- There is no clear evidence of fetal harm after inadvertent exposure during the 1st trimester.

Estropipate—(Harmonet; Ogen; Ortho-Est)

International Brand Name—Esgen (Korea); Genoral (Australia); Harmogen (England, Ireland); Ogen (Canada, Indonesia, Korea); Ortho-Est (South Africa); Sultrex (Argentina)

Drug Class ..... Estrogens; Hormones

Indications ..... Vasomotor symptoms of menopause, osteoporosis prevention, hormone replacement for hypogonadism

Mechanism ..... Binds to estrogen receptors, developing and maintaining female sex characteristics; it has both receptor- and non–receptor-mediated activities.

Dosage with Qualifiers .....

Vasomotor symptoms—0.625-5mg PO qd, cycle 21d on and 7d off, add a progestin days 14-21 if uterus present
Osteoporosis prevention—0.625mg PO qd, cycle 21d on and 7d off, add a progestin days 14-21 if uterus present
Hypogonadism—1.75-7.5mg PO qd, cycle 21d on and 7d off, add a progestin days 14-21 if uterus present

- **Contraindications**—hypersensitivity, pregnancy, undiagnosed vaginal bleeding, thromboembolic disease, estrogen-dependent breast cancer
- **Caution**—lactation, hepatic dysfunction

Maternal Considerations .....

Estropipate was formerly known as piperazine estrone sulfate. There are no indications for **estropipate** during pregnancy. Recent studies suggest estrogen plus **medroxyprogesterone** for the treatment of menopausal symptoms increases the risk of breast cancer and CV disease. It has been long known to increase the risk of endometrial cancer. (See **Estradiol**.)
Side effects include thromboembolism, stroke, MI, endometrial and breast cancer, gallbladder disease, pancreatitis, hypertension, breast tenderness, hepatic adenoma, bloating, N/V, headache, dizziness, depression, weight gain, libido changes, intolerance to contact lenses, migraine, and rash.

Fetal Considerations ..... Estrogen has myriad effects on the developing embryo/fetus; many are poorly understood (see **Estradiol**).

Breastfeeding Safety ..... See **Estradiol.**

Drug Interactions ..... Estrogens are partially metabolized by CYP3A4. Thus, CYP3A4 inducers (e.g., St. John's wort, **phenobarbital, carbamazepine,**

rifampin) may reduce plasma estrogen, possibly decreasing therapeutic effects and/or changing the uterine bleeding profile, and inhibitors (e.g., **erythromycin, clarithromycin, ketoconazole, itraconazole, ritonavir,** grapefruit juice) may increase plasma estrogens and result in side effects
The following interactions should be considered in any patient treated with any estrogen: accelerated PT, PTT, and platelet aggregation time; increased platelet count; increased factors II, VII antigen, VIII antigen, VIII coagulant activity, IX, X, XII, VII-X complex, II-VII-X complex, and β-thromboglobulin; decreased levels of anti-factor Xa and ATIII, and decreased ATIII activity; increased levels of fibrinogen and fibrinogen activity; increased plasminogen antigen and activity; increased plasma HDL and HDL-2 subfraction concentrations, reduced LDL-C concentration, and increased triglyceride levels.

References ..... See **Estradiol.**

Summary .....

Pregnancy Category: X
Lactation Category: S

- There is no indication for **estropipate** during pregnancy.
- There is no clear evidence of fetal harm after inadvertent exposure during the 1st trimester.

Ethacrynic acid—(Edecrin)

International Brand Name—Edecril (Australia); Edecrin (Canada); Edecrina (Sweden); Hydromedin (Germany); Reomax (Italy)

Drug Class ..... Diuretics, loop

Indications ..... Hypertension, peripheral edema

Mechanism ..... Inhibits sodium and chloride resorption in the loop of Henle and proximal/distal tubules

Dosage with Qualifiers .....

Hypertension—begin 25mg PO qd; max 100mg/d
Peripheral edema—25mg qd; max 200mg PO bid

- **Contraindications**—hypersensitivity, anuria
- **Caution**—renal or hepatic dysfunction

Maternal Considerations .....

There are no adequate reports or well-controlled studies of **ethacrynic acid** in pregnant women. **Ethacrynic acid** is a potent loop diuretic and rarely indicated. It was used in the past for preeclampsia, pulmonary edema, and diabetes insipidus.
Side effects include hepatotoxicity, neutropenia, thrombocytopenia, agranulocytosis, anorexia, abdominal pain, N/V, diarrhea, hyperglycemia, phlebitis, deafness, tinnitus, rash, and weakness.

Fetal Considerations .....

There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **ethacrynic acid** crosses the human placenta. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically. **Ethacrynic acid** is an inhibitor of glutathione transferases, and glutathione is the principle endogenous antioxidant.

Breastfeeding Safety .....

There is no published experience in nursing women. It is unknown whether **ethacrynic acid** enters human breast milk.

Drug Interactions

Reduces the renal clearance of **lithium,** increasing the risk of toxicity.
May increase the ototoxicity of aminoglycosides and some cephalosporins. Their concurrent use should be avoided.
Displaces **warfarin** from plasma protein and as a result may necessitate a reduction in the **warfarin** dose.
NSAIDs reduce the diuretic, natriuretic, and antihypertensive effects of loop, potassium-sparing, and thiazide diuretics. Patients should be observed closely to determine if the desired effect of the diuretic continues.

References

Wilson AL, Matzke GR. Drug Intell Clin Pharm 1981; 15:21-6.

Summary

Pregnancy Category: B
Lactation Category: U

- Superior agents with fewer side effects for which there is more experience during pregnancy are preferred.

Ethambutol—(Afimocil; Carnotol; Cidanbutol; Coxytol; Danbutol; Myambutol)

International Brand Name—Althocin (Greece); Ambutol (Malaysia); Apo-Ethambutol (New Zealand); Arbutol (Indonesia); Blomison (Greece); Clobutol (Portugal); Combutol (India); Conbutol (Thailand); Corsabutol (Indonesia); Dexambutol (France); Ebutol (Japan, Taiwan); EMB (Germany); EMB-Fatol (Hong Kong); Esanbutol (Japan); Etambutol (Brazil, Bulgaria); Etapiam (Italy); Etham (Thailand); Ethambin-PIN (Philippines); Ethbutol (Thailand); ETH Ciba 400 (Indonesia); Etibi (Austria, Canada, Indonesia, Italy); Holtresis (Philippines); Interbutol (Philippines); Lambutol (Thailand); Myambutol (Austria, Belgium, Denmark, Ecuador, France, Germany, Greece, India, Ireland, Korea, Malaysia, Mexico, Netherlands, Portugal, Spain, Sweden, Switzerland, Taiwan, Thailand); Mycobutol (South Africa); Mycrol (South Africa); Odetol (Philippines); Servambutol (Peru); Stambutol (Finland); Sural (Czech Republic, Hungary); Tambutol (Korea); Tibigon (Indonesia); Tibitol (India, Indonesia); Tibutol (Peru); Tobutol (Thailand)

Drug Class

Antimycobacterials

Indications

Mycobacterial infections

Mechanism

Inhibits growing *Mycobacterium*

Dosage with Qualifiers

Mycobacterial infections—15-25mg/kg qd, max 1g/dose
Tuberculosis adjuvant therapy—15-25mg/kg qd, max 2.5g/dose; given as part of multidrug therapy

NOTE: renal dosing.

- **Contraindications**—hypersensitivity, optic neuritis
- **Caution**—renal dysfunction, ophthalmologic disorders

Maternal Considerations

There are no adequate reports or well-controlled studies of **ethambutol** in pregnant women. The published experience consists of relatively small to moderate sized series and case reports. However, untreated tuberculosis poses a significant threat to mother, fetus, and family. Adherence to treatment can be made difficult because of a general fear of any medication and pregnancy-related nausea. What information exists suggests that all 4 first-line drugs for the treatment of tuberculosis (**isoniazid, rifampin, ethambutol,** and **pyrazinamide**) have excellent safety records in pregnancy.
Side effects include thrombocytopenia, neuropathy (optic, peripheral), anorexia, N/V, joint pain, abdominal pain, fever, headache, hallucinations, pruritus, elevated LFTs.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. **Ethambutol** reportedly crosses the human placenta, achieving an F:M ratio approximating unity. There are no reports suggesting an adverse fetal effect. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically.

Breastfeeding Safety

There are no adequate reports or well-controlled studies in nursing women. Only small quantities of **ethambutol** are excreted into breast milk, and it is generally considered compatible with breastfeeding. The dose ingested by the neonate is inadequate to treat tuberculosis.

Drug Interactions

Antacids may reduce absorption if given within 4h.

References

Bothamley G. Drug Saf 2001; 24:553-65.
Brost BC, Newman RB. Obstet Gynecol Clin North Am 1997; 24:659-73.
Holdiness MR. Early Hum Dev 1987; 15:61-74.
Shneerson JM, Francis RS. Tubercle 1979; 60:167-9.
Tripathy SN. Int J Gynaecol Obstet 2003; 80:247-53.
Tran JH, Montakantikul P. J Hum Lact 1998; 14:337-40.

Summary

Pregnancy Category: B
Lactation Category: S

- Pregnancy does not alter the importance of treating mycobacterial infection.
- **Ethambutol** is considered safe and effective during pregnancy and lactation.

Ethinyl estradiol—(Estinyl; Feminone; Mikrofollin)

International Brand Name—Estinyl (South Africa); Estinyl Oestradiol (France); Esto (Korea); Ethinylestradiolum (Netherlands); Etinilestradiolo (Italy); Ginormon (Portugal); Lynoral (India, Indonesia, Netherlands); Manodiol (Thailand); Progynon C (Austria, Germany, Poland)

Drug Class

Estrogens; Hormones

Indications

Contraception (used with a progestational agent), vasomotor symptoms of menopause, osteoporosis prevention, atrophic vaginitis, primary ovarian failure, breast cancer palliation

Mechanism

Synthetic estradiol with both receptor- and non–receptor-mediated activities

Dosage with Qualifiers

Vasomotor symptoms—1-2mg PO qd, cycle 21d on and 7d off, add a progestin days 14-21 if uterus present
Osteoporosis prevention—0.5mg PO qd, cycle 21d on and 7d off, add a progestin days 14-21 if uterus present
Atrophic vaginitis—1-2mg PO qd, cycle 21d on and 7d off, add a progestin days 14-21 if uterus present
Primary ovarian failure—1-2mg PO qd
Breast cancer palliation—10mg PO tid ×3mo

- **Contraindications**—hypersensitivity, pregnancy, undiagnosed vaginal bleeding, thromboembolic disease, estrogen-dependent breast cancer
- **Caution**—lactation, hepatic dysfunction

Maternal Considerations

There are no indications for **ethinyl estradiol** during pregnancy. Recent studies suggest estrogen plus **medroxyprogesterone** for the treatment of menopausal symptoms increases the risk of breast cancer and CV disease.
Side effects include thromboembolism, stroke, MI, endometrial and breast cancer, gallbladder disease, pancreatitis, hypertension, breast tenderness, hepatic adenoma, bloating, N/V, headache, dizziness, depression, weight gain, libido changes, intolerance to contact lenses, migraine, and rash.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. While **diethylstilbestrol** and other synthetic/environmental estrogens are recognized teratogens with the potential for transgenerational effects, few studies support this effect for naturally occurring substances like **estradiol.** There is no clear evidence of fetal harm after inadvertent exposure during the 1st trimester. Some studies have suggested prenatal exposure to **estradiol** might alter immune programming.

Breastfeeding Safety

Though **estradiol** is excreted into breast milk and has been reported to reduce the amount of milk produced, it is not effective as an inhibitor of lactation. All pharmacokinetic studies have shown that the transfer to breast milk of both **progesterone** and estrogen when taking a contraceptive pill is of the same order as natural hormones. Estrogen-containing contraceptives should be initiated after the 6th week of lactation when the lipid profile has returned to normal and the risk of thrombosis is identical to that of the general population.

Drug Interactions

Estrogens are partially metabolized by CYP3A4. Thus, CYP3A4 inducers (e.g., St. John's wort, **phenobarbital, carbamazepine, rifampin**) may reduce plasma estrogen, possibly decreasing therapeutic effects and/or changing the uterine bleeding profile, and inhibitors (e.g., **erythromycin, clarithromycin, ketoconazole, itraconazole, ritonavir,** grapefruit juice) may increase plasma estrogens and result in side effects
The following interactions should be considered in any patient treated with any estrogen: accelerated PT, PTT, and platelet aggregation time; increased platelet count; increased factors II, VII antigen, VIII antigen, VIII coagulant activity, IX, X, XII, VII-X complex, II-VII-X complex, and β-thromboglobulin; decreased levels of anti-factor Xa and ATIII, and decreased ATIII activity; increased levels of fibrinogen and fibrinogen activity; increased plasminogen antigen and activity; increased plasma HDL and HDL-2 subfraction concentrations, reduced LDL-C concentration, and increased triglyceride levels.

References

See **Estradiol.**

Summary

Pregnancy Category: X
Lactation Category: S

- There is no indication for **ethinyl estradiol** during pregnancy.
- There is no clear evidence of fetal harm after inadvertent exposure during the 1st trimester.

Ethosuximide—(Thosutin; Zarontin)

International Brand Name—Emeside (England, Ireland, Korea); Ethosuximide (India); Ethymal (Netherlands); Etosuximida (Spain); Petimid (Turkey); Petinimid (Austria, Czech Republic); Petnidan (Germany); Suxilep (Bulgaria, Germany, Russia); Suximal (Portugal); Suxinutin (Austria, Bulgaria, Czech Republic, Finland, Hungary, Poland, Sweden, Switzerland); Zarondan (Denmark, Norway); Zarontin (Argentina, Belgium, Canada, England, France, Greece, Ireland, Italy, Japan, Kenya, Malaysia, Netherlands, South Africa, Spain, Uruguay, Zimbabwe)

Drug Class ..... Anticonvulsants; Succinimides

Indications ..... Treatment of absence epilepsy (petit mal)

Mechanism ..... Depresses motor cortex and elevates the threshold of the CNS for convulsion

Dosage with Qualifiers ..... Absence epilepsy—250mg PO bid; monitor levels, max 1.5g/d

- **Contraindications**—hypersensitivity
- **Caution**—bone marrow depression, hepatic or renal dysfunction, mixed seizures, abrupt withdrawal, porphyria

Maternal Considerations ..... There are no adequate reports or well-controlled studies of **ethosuximide** in pregnant women. Metabolism does not appear to be significantly altered by pregnancy, only the volume of distribution. Patients may experience drowsiness. Discontinuation of the drug may be considered during pregnancy if the risk of convulsion does not pose a significant health threat to the mother. There is no interaction between **ethosuximide** and oral contraceptive agents.
Side effects include agranulocytosis, SLE, Stevens-Johnson syndrome, pancytopenia, anorexia, dyspepsia, N/V, diarrhea, irritability, headache, dizziness, rash, hirsutism, and gingival hyperplasia.

Fetal Considerations ..... There are no adequate reports or well-controlled studies in human fetuses. **Ethosuximide** crosses the human placenta, achieving an F:M ratio approximating unity. The associations between **ethosuximide** and either birth defects or behavioral disorders are unclear.

Breastfeeding Safety ..... There are no adequate reports or well-controlled studies in nursing women. **Ethosuximide** is excreted into human breast milk, achieving M:P ratios approximating 0.8-0.9 with an estimated total exposure of 3.6-11mg/kg. Serum concentrations in breastfed neonates range from 15 to 40ng/ml.

Drug Interactions ..... May interact with other antiepileptic drugs (e.g., may elevate **phenytoin** levels; may be reduced by **valproate**).

References ..... Koup JR, Rose JQ, Cohen ME. Epilepsia 1978; 19:535-9.
Kuhnz W, Koch S, Jakob S, et al. Br J Clin Pharmacol 1984; 18:671-7.
Samren EB, van Duijn CM, Koch S, et al. Epilepsia 1997; 38:981-90.
Tejerizo Lopez LC, de Santiago Obeso J, Henriquez Esquiroz JM, et al. An Esp Pediatr 1987; 27:352-6.
Tomson T, Villen T. Ther Drug Monit 1994; 16:621-3.

Summary .....
Pregnancy Category: C
Lactation Category: NS (possibly)

- **Ethosuximide** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Ethyl alcohol—(Ethanol)

International Brand Name—None identified.

Drug Class	Toxicology
Indications	Methanol or ethylene glycol intoxication
Mechanism	Inhibits alcohol dehydrogenase
Dosage with Qualifiers	Methanol intoxication—begin 1000mg/kg IV over 1-2h, then 100mg/kg/h IV over 1-2h to keep ethanol level at 100-130mcg/dl Ethylene glycol intoxication—begin 1000mg/kg IV over 1-2h, then 100mg/kg/h IV over 1-2h to keep ethanol level at 100-130mcg/dl • **Contraindications**—hypersensitivity, epilepsy, diabetic coma • **Caution**—hepatic or renal dysfunction, diabetes mellitus, gout
Maternal Considerations	**Ethyl alcohol** is one of the most commonly abused drugs during pregnancy. The patient may misrepresent **ethyl alcohol** use. Antenatal alcohol interviews have the greatest correlation with postnatal outcome and should be part of each prenatal record. ***Side effects*** include euphoria and intoxication.
Fetal Considerations	**Ethyl alcohol** is the most common teratogen (prevalence 0.5-2/1000 births) and typically reflects chronic consumption. In addition to the well-described fetal alcohol syndrome (pre- and postnatal IUGR, CNS anomalies, and a wide spectrum of malformations, the most typical being the craniofacial features), recent evidence suggests **ethyl alcohol** may decrease endothelial responses. Tobacco and/or cocaine use are synergistic in their adverse fetal effects. The effects of antenatal exposure on brain development are varied.
Breastfeeding Safety	**Ethyl alcohol** is excreted into the breast milk, but the quantity ingested by the neonate is too small to have a significant impact.
Drug Interactions	Potentially alters the metabolism of drugs too numerous to list here. Consult package insert before prescribing a new agent to an alcoholic patient. Enhances the effects of CNS-depressant drugs (e.g., **tramadol, hydromorphone, morphine, oxymorphone**).
References	Jacobson SW, Chiodo LM, Sokol RJ, Jacobson JL. Pediatrics 2002; 109:815-25. Mattson SN, Schoenfeld AM, Riley EP. Alcohol Res Health 2001; 25:185-91. Turcotte LA, Aberle NS, Norby FL, et al. Alcohol 2002; 26:75-81.
Summary	**Pregnancy Category: X** **Lactation Category: S** • Each intake interview during pregnancy should include specific questions on maternal **ethyl alcohol** usage.

Etidocaine hydrochloride—(Duranest)

International Brand Name—None identified.

Drug Class	Anesthetics, local
Indications	Anesthesia for minor surgery
Mechanism	Stabilizes the neuronal membrane by inhibiting ionic fluxes required for initiation and transmission
Dosage with Qualifiers	Nerve block—max 8mg/kg at a single injection; up to 400mg *NOTE: contains* ***epinephrine.*** • **Contraindications**—hypersensitivity • **Caution**—severe shock, heart block, peripheral vascular disease, hypertension
Maternal Considerations	**Etidocaine** is a rapid-onset (3-5min), long-duration (5-10h) local anesthetic agent with more profound motor block than seen after injection of equianalgesic concentrations of **bupivacaine.** It is a popular agent in some locales for use in epidural and spinal anesthesia. However, it is not used for labor epidural analgesia due to the motor block. There are no adequate reports or well-controlled studies of **etidocaine** in pregnant women. Tachycardia may be a sign of intravascular injection. ***Side effects*** include maternal hypotension, fetal bradycardia (after paracervical block), tachycardia, convulsions, nervousness, and light-headedness.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. **Etidocaine** crosses the human placenta, achieving an F:M ratio approximating 0.3. Uterine blood flow is preserved in the absence of maternal hypotension. Local anesthetics cross when used for epidural, paracervical, pudendal, or caudal nerve blocks and may cause varying degrees of toxicity. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically.
Breastfeeding Safety	There is no published experience in nursing women. It is unknown whether **etidocaine** enters human breast milk. Considering the indications and dosing, limited **etidocaine** use is unlikely to pose a clinically significant risk to the breastfeeding neonate.
Drug Interactions	No clinically significant interactions identified.
References	Morgan DJ, Cousins MJ, McQuillan D, Thomas J. Eur J Clin Pharmacol 1977; 12:359-65. Nau H. Dev Pharmacol Ther 1985; 8:149-81. Wilson J Acta Anesth Scand Suppl 1975; 60:97-9.
Summary	**Pregnancy Category: B** **Lactation Category: S** (likely) • A local anesthetic with a large clinical experience during pregnancy.

Etidronate—(Didronel)

International Brand Name—Didronat (Turkey); Didronate (Denmark, Norway, Sweden); Didronel (Australia, Austria, Belgium, Canada, England, France, Greece, Hong Kong, Ireland, Israel, Italy, Japan, Netherlands, Portugal, Switzerland); Difosfen (Argentina, Colombia, Costa Rica, Dominican Republic, El Salvador, Guatemala, Panama, Peru, Singapore, Spain, Thailand, Uruguay); Dinol (Korea); Dronate-OS (India); Etibon (Taiwan); Osteotop (Chile, Peru)

Drug Class	Bisphosphonates
Indications	Paget's disease, hypercalcemia
Mechanism	Inhibits bone formation and growth and osteoclast reabsorption
Dosage with Qualifiers	Paget's disease—5-10mg/kg/d; max 10mg/kg/d for <6mo, or 11-20mg/kg/d for <3mo Hypercalcemia—7.5 mg/kg/d IV ×3-7d, then 20mg/kg/d PO ×30-90d • **Contraindications**—hypersensitivity, renal dysfunction • **Caution**—long bone fracture, enterocolitis, cardiac failure
Maternal Considerations	There is no published experience with **etidronate** during pregnancy. ***Side effects*** include fractures, seizures, N/V, diarrhea, and bone pain.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **etidronate** crosses the human placenta. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically.
Breastfeeding Safety	There is no published experience in nursing women. It is unknown whether **etidronate** is excreted into human breast milk.
Drug Interactions	There are isolated reports of patients experiencing an increased PT when on **warfarin.** The majority of these were without clinically significant sequelae. Although the relevance and the mechanism is unclear, patients on **warfarin** should have their PT monitored.
References	Nolen GA, Buehler EV. Toxicol Appl Pharmacol 1971; 18:548-61.
Summary	**Pregnancy Category: B** **Lactation Category: U** • There is no published experience during pregnancy. • **Etidronate** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Etodolac—(Lodine)

International Brand Name—Ecridoxan (Greece); Entrang (Korea); Etodin (Korea); Etonox (Thailand); Etopan (Israel); Etopan XL (Israel); Hypen (Japan); Lodine LP (France); Lodine Retard (Mexico); Lodine SR (Hong Kong); Lonene (Indonesia); Lonine (Greece, Taiwan); Osteluc (Japan); Tedolan (Denmark); Toselac (Korea); Ultradol (Canada)

Drug Class ..... Analgesics, non-narcotic; NSAIDs

Indications ..... Mild to moderate pain, osteoarthritis, rheumatoid arthritis

Mechanism ..... Inhibits cyclooxygenase and lipoxygenase and reduces prostaglandin synthesis

Dosage with Qualifiers .....

Pain—200-400mg PO q6-8h prn, max 1.2g qd
Osteoarthritis—300-500mg PO bid, max 1.2g qd
Rheumatoid arthritis—300-500mg PO bid, max 1.2g qd

- **Contraindications**—hypersensitivity to it or other NSAIDs
- **Caution**—GI bleeding, hypertension, CHF

Maternal Considerations .....

Etodolac is an NSAID antipyretic analgesic. There is no published experience during human pregnancy. (See **Indomethacin.**)
Side effects include anaphylaxis, GI bleeding, acute renal failure, thrombocytopenia, agranulocytosis, interstitial nephritis, hepatotoxicity, Stevens-Johnson syndrome, dyspepsia, nausea, constipation, tinnitus, and fluid retention.

Fetal Considerations .....

There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **etodolac** crosses the human placenta. Other NSAIDs do cross. The pharmacologic profile suggests it is likely to have risks similar to those of **indomethacin,** including oligohydramnios and ductal constriction. Rodent studies performed at doses approximating the MRHD are associated with an increased prevalence of limb abnormalities. Higher doses delayed parturition and increased the perinatal loss rate. (See **Indomethacin.**)

Breastfeeding Safety .....

There is no published experience in nursing women. It is not known whether **etodolac** is excreted into human breast milk. (See **Indomethacin.**)

Drug Interactions .....

NSAIDs may diminish the antihypertensive effect of ACEIs.
NSAIDs reduce renal clearance of **lithium** and increase the plasma levels.
NSAIDs reduce renal elimination and increase plasma **cyclosporine, digoxin, lithium,** and **methotrexate.** Nephrotoxicity associated with **cyclosporine** may also be increased.
Antacids may decrease the peak concentration by 15-20%, but have no effect on the T_{max}.
Protein binding is reduced when administered with **aspirin,** although the clearance of free **etodolac** is not altered. It is recommended **aspirin** be avoided.
May reduce the natriuretic effect of **furosemide** and thiazides in some patients. This response is attributed to the inhibition of renal prostaglandin synthesis.
Phenylbutazone increases (by about 80%) the free fraction of **etodolac.** Their combined use is not recommended.
The effects of **warfarin** and NSAIDs on GI bleeding are synergistic. Short-term pK studies reveal the combined use of **warfarin** and **etodolac** results in decreased protein binding of

warfarin, but no change in free **warfarin** clearance. There is no significant difference in the pharmacodynamic effect of **warfarin** administered alone and **warfarin** administered with **etodolac** as measured by PT. Thus, concomitant therapy should not require dosage adjustment of either drug.

References — There is no published experience in pregnancy or during lactation.

Summary

Pregnancy Category: C
Lactation Category: U

- The pharmacologic profile suggests it is likely to have risks similar to those of **indomethacin.**
- There are alternative agents for which there is more experience during pregnancy and lactation.

Etomidate—(Amidate)

International Brand Name—Etomidato-Lipuro (Argentina); Hypnomidate (Austria, Belgium, Brazil, Bulgaria, Czech Republic, England, France, Germany, Greece, Mexico, Netherlands, Paraguay, Poland, Portugal, Russia, South Africa, Spain, Switzerland, Taiwan, Turkey)

Drug Class — Anesthetics, general

Indications — Induction of general anesthesia

Mechanism — Unknown

Dosage with Qualifiers — Induction of general anesthesia—0.3mg/kg IV (range 0.2-0.6mg/kg) over 30-60sec

- **Contraindications**—hypersensitivity
- **Caution**—unknown

Maternal Considerations — **Etomidate** is a short-acting (3-5min) hypnotic drug without analgesic activity. It has little to no effect on cardiac contractility, and is therefore used to induce general anesthesia for cesarean delivery in women with coexisting cardiac disease.
Side effects include shock, myoclonic movements, N/V, apnea, and injection site reactions.

Fetal Considerations — There are no adequate reports or well-controlled studies of **etomidate** in human fetuses. Transfer across the rodent placenta occurs, reaching concentrations roughly equal to maternal plasma. Rodent studies reveal no evidence of teratogenicity, though embryo and fetal toxicity occurs, and IUGR is seen when the mothers are exposed long-term to high concentrations.

Breastfeeding Safety — There is no published experience in pregnancy. It is unknown whether **etomidate** enters breast milk. However, considering the indications and short t/2, it is unlikely the breastfed neonate would ingest clinically relevant amounts.

Drug Interactions — May enhance CNS depression when used with other CNS depressants.

References

Beltrame D, di Salle E, Giavini E, et al. Reprod Toxicol 2001; 15:195-213.

Downing JW, Buley RJ, Brock-Utne JG, Houlton PC. Br J Anaesth 1979; 51:135-40.
Houlton PJ, Downing JW, Buley RJ, Brock-Utne JG. S Afr Med J 1978; 54:773-5.

Summary

Pregnancy Category: C
Lactation Category: S (likely)

- **Etomidate** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.
- There are alternative agents for which there is more experience during pregnancy and lactation.

Etretinate—(Tegison)

International Brand Name—Tigason (Bulgaria, China, Czech Republic, Greece, Hungary, Israel, Italy, Poland, Portugal, Spain, Sweden, Taiwan, Thailand)

Drug Class

Dermatologics; Retinoids

Indications

Severe psoriasis

Mechanism

Unknown

Dosage with Qualifiers

Severe psoriasis—0.75-1mg/kg in 2-3 divided doses until response, then maintenance of 0.5-0.75mg/kg/d; max 1.5mg/kg

- **Contraindications**—hypersensitivity
- **Caution**—hepatic dysfunction

Maternal Considerations

There are no published studies of **etretinate** in pregnant women. Drug levels may persist for years after treatment, though the relevance of these levels to subsequent pregnancy outcome is unknown. Case reports note normal outcomes several years after treatment ended. Psoriasis is not lethal, and the use of **etretinate** is absolutely contraindicated during pregnancy. Women should be tested for pregnancy within 2w of initiating therapy and use effective contraception.
Side effects include pseudotumor cerebri, hepatotoxicity, corneal opacities, hyperostosis, hyperlipidemia, and elevated hepatic transaminases.

Fetal Considerations

Etretinate is a human and rodent teratogen, with the majority of fetuses exposed during organogenesis affected. Multiple organ systems are affected, including NTDs, facial dysmorphia, limb and digit malformations, microcephaly, and skeletal defects. Exposed fetuses should be referred to an appropriate fetal evaluation unit. **Etretinate** has been used to treat harlequin fetuses with improvement in their skin condition but no change in mortality.

Breastfeeding Safety

There is no published experience in nursing women. It is unknown whether **etretinate** enters human breast milk. It is excreted into rodent milk.

Drug Interactions

No clinically relevant interactions identified.

References

Beltrame D, di Salle E, Giavini E, et al. Reprod Toxicol 2001; 15:195-213.
Reiners J, Lofberg B, Kraft JC, et al. Reprod Toxicol 1988; 2:19-29.

Summary	**Pregnancy Category: X** **Lactation Category: U** • **Etretinate** is absolutely contraindicated during pregnancy.

Exemestane—(Aromasin)

International Brand Name—Aromasin (Australia, Canada, Colombia, England, Germany, Hong Kong, Ireland, Korea, Singapore, Thailand); Aromasine (France)

Drug Class	Antineoplastics, aromatase inhibitor; Hormone modifiers
Indications	Estrogen-sensitive breast cancer in women who have progressed on **tamoxifen**
Mechanism	Irreversible, steroid aromatase inhibitor
Dosage with Qualifiers	Adjuvant therapy for breast cancer—25mg PO qd • **Contraindications**—hypersensitivity • **Caution**—hepatic or renal dysfunction
Maternal Considerations	There is no published experience with **exemestane** during pregnancy. ***Side effects*** include hot flashes, nausea, fatigue, increased sweating, and increased appetite.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **exemestane** crosses the human placenta. It does cross the rodent placenta, achieving concentrations roughly equal to maternal plasma. While increases in embryo resorption and IUGR are seen, there is no increase in the incidence of malformations.
Breastfeeding Safety	There is no published experience in nursing women. It is unknown whether **exemestane** enters human breast milk. It is excreted into rodent milk.
Drug Interactions	Agents that induce CYP3A4 (e.g., **rifampicin, phenytoin, carbamazepine, phenobarbital,** St. John's wort) may decrease **exemestane.** Dose modification is recommended for patients also receiving a potent CYP3A4 inducer.
References	Beltrame D, di Salle E, Giavini E, et al. Reprod Toxicol 2001; 15:195-213.
Summary	**Pregnancy Category: D** **Lactation Category: U** • **Exemestane** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Factor IX—(Alphanine; Bebulin VH; Immuno; Konyne 80; Mononine; Profilnine SD; Proplex T)

International Brand Name—Bebulin (Denmark, Spain); Bebulin S-Tim 4 (Austria); Bebulin Team 4 (Russia); Bebulin TIM 4 (Bulgaria, Hungary); Benefix (Argentina, Brazil, Chile, Mexico); Berinin P (Mexico); Betafact (Israel); Facnyne (Korea); Factor IX S-TIM (Germany); Immunine (Germany, Sweden); Immunine VH (Canada); Inmunine (Venezuela); Konyne 80 (Mexico); Mononine (Belgium, Denmark, England, France, Germany, Ireland, Netherlands, Spain, Sweden); Novact M (Japan); Octanine F (Uruguay); Profilnine HD (Philippines); Profilnine SD (Malaysia, Thailand); Proplex T (Indonesia, Taiwan); Replenine VF (Israel, Malaysia)

Drug Class ..... Blood clotting factors; Blood components, substitute

Indications ..... Factor IX deficiency (prevention and control of bleeding), treatment of anticoagulant overdose

Mechanism ..... Factor IX replacement

Dosage with Qualifiers ..... Bleeding—dose (IU) = kg ×% desired increase in factor IX ×1.2 (1.2 for recombinant, otherwise ×1 for concentrate), given slow IV push
Prophylaxis—20-30IU/kg 1-2×/w given slow IV push
Anticoagulant overdose—dose (IU) = kg ×% desired increase in factor IX, given slow IV push

- **Contraindications**—hypersensitivity to mouse proteins, hepatic dysfunction, DIC, hyperfibrinolytic states
- **Caution**—thrombophilia

Maternal Considerations ..... **Factor IX** is a stabile, lyophilized concentrate either recombinant or made from pooled human plasma. The latter is purified by immunoaffinity chromatography, which reduces the risk of virus transmission. There are no adequate reports or well-controlled studies in pregnant women. The published literature consists of case series and single reports. **Factor IX** deficiency is typically an X-linked disorder, and thus symptoms occur only in women with unbalanced lyonization. Postpartum hemorrhage is the most common complication, and it occurs more often in women receiving fewer than 4d of factor IX replacement.
Side effects include thromboembolic disease, viral disease, flushing, tingling, fever, chills, N/V, urticaria, headache, BP changes, and injection site reaction.

Fetal Considerations ..... There are no adequate reports or well-controlled studies of **factor IX** in human fetuses. Placental transfer is unlikely. Rodent teratogenicity studies have not been conducted.

Breastfeeding Safety ..... There are no adequate reports or well-controlled studies in nursing women. It is unknown whether **factor IX** enters human breast milk. However, any ingested factor would likely be degraded.

Drug Interactions ..... No clinically relevant interactions identified.

References ..... Shobeiri SA, West EC, Kahn MJ, Nolan TE. Obstet Gynecol Surv 2000; 55:729-37.
Yang MY, Ragni MV. Haemophilia 2004; 10:483-90.

Summary .....

Pregnancy Category: C
Lactation Category: S

- Though rarely indicated in pregnancy or during lactation, **factor IX** replacement is likely safe during pregnancy.

Famciclovir—(Famvir)

International Brand Name—Combivent (Argentina, Austria, Belgium, Brazil, Canada, Chile, China, Colombia, Denmark, England, France, Hong Kong, Indonesia, Ireland, Korea, Mexico, Paraguay, Peru, Philippines, Thailand, Uruguay, Venezuela); Famtrex (India); Famvir (Australia, Canada, Ecuador, Hong Kong, Indonesia, Israel, Taiwan, Thailand); Oravir (France); Pentavir (Argentina)

Drug Class	Antivirals
Indications	Treatment of genital herpes and herpes zoster
Mechanism	Inhibits viral DNA polymerase
Dosage with Qualifiers	Genital herpes (1st episode)—250mg PO tid ×7d Genital herpes (recurrent)—125mg PO bid ×5d Genital herpes (prophylaxis)—250mg PO bid Herpes zoster—500mg PO tid ×7d *NOTE: renal dosing.* • **Contraindications**—hypersensitivity • **Caution**—renal dysfunction
Maternal Considerations	**Famciclovir** is metabolized to the active **penciclovir.** There are no adequate reports or well-controlled studies in pregnant women. With a dosing profile superior to **acyclovir,** drugs in this class decrease both asymptomatic shedding and the number of clinical recurrences. It is likely that the same is true during pregnancy, a supposition supported by randomized trials and cohort studies demonstrating a lower-than-expected asymptomatic shedding rate. Drug clearance is slower in nonpregnant women compared to men. ***Side effects*** include headache, N/V, diarrhea, fatigue, itching, paresthesias, and flatulence.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **famciclovir** crosses the human placenta. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically.
Breastfeeding Safety	There is no published experience in nursing women. It is unknown whether **famciclovir** is excreted in human breast milk. **Famciclovir** is excreted in concentrations higher than plasma in lactating rats.
Drug Interactions	Concurrent use with **probenecid** or other drugs eliminated by active renal tubular secretion may increase the plasma concentrations of **penciclovir.** The conversion of 6-deoxypenciclovir to **penciclovir** is catalyzed by aldehyde oxidase. Interactions with other drugs metabolized by this enzyme are possible.
References	Baker DA. Int J Fertil Womens Med 1998; 43:243-8. Leung DT, Sacks SL. Drugs 2000; 60:1329-52. Scott LL. Clin Obstet Gynecol 1999; 42:134-48.
Summary	**Pregnancy Category: B** **Lactation Category: U** • This class of agents has several potential applications during pregnancy. • Physicians are encouraged to register pregnant women under the Famciclovir Pregnancy Registry (1-888-669-6682) maintained by the manufacturer for a better follow-up of the outcome while under treatment with **famciclovir.**

Famotidine—(Pepcid)

International Brand Name—Agufam (Thailand); Amfamox (Australia); Antiflam (Uruguay); Apo-Famotidine (New Zealand); Apogastine (Israel); Asid (Brazil); Ausfam (Australia); Beilande (Hong Kong); Bestidine (Korea); Blocacid (Singapore); Brolin (Spain); Cepal (Greece); Durater (Dominican Republic, El Salvador, Guatemala, Honduras, Mexico, Panama); Facid (Indonesia); Fadin (Taiwan); Fadine (Hong Kong, Malaysia, Thailand); Fadul (Germany); Fafotin (Korea); Famine (Hong Kong); Famo (Germany, Israel); FamoABZ (Germany); Famoc (Singapore); Famocid (India); Famodil (Italy); Famodin (Bulgaria); Famogal (Colombia); Famogard (Russia); Famohexal (Australia); Famolta (Hong Kong); Famonerton (Germany); Famopril (Singapore); Famopsin (Hong Kong, Malaysia, Thailand); Famos (Indonesia); Famosan (Bulgaria); Famosia (Thailand); Famotal (Norway); Famotep (Portugal); Famotin (Ecuador, Singapore); Famotine (Peru); Famowal (India); Famox (Hong Kong, New Zealand, Taiwan); Famoxal (Mexico); Fanox (Spain); Fararidin (Korea); Farmotex (Mexico); Farotin (Korea); Fenox (Colombia); Ferotine (Korea); Fibonel (Chile, Ecuador); Fudone (South Africa); Fuweidin (Taiwan); Gardin (Korea); Gaster (China, Indonesia, Japan, Taiwan); Gastren (Paraguay); Gastridin (Italy); Gastrion (Spain); Gastro (Israel); Gastroflux (Philippines); H2 Bloc (Philippines); Incifam (Indonesia); Kemofam (Indonesia); Kimodin (Taiwan); Logos (South Africa); Motiax (Italy); Motidine (Hong Kong, Singapore); Pepcid (Australia, Canada, England, Ireland, South Africa, Sweden); Pepcidac (France); Pepcid AC (Canada, New Zealand); Pepcidin (Denmark, Finland, Netherlands, Norway, Sweden, Turkey); Pepcidina (Portugal); Pepcidine (Austria, Belgium, Costa Rica, Ecuador, El Salvador, Guatemala, Honduras, Hong Kong, Malaysia, Mexico, New Zealand, Nicaragua, Panama, Peru, Philippines, Russia, Switzerland); Pepcidin Rapitab (Norway); Pepdif (Turkey); Pepdine (France); Pepdul (Germany); Pepfamin (Thailand); Peptan (Greece); Pepticon (Korea); Pepzan (Hong Kong, Malaysia, New Zealand, Thailand); Purifam (Indonesia); Quamatel (China, Hong Kong); Restadin (Indonesia); Rogasti (Israel); Sedanium-R (Greece); Stadin (Korea); Stomax (Israel); Supertidine (Taiwan); Tamin (Spain); Topcid (India); Ulcatif (Israel); Ulcedine (Hong Kong); Ulcefam (Philippines); Ulcelac (Argentina); Ulcenol (Venezuela); Ulceran (Hong Kong, Malaysia, Singapore); Ulcidine (Canada); Ulcofam (Thailand); Ulfadin (Colombia); Ulfagel (Ecuador); Ulfam (Indonesia); Ulfamid (Poland); Ulped (Costa Rica, Dominican Republic, El Salvador, Guatemala, Honduras, Nicaragua, Panama); Ulped AR (Costa Rica, Dominican Republic, El Salvador, Guatemala, Honduras, Nicaragua, Panama); Voker (Malaysia); Weimok (Taiwan); Winiful (Taiwan); Wiretin (Korea); Yamarin (South Africa)

Drug Class	Antihistamines, H_2; Gastrointestinals
Indications	Treatment of GERD, gastric ulcer disease, and Zollinger-Ellison syndrome
Mechanism	H_2-receptor antagonist
Dosage with Qualifiers	GERD—20-40mg PO qhs for 12w Gastric ulcer—20-40mg PO qhs for 4-6w Zollinger-Ellison syndrome—20-60mg PO q6h, max 160mg PO q6h *NOTE: renal dosing.* • **Contraindications**—hypersensitivity, PKU • **Caution**—renal dysfunction
Maternal Considerations	There are no adequate reports or well-controlled studies of **famotidine** in pregnant women. There are only rare reports of its use during pregnancy. A single dose of **famotidine** administered to parturients PO 3h before surgery is more effective neutralizing gastric secretion than **omeprazole.** One epidemiologic study concluded the use of H_2 antagonists during pregnancy was associated with a higher prevalence of preterm birth. ***Side effects*** include pancytopenia, leukopenia, thrombocytopenia, jaundice, bronchospasm, headache, taste change, constipation, diarrhea, acne, dizziness, dry skin, periorbital edema, myalgias, elevated LFTs, tinnitus, proteinuria, and elevated BUN/Cr levels.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. **Famotidine** crosses the placenta, achieving an F:M ratio approximating 0.40. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically.
Breastfeeding Safety	There are no adequate reports or well-controlled studies in nursing women. **Famotidine** is excreted into human milk to a

	lesser extent than **cimetidine** and **ranitidine** and is thus the preferred agent if a drug of this class is indicated. The daily infant dose has been estimated to be 10.8mcg/kg/d.
Drug Interactions	No clinically significant interactions identified.
References	Dicke JM, Johnson RF, Henderson GI, et al. Am J Med Sci 1988; 295:198-206. Garbis H, Elefant E, Diav-Citrin O, et al. Reprod Toxicol 2005; 19:453-8. Jacoby EB, Porter KB. Am J Perinatol 1999; 16:85-8. Lin CJ, Huang CL, Hsu HW, Chen TL. Acta Anaesthesiol Sin 1996; 34:179-84.
Summary	**Pregnancy Category: B** **Lactation Category: S** • **Famotidine** is effective for the treatment of GERD and peptic ulcer disease, and has a reassuring safety profile in animals. • There is little published experience during human pregnancy and lactation. • There are alternative agents for which there is more experience during pregnancy and lactation.

Felbamate—(Felbatol; Taloxa)

International Brand Name—Felbamyl (Argentina); Taloxa (France, Netherlands, Sweden)

Drug Class	Anticonvulsants
Indications	Second-line therapy for seizure disorders
Mechanism	Unknown
Dosage with Qualifiers	Seizure disorder—400-1200mg PO tid, max 3600mg/d *NOTE: renal dosing.* • **Contraindications**—hypersensitivity • **Caution**—hepatic or renal dysfunction, history of blood dyscrasias
Maternal Considerations	Epilepsy is a common neurologic disorder affecting 1 million American reproductive-age women. There are no adequate reports or well-controlled studies of **felbamate** in pregnant women. Drug interactions between enzyme-inducing antiepileptic drugs such as **felbamate** and hormonal contraceptives are well-documented, increasing the risk of an unplanned pregnancy. Using either a higher-hormone-content oral contraceptive or a second contraceptive is suggested. Planned pregnancy is highly recommended, and counseling before conception crucial, covering folic acid supplementation, optimal control of seizure activity, monotherapy with the lowest effective antiepileptic drug dose, and medication adherence. Drug dose adjustments are often necessary during pregnancy and should be based on clinical symptoms and not solely on serum drug concentrations. ***Side effects*** include aplastic anemia, hepatic failure, anorexia, N/V, headache, insomnia, dizziness, somnolence, constipation, nervousness, tremor, diplopia, depression, abdominal pain, and ataxia.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **felbamate** crosses the human placenta. It does cross the rodent placenta. Rodent studies are reassuring, revealing no evidence of teratogenicity despite the use of doses higher than those used clinically. IUGR was noted.

Breastfeeding Safety

There are no adequate reports or well-controlled studies in nursing women. **Felbamate** is excreted into human breast milk, though the kinetics remain to be elucidated. **Felbamate** is excreted into rodent breast milk, and there is a higher death rate in breastfed pups. If breastfeeding continues, the infant should be monitored for possible adverse effects, the drug given at the lowest effective dose, and breastfeeding avoided at times of peak drug levels.

Drug Interactions

The addition of **felbamate** to antiepileptic drugs (AEDs) affects the steady-state concentrations of AEDs. Briefly, the concentration of **phenytoin** is increased 20-40%, **valproate** increased 10-15%, **carbamazepine** decreased 30%, and **carbamazepine-epoxide** increased some 50%.
AEDs can also alter **felbamate** concentrations. **Phenytoin** causes a near doubling of **felbamate** clearance at steady state and, therefore, a 45% decrease in steady-state trough concentrations compared to the same dose of **felbamate** given as monotherapy. **Carbamazepine** causes a 50% increase in **felbamate** clearance at steady state and, therefore, the addition of **carbamazepine** results in a 40% decrease in the steady-state trough concentrations of **felbamate** compared to the same dose given as monotherapy.

References

Chang SI, McAuley JW. Ann Pharmacother 1998; 32:794-801.
Morrell MJ. Epilepsia 1996; 37(Suppl 6):S34-44.

Summary

Pregnancy Category: C
Lactation Category: U

- **Felbamate** is a second-line treatment for several seizure disorders.
- **Felbamate** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Felodipine—(Plendil)

International Brand Name—AGON SR (New Zealand); Dilahex (Philippines); Dilofen ER (Philippines); Dilopin (Korea); Fedil (Taiwan); Felim (Thailand); Felobal (Korea); Felo-BASF (Germany); Felo-BASF Retardtab (Germany); Felocor (Germany); Felocor Retardtab (Germany); Felodur ER (Australia); Felo ER (New Zealand); Felogamma Retard (Germany); Felogard (India); Felop (Philippines); Felopine-SR (Taiwan); Flodil LP (France); Hydac (Denmark, Finland, Sweden); Keydipin ER (Korea); Lodistad MR (Philippines); Modip (Germany); Munobal (Germany, Japan, Mexico, Philippines, Venezuela); Munobal Retard (Austria, Germany, Switzerland); Nirmadil (Indonesia); Penedil (Israel); Plendil (Argentina, Belgium, Bulgaria, Canada, Czech Republic, Denmark, England, Finland, Greece, Hong Kong, Hungary, Indonesia, Ireland, Malaysia, Mexico, Netherlands, Paraguay, Peru, Philippines, Poland, Russia, Sweden, Switzerland, Taiwan, Thailand, Turkey); Plendil Depottab (Norway); Plendil ER (Philippines); Plendil Retard (Austria); Polo (Taiwan); Renedil (Belgium, Canada); Selepine (Korea); Splendil (Japan); Splendil ER (Korea); Versant XR (Philippines)

Drug Class

Antihypertensives; Calcium channel blockers

Indications

Treatment of chronic hypertension

Mechanism

Dihydropyridine calcium channel blocker

Dosage with Qualifiers

Chronic hypertension—5mg PO qd, max 20mg/d

- **Contraindications**—hypersensitivity
- **Caution**—hepatic dysfunction, CHF

Maternal Considerations

There are no adequate reports or well-controlled studies of **felodipine** in pregnant women. The published experience consists of isolated case reports where **felodipine** was used successfully for the treatment of severe hypertension during pregnancy without adverse effect. Calcium channel blockers are the most effective tocolytic agents. **Felodipine** decreases placental blood flow and prolongs parturition in rabbits.

Side effects include edema, headache, flushing, dizziness, nausea, abdominal pain, diarrhea, rhinorrhea, chest pain, palpitations, muscle cramps, and weakness.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **felodipine** crosses the human placenta. **Felodipine** is associated with an increased prevalence of digital anomalies in rodents possibly secondary to the observed decrease in placental blood flow. Prolonged parturition is associated with an increased perinatal mortality.

Breastfeeding Safety

There is no published experience in nursing women. It is unknown whether **felodipine** enters human breast milk. It is excreted into rodent milk.

Drug Interactions

Felodipine is metabolized by CYP3A4. Its use with CYP3A4 inhibitors (e.g., **ketoconazole, itraconazole, erythromycin,** grapefruit juice, **cimetidine**) may lead to a severalfold increase in plasma **felodipine** levels enhancing its effects (lower BP and increased HR).

Maximum plasma concentrations of **felodipine** are considerably lower in epileptic patients on long-term anticonvulsant therapy (e.g., **phenytoin, carbamazepine, phenobarbital**) compared to healthy volunteers. Since a clinically significant interaction may be anticipated, alternative antihypertensive therapy should be considered for these women.

References

Casele HL, Windley KC, Prieto JA, et al. J Reprod Med 1997; 42:378-81.

Danielson MK, Danielsson BR. Arzneimittelforschung 1993; 43:106-9.

Danielsson BR, Reiland S, Rundqvist E, Danielson M. Teratology 1989; 40:351-8.

Lundgren Y, Thalen P, Nordlander M. Pharmacol Toxicol 1992; 71:361-4.

Summary

Pregnancy Category: C

Lactation Category: U

- **Felodipine** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.
- There are other agents with a superior safety profile for which there is more experience during pregnancy and lactation.

Fenofibrate—(Tricor)

International Brand Name—Apo-Feno-Micro (Hong Kong, Malaysia); Aterolis (Uruguay); Bisterol SR (Korea); Climage (Greece); Controlip (Costa Rica, Dominican Republic, El Salvador, Guatemala, Honduras, Mexico, Nicaragua, Panama); Durafenat (Germany); Durafenat Micro (Germany); Evothyl (Indonesia); Fegenor (France); Felosma (Indonesia); Fenobrate (Argentina); Fenofanton (Germany); Fenogal Lidose (Singapore); Fenox (Thailand); Fibrafen (Philippines); Hyperchol (Indonesia); Lexemin (Hong Kong, Singapore, Thailand); Lipanthyl (Belgium, Bulgaria, China, Cyprus, Czech Republic, France, Germany, Greece, Hong Kong, Hungary, Indonesia, Italy, Kuwait, Malaysia, Philippines, Poland, Russia, Switzerland, Taiwan, Thailand); Lipantil (England, Portugal); Liparison (Spain); Lipidax (Italy); Lipidil (Brazil, Chile, Ecuador, Germany); Lipidil Supra (Korea); Lipilo (China); Lipofen (Portugal); Lipolin (Taiwan); Lipovas (Spain); Lipsin (Austria, South Africa); Livesan Ge (France); Nopid 200 (Korea); Normalip (Germany); Normolip (Colombia); Nubrex (Philippines); Qualipantyl (Hong Kong); Rapidil (Korea); Redose 200 (Korea); Rorit (Korea); Secalip (France); Trichol (Indonesia); Trolip (Hong Kong, Indonesia, Philippines); Zerlubron (Greece); Zumafib (Indonesia)

Drug Class	Antihyperlipidemics
Indications	Hyperlipidemia
Mechanism	Unclear; interferes with triglyceride synthesis
Dosage with Qualifiers	Hypertriglyceridemia—begin 54mg PO qd with meals, adjusting q4-8w; max 160mg qd Hypercholesterolemia—begin 54mg PO qd with meals, adjusting q4-8w; max 160mg qd Mixed dyslipidemia—begin 54mg PO qd with meals, adjusting q4-8w; max 160mg qd *NOTE: 54mg tablet = 67mg capsule.* • **Contraindications**—hypersensitivity, hepatic or renal dysfunction, gallbladder disease • **Caution**—oral anticoagulants
Maternal Considerations	There are no adequate reports or well-controlled studies of **fenofibrate** in pregnant women. One rodent study concludes that pregnant and nonpregnant rats respond differently to **fenofibrate,** and that high maternal doses were associated with delayed delivery. Since hyperlipidemia is not acutely life-threatening, cessation of medication during pregnancy is suggested. ***Side effects*** include hepatitis, pancreatitis, cholelithiasis, myositis, myopathy, elevated LFTs, abdominal pain, headache, constipation, rhinitis, and nausea.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **fenofibrate** crosses the human placenta. **Fenofibrate** causes IUGR given at doses equivalent to the MRHD, and is embryotoxic and teratogenic (predominantly bony abnormalities) at doses 7-10× the MRHD.
Breastfeeding Safety	There is no published experience in nursing women. It is unknown whether **fenofibrate** enters human breast milk.
Drug Interactions	May increase the anticoagulant affect of **warfarin**-type drugs. Use with HMG-CoA reductase inhibitors should be avoided unless the benefit of further alterations in lipid levels is likely to outweigh the increased risk of the combination. Since bile acid sequestrants can bind drugs given concurrently, women should take **fenofibrate** at least 1h before or 4-6h after a bile acid–binding resin to avoid impeding its absorption. Because **cyclosporine** can produce nephrotoxicity with decreases in CrCl and increases in serum creatinine, and because renal excretion is the primary elimination route of fibrate drugs

including **fenofibrate,** there is a risk that an interaction will lead to deterioration in renal function.

References — Soria A, Bocos C, Herrera E. J Lipid Res 2002; 43:74-81.

Summary

Pregnancy Category: C
Lactation Category: U

- **Fenofibrate** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.
- Hyperlipidemia is not acutely life-threatening; cessation of medication during pregnancy is suggested.
- There are alternative agents for which there is more experience during pregnancy and lactation.

Fenoldopam—(Corlopam)

International Brand Name—None identified.

Drug Class — Adrenergic agonists; α_2-agonist; Antihypertensives; D_1 agonists; Dopamine agonists

Indications — Acute severe hypertension

Mechanism — Dopamine D_1-like and α_2-adrenergic receptor agonist

Dosage with Qualifiers — Severe hypertension—0.025-0.3mcg/kg/min IV; increase q15min 0.05-0.1mcg/kg/min until reaching max dose of 1.6mcg/kg/min for 48h

- **Contraindications**—hypersensitivity
- **Caution**—glaucoma, acute CVD, hypokalemia, sulfite allergy, asthma, hepatic dysfunction

Maternal Considerations — **Fenoldopam** is an alternative for treatment of a hypertensive crisis if unresponsive to sodium **nitroprusside.** There are no adequate reports or well-controlled studies of **fenoldopam** in pregnant women. In isolated systems, it causes relaxation of the rodent myometrium.
Side effects include reflex tachycardia, MI, CHF, arrhythmias, leukocytosis, hypokalemia, headache, flushing, N/V, sweating, back pain, abdominal pain, palpitations, constipation, and nasal congestion.

Fetal Considerations — There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **fenoldopam** crosses the human placenta. It relaxes thromboxane-constricted human umbilical arteries. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically. **Fenoldopam** induces a diuresis in fetal sheep.

Breastfeeding Safety — There is no published experience in nursing women. It is unknown whether **fenoldopam** enters human breast milk. It is excreted into rodent milk.

Drug Interactions — Use with β-blockers should be avoided as unexpected hypotension could result from β blockade of the sympathetic reflex response to **fenoldopam.**

■ **References**

Estan L, Berenguer A, Martinez-Mir I, et al. Gen Pharmacol 1993; 24:397-401.
Sato N, Tanaka KA, Szlam F, et al. Anesth Analg 2003; 96:539-44.
Segar JL, Smith FG, Guillery EN, et al. Am J Physiol 1992; 263:R868-73.

■ **Summary**

Pregnancy Category: B
Lactation Category: U

- **Fenoldopam** is an alternative to sodium **nitroprusside** in women with hypertensive crisis unresponsive to other antihypertensive agents.

Fenoprofen—(Nalfon)

International Brand Name—Fenoprex (Argentina); Fenopron (England, Hong Kong, Ireland, Japan, Korea, South Africa, Venezuela); Fepron (Ireland, Italy, Netherlands); Nalfon (Austria, Canada, Denmark, Mexico, Russia, Spain); Nalgesic (France); Progesic (England); Trandor (Brazil)

■ **Drug Class**

Analgesics, non-narcotic; NSAIDs

■ **Indications**

Arthritis, mild to moderate pain

■ **Mechanism**

Inhibits both cyclooxygenase and lipoxygenase; reduces prostaglandin synthesis

■ **Dosage with Qualifiers**

Osteoarthritis or rheumatoid arthritis—300-600mg PO tid or qid; max 3200mg/d
Pain relief—200mg PO q4-6h prn

NOTE: take with meals.

- **Contraindications**—hypersensitivity to drug or class, NSAID asthma
- **Caution**—GI bleeding, hypertension, CHF, nasal polyps

■ **Maternal Considerations**

Fenoprofen is a nonsteroidal, anti-inflammatory, antipyretic agent. There are no adequate reports or well-controlled studies of **fenoprofen** in pregnant women. Similar to other NSAIDs, it is effective for the relief of episiotomy pain. In rodents, **fenoprofen** prolongs parturition, and it reduces contractions of isolated myometrium from monkeys and humans.
Side effects include anaphylaxis, GI bleeding, renal failure, bronchospasm, thrombocytopenia, agranulocytosis, hepatic toxicity, dyspepsia, nausea, headache, constipation, abdominal pain, dizziness, rash, fluid retention, and tinnitus.

■ **Fetal Considerations**

There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **fenoprofen** crosses the human placenta. **Fenoprofen** prolongs gestation in rodents, as do other NSAIDs. It is otherwise poorly studied during pregnancy.

■ **Breastfeeding Safety**

There is no published experience in nursing women. It is unknown whether **fenoprofen** enters human breast milk.

■ **Drug Interactions**

NSAIDs can diminish the antihypertensive effect of ACEIs.
Aspirin decreases the biologic t/2 of **fenoprofen.**
Clinical studies and post-marketing observations show that **fenoprofen** may reduce the natriuretic effect of **furosemide** and thiazides. Observe closely for signs of renal failure when diuretics are used with NSAIDs.

NSAIDs increase plasma **lithium** and reduce renal **lithium** clearance. Patients should be observed carefully for signs of **lithium** toxicity.
NSAIDs competitively inhibit **methotrexate** accumulation in rabbit kidney slices. Caution should be used when NSAIDs are administered concomitantly with **methotrexate.**
The effects of **warfarin** and NSAIDs on GI bleeding are synergistic.
Chronic administration of **phenobarbital** may decrease the plasma t/2 of **fenoprofen.** A dosage adjustment of **fenoprofen** may be required if **phenobarbital** is added or withdrawn.
In vitro studies reveal that **fenoprofen** may displace other drugs that are albumin bound from their binding sites. Patients receiving hydantoins, sulfonamides, or sulfonylureas should be observed for increased activity and, therefore, signs of toxicity from these drugs.

References

Gruber CM, Bauer RO, Bettigole JB, et al. J Med 1979; 10:65-8.
Johnson WL, Harbert GM, Martin CB. Am J Obstet Gynecol 1975; 123:364-75.

Summary

Pregnancy Category: B (**D** in 3rd trimester)
Lactation Category: U

- **Fenoprofen** offers no clear advantage over other NSAIDs for which there is more experience during pregnancy and lactation.

Fentanyl—(Fentanyl Oralet; Oralet; Sublimaze)

International Brand Name—Beatryl (Israel); Fenodid (Mexico); Fentabbott (Brazil); Fentanest (Italy, Mexico, Spain); Leptanal (Norway, Sweden); Sublimaze (Argentina, England, Ireland, Philippines, South Africa); Trofentyl (India)

Drug Class

Analgesics, narcotic; Anesthetics, general

Indications

Anesthesia, preoperative analgesia, regional anesthesia, postoperative pain relief

Mechanism

Binds to various opiate receptors

Dosage with Qualifiers

Anesthesia, adjunct—2-50mcg/kg IV depending on needs
Preoperative analgesia—50-100mcg IV 30-60min prior to surgery
Labor epidural anesthesia—approximately 25mcg intrathecal; 40-50mcg epidural: usually followed by a dose of 20-30mcg/h mixed in solution of dilute local anesthetics (consult a specialty text)
Labor analgesia (IV) —begin 50mcg IV, thereafter 25mcg q20-30min prn
Postoperative pain relief—50-100mcg IV q1-2h prn

NOTE: also available in oral and transdermal forms.

- **Contraindications**—hypersensitivity to drug or class
- **Caution**—hepatic, renal, or pulmonary dysfunction; bowel obstruction; CNS depressant use; hypotension; biliary disease; seizure disorder; inflammatory bowel disease

Maternal Considerations

Fentanyl is a short-acting opiate with considerable risk of abuse. It is often combined during labor with local anesthetics to minimize motor blockade for epidural anesthesia. **Fentanyl** may be used safely in women with severe preeclampsia. It is a useful adjunct to a paracervical block for suction curettage. The chance

of a successful external version is increased by its use with spinal blockade. Its addition to 2.2ml of 0.5% hyperbaric **bupivacaine** with 0.2ml of **morphine** 0.2mg intrathecally reduces the incidence and severity of intraoperative and postoperative shivering after spinal anesthesia for cesarean delivery without increasing other side effects.
Side effects include respiratory depression or arrest, dependency, laryngospasm, bronchospasm, arrhythmias, ileus, cardiac arrest, N/V, weakness, dry mouth, confusion, sweating, euphoria, itching, hypotension, and bradycardia.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. **Fentanyl** rapidly crosses the human placenta, achieving an F:M ratio approximating unity. It crosses the fetal blood-brain barrier and has been used for fetal analgesia where a reduction in endorphin levels is demonstrated. Rodent studies are generally reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically. It is embryotoxic in rodents.

Breastfeeding Safety

There are no adequate reports or well-controlled studies in nursing women. **Fentanyl** enters human breast milk, but is not likely to pose a risk to the neonate of an alert, breastfeeding woman.

Drug Interactions

Metabolized by the CYP3A4 isoform in the liver and intestinal mucosa to norfentanyl. Drugs that inhibit CYP3A4 activity may increase the bioavailability of oral **fentanyl** and decrease the systemic clearance. The expected clinical results would be increased or prolonged opioid effects. Patients who begin or end therapy with potent inhibitors of CYP3A4 such as macrolide antibiotics (e.g., **erythromycin, clarithromycin**), azole antifungal agents (e.g., **ketoconazole, itraconazole**), protease inhibitors (e.g., **ritanovir, nelfinavir**), **diltiazem,** and **nefazadone** while receiving **fentanyl** should be monitored for a change in opioid effects. In contrast, agents that induce CYP3A4 activity (e.g., **rifampin, carbamazepine, phenytoin, St. John's wort**) may increase clearance of **fentanyl** and reduce its efficacy.
The concomitant use of **fentanyl** with other CNS depressants, including but not limited to other opioids, sedatives, hypnotics, tranquilizers (e.g., benzodiazepines), general anesthetics, phenothiazines, skeletal muscle relaxants, and alcohol, may cause respiratory depression, hypotension, and profound sedation, or potentially result in coma or death. The dose of one or both agents should be significantly reduced if such combined therapy is planned.
Not recommended for use in patients who have received MAOIs within 14d because severe and unpredictable potentiation by MAOIs has been reported with opioid analgesics.

References

Birnbach DJ, Matut J, Stein DJ, et al. Anesth Analg 2001; 93:410-3.
Cheng CJ, Sia AT, Lim EH, et al. Can J Anaesth 2001; 48:570-4.
Cooper J, Jauniaux E, Gulbis B, et al. Br J Anaesth 1999; 82:929-31.
Fisk NM, Gitau R, Teixeira JM, et al. Anesthesiology 2001; 95:828-35.
Head BB, Owen J, Vincent RD Jr, et al. Obstet Gynecol 2002; 99:452-7.
Leuschen MP, Wolf LJ, Rayburn WF. Clin Pharm 1990; 9:336-7.
Techanivate A, Rodanant O, Tachawattanawisal W, Somsiri T. J Med Assoc Thai 2005; 88:1214-21.

Wong CY, Ng EH, Ngai SW, Ho PC. Hum Reprod 2002; 17:1222-5.

Summary

Pregnancy Category: C
Lactation Category: S

- **Fentanyl** is a short-acting opiate widely used during pregnancy for analgesia of multiple types.

Ferrous gluconate—(Fergon)

International Brand Name—None identified.

Drug Class

Hematinics; Vitamins/minerals

Indications

Iron deficiency and supplementation

Mechanism

Essential component in many proteins, including hemoglobin

Dosage with Qualifiers

Iron deficiency—2-3mg/kg elemental Fe PO qd in divided doses
Iron supplementation—15-30mg elemental Fe qd

NOTE: 300mg = 35mg elemental Fe; do not take within 2h of tetracyclines or antacids, which may bind the Fe. Also available in parenteral form.
NOTE: available as ferrous fumarate and ferrous sulfate.

- **Contraindications**—hypersensitivity to drug or class, hemochromatosis, hemolytic anemia, thalassemia, hemosiderosis, peptic ulcer disease, ulcerative colitis
- **Caution**—chronic therapy

Maternal Considerations

Iron is absorbed in the duodenum and upper jejunum. About 10% of the delivered dose is absorbed by replete women, and 20-30% in deficient women. Though iron supplementation is widely practiced during pregnancy in the industrialized world, there is no convincing evidence it changes either long- or short-term outcomes. Severe anemia may be an important cause of maternal death, but there is a lack of convincing evidence regarding the risks of mild to moderate maternal anemia. One RCT performed in the US on low-income women with adequate iron stores concluded that the mean birth weight was higher by 108g (p =.03), and the incidence of preterm delivery lower (8% vs 14%; p =.05) with supplementation compared to the control group. In this trial, iron supplementation did not alter the prevalence of SGA infants or 3rd trimester iron status. Women anemic due to iron deficiency should first receive a reticulocytic dose followed by supplementation for the duration of pregnancy. Women with disorders of iron utilization (e.g., thalassemia) should not be routinely supplemented.
Side effects include dyspepsia, N/V, diarrhea, constipation, and dark stools.

Fetal Considerations

There is no evidence that maternal iron supplementation influences the fetal iron status.

Breastfeeding Safety

Maternal iron supplementation does not alter the iron concentration in breast milk.

Drug Interactions

Drugs that alter gastric pH, such as antiacids, H_2 blockers, proton pump inhibitors, and some NSAIDs, may decrease absorption.

Iron may decrease the absorption of numerous compounds, including **cefdinir, didanosine, levodopa, mycophenolate, penicillamine,** quinolones, **tetracycline,** and thyroid hormones.

References

Graves BW, Barger MK. J Midwifery Womens Health 2001; 46:159-66.
Pena-Rosas JP, Viteri FE. Cochrane Database Syst Rev 2006; (3):CD004736.
Rasmussen K. J Nutr 2001; 131:590S-601S.
Siega-Riz AM, Hartzema AG, Turnbull C, et al. Am J Obstet Gynecol 2006; 194:512-9.

Summary

Pregnancy Category: A
Lactation Category: S

- Though the risk of routine iron supplementation during pregnancy and lactation is probably minimal, there is no clear improvement in perinatal outcome or reduction in maternal morbidity in the industrialized world.

Fexofenadine—(Allegra)

International Brand Name—Telfast (France, Germany, Hong Kong, Israel, South Africa, Thailand); Telfast BD (Indonesia)

Drug Class

Antihistamines, H_1

Indications

Allergic rhinitis, chronic urticaria

Mechanism

Selective H_1 antagonist

Dosage with Qualifiers

Allergic rhinitis—180mg PO qd
Chronic urticaria—60mg PO bid

NOTE: may be combined with ***pseudoephedrine.***

- **Contraindications**—hypersensitivity to drug or class
- **Caution**—renal dysfunction

Maternal Considerations

Fexofenadine is a 3rd-generation antihistamine effective for the symptomatic relief of allergic rhinitis. While increasingly preferred for its nonsedating properties, there are no published controlled trials or population studies of **fexofenadine** during pregnancy. The published clinical literature consists of a single case report where it was used for the treatment of PUPPP.
Side effects include dysmenorrhea, drowsiness, nausea, flu-like symptoms, dyspepsia, and fatigue.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **fexofenadine** crosses the human placenta. While there is no evidence of teratogenicity in rodents, there is a dose-dependent increase in IUGR and decrease in the survival of pups.

Breastfeeding Safety

There is no published experience in nursing women. It is unknown whether **fexofenadine** enters human breast milk. However, there is one study of **terfenadine,** of which **fexofenadine** is a metabolite. The average M:P ratio was 0.2. The authors estimated the theoretic infant dose was 6.2mcg/kg/d, or <0.5% of the weight adjusted maternal dose.

Drug Interactions

Use with **ketoconazole** or **erythromycin** increases the plasma **fexofenadine** level. **Fexofenadine** has no effect on the pharmacokinetics of **erythromycin** and **ketoconazole.** The changes in plasma levels are within the range of plasma levels achieved in adequate and well-controlled clinical trials and may be due to transport-related effects, such as P-glycoprotein. Administration within 15min of an aluminum- and magnesium-containing antacid (Maalox) decreased **fexofenadine** AUC by 41% and C_{max} by 43%. **Fexofenadine** should not be taken closely in time with aluminum- and magnesium-containing antacids. Fruit juices such as grapefruit, orange, and apple may reduce the bioavailability of **fexofenadine** by more than ⅓.

References

Buccolo LS, Viera AJ. J Reprod Med 2005; 50:61-3.
Lucas BD Jr, Purdy CY, Scarim SK, et al. Clin Pharmacol Ther 1995; 57:398-402.
Mazzotta P, Loebstein R, Koren G. Drug Saf 1999; 20:361-75.

Summary

Pregnancy Category: C
Lactation Category: S (likely)

- **Fexofenadine** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.
- There are alternative agents, including inhaled steroids and 1st-generation antihistamines such as **chlorpheniramine,** for which there is wide experience during pregnancy and lactation.

Filgrastim—(Neupogen)

International Brand Name—Biofigran (Colombia); Gran (Japan); Granulokine (Philippines); Grasin (Korea); Grimatin (Japan); Neotromax (Peru); Neutromax (Peru)

Drug Class

Biologic response modifiers; Hematopoietic agents

Indications

Severe chronic neutropenia, AIDS neutropenia, neutropenia post–bone marrow transplantation, chemotherapy-induced neutropenia, progenitor cell donors

Mechanism

Human granulocyte colony-stimulating factor

Dosage with Qualifiers

Severe chronic neutropenia—10mcg/kg SC qd
AIDS neutropenia—1-10mcg/kg SC qd
Neutropenia post–bone marrow transplantation—10mcg/kg IV qd >24h after either chemotherapy or transplantation
Chemotherapy-induced neutropenia—5mcg/kg SC/IV qd ×2w; may increase by 5mcg/kg per chemo cycle
Progenitor cell donors—10mcg/kg SC qd

- **Contraindications**—hypersensitivity to drug or class, hypersensitivity to *E. coli* proteins
- **Caution**—hepatic or renal dysfunction

Maternal Considerations

There are no adequate reports or well-controlled studies of **filgrastim** in pregnant women. It has been used to treat severe chronic neutropenia and chemotherapy-induced neutropenia during pregnancy without obvious adverse effect. The published literature is confined to case reports and usually complicated by polypharmacy.

Side effects include anaphylaxis; thrombocytopenia; N/V; musculoskeletal, abdominal, and bone pain; rash; splenomegaly; hypotension; local swelling; and erythema.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **filgrastim** crosses the human placenta. There is no evidence to suggest it is a human teratogen. However, rodent studies using high doses reveal evidence of embryotoxicity, IUGR, and delayed external differentiation.

Breastfeeding Safety

There are no adequate reports or well-controlled studies in nursing women. It is unknown whether **filgrastim** enters human breast milk.

Drug Interactions

Drug interactions have not been fully evaluated. Drugs that may potentiate the release of neutrophils, such as **lithium,** should be used with caution.

References

Cottle TE, Fier CJ, Donadieu J, Kinsey SE. Semin Hematol 2002; 39:134-40.
Dale DC, Cottle TE, Fier CJ, et al. Am J Hematol 2003; 72:82-93.

Summary

Pregnancy Category: C
Lactation Category: U

- **Filgrastim** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Flavoxate—(Urispas)

International Brand Name—Baduson (Taiwan); Bladderon (Japan); Bladuril (Colombia, Mexico, Peru); Cleanxate (Singapore); Flavate (India); Flavorin (Thailand); Flavo-Spa (Thailand); Fucotin (Taiwan); Genurin (China, Italy, Singapore, Taiwan); Harnin (Japan); Patricin (Japan); Spagerin (Korea); Spasdic (Thailand); Spasuret (Germany); Spasuri (Thailand); Tonlin (Taiwan); Urispadol (Denmark); Urispas (Austria, Belgium, Bulgaria, England, France, Hong Kong, India, Ireland, Malaysia, Portugal, Russia, Switzerland, Turkey); Urispas (200 mg) (Canada, Netherlands); Uronid (Spain); Uropeace (Korea); Uroxate (Taiwan, Thailand); Voxate (Thailand); Yungken (Taiwan)

Drug Class

Anticholinergics; Antispasmodics

Indications

Bladder spasm

Mechanism

Antagonizes muscarinic receptors

Dosage with Qualifiers

Bladder spasm—100-200mg PO tid or qid

- **Contraindications**—hypersensitivity to drug or class, intestinal obstruction, GI bleeding, achalasia
- **Caution**—unknown

Maternal Considerations

There is no published experience with **flavoxate** during pregnancy. In nonpregnant women, **flavoxate** first increases, then decreases, uterine contractions.
Side effects include leukopenia, N/V, dry mouth, dizziness, blurred vision, tachycardia, palpitations, headache, drowsiness, dysuria, urticaria, and fever.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **flavoxate** crosses the placenta. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically.

Breastfeeding Safety	There is no published experience in nursing women. It is unknown whether **flavoxate** enters human breast milk.
Drug Interactions	**Flavoxate** may alter the absorption of numerous drugs by slowing GI motility.
References	Coutinho EM, Darze E, Gesteira SK. Int J Gynaecol Obstet 1980; 17:581-4.
Summary	**Pregnancy Category: B** **Lactation Category: U** • **Flavoxate** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk. There are few if any indications.

Flecainide—(Tambocor)

International Brand Name—Almarytm (Italy); Apocard (Spain); Aristocor (Austria); Flecadura (Germany); Flecaine (France); Flecaine LP (France); Flecatab (Australia); Tambocor (Argentina, Belgium, Canada, Chile, Costa Rica, Denmark, Dominican Republic, El Salvador, England, Finland, Germany, Guatemala, Honduras, Hong Kong, Ireland, Japan, Korea, Malaysia, Mexico, Netherlands, Norway, Panama, Philippines, Sweden, Switzerland, Taiwan, Thailand, Uruguay)

Drug Class	Antiarrhythmics, class IC
Indications	Ventricular or atrial arrhythmias
Mechanism	Depresses action potential by stabilizing cell membranes
Dosage with Qualifiers	Ventricular arrhythmia—100mg PO q12h (max 400mg qd; increase dose by 50mg/d q4d) Atrial arrhythmia—50mg PO q12h (max 400mg qd; increase dose by 50mg/d q4d) • **Contraindications**—hypersensitivity to drug or class, cardiogenic shock, severe AV block, bi- or trifascicular block • **Caution**—CHF, hepatic or renal dysfunction, prolonged QT interval
Maternal Considerations	There are no adequate reports or well-controlled studies of **flecainide** in pregnant women. **Flecainide** has been used successfully for the treatment of maternal arrhythmias during pregnancy. ***Side effects*** include ventricular arrhythmia, CHF, cardiac arrest, arrhythmia, dizziness, blurred vision, dyspepsia, headache, N/V, fatigue, weakness, constipation, and chest pain.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. **Flecainide** rapidly crosses the placenta, achieving an F:M ratio approximating unity in the early 3rd trimester, and like **digoxin,** is concentrated in AF. However, better controlled studies in the baboon suggest an F:M ratio of 0.49. An accepted second-line agent for the treatment of fetal SVT, the popularity of **flecainide** as a first-line agent, especially with hydrops, is growing. An elevated umbilical venous pressure, such as that associated with hydrops fetalis, reduces the placental transport of both **flecainide** and **digoxin.**
Breastfeeding Safety	Though **flecainide** is excreted in human breast milk, achieving an M:P ratio approximating 2.5, the quantity consumed would be

unlikely to produce a neonatal plasma level above 100ng/ml, a subtherapeutic level.

Drug Interactions

A 13-19% increase in plasma **digoxin** levels occurred at 6h postdose during administration of multiple oral doses of **flecainide** to healthy subjects stabilized on a maintenance dose of **digoxin**.

In a study involving healthy subjects receiving **flecainide** and **propranolol** concurrently, plasma **flecainide** increased 20% and **propranolol** increased 30% compared to control. Each had negative inotropic effects that were additive. In clinical trials, patients receiving β-blockers and **flecainide** did not experience an increased incidence of side effects. Nevertheless, the possibility of additive negative inotropic effects of β-blockers and **flecainide** should be recognized.

Plasma **flecainide** may increase 2-fold or more when **amiodarone** is added if the **flecainide** dosage is not reduced.

Drugs that inhibit CYP11D6, such as **quinidine,** might increase plasma **flecainide** concentrations in patients who are on chronic **flecainide** therapy; especially if these patients are extensive metabolizers.

References

Bourget P, Pons JC, Delouis C, et al. Ann Pharmacother 1994; 28:1031-4.

Dimas VV, Taylor MD, Cunnyngham CB, et al. Pediatr Cardiol 2005; 26:815-20.

Ebenroth ES, Cordes TM, Darragh RK. Pediatr Cardiol 2001; 22:483-7.

Fagih B, Sami M. Can J Cardiol 1999; 15:113-7.

Krapp M, Baschat AA, Gembruch U, et al. Ultrasound Obstet Gynecol 2002; 19:158-64.

McQuinn RL, Pisani A, Wafa S, et al. Clin Pharmacol Ther 1990; 48:262-7.

Palmer CM, Norris MC. Am J Dis Child 1990; 144:144.

Schmolling J, Renke K, Richter O, et al. Ther Drug Monit 2000; 22:582-8.

Simpson JM, Sharland GK. Heart 1998; 79:576-81.

Summary

Pregnancy Category: C
Lactation Category: S

- **Flecainide** is one of the drugs of choice for the treatment of fetal hydrops secondary to SVT.
- **Flecainide** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Fluconazole—(Diflucan)

International Brand Name—Baten (Colombia, Dominican Republic, El Salvador, Guatemala, Honduras, Panama); Biozole (Malaysia); Biozolene (Italy); Cancid (Indonesia); Cryptal (Indonesia); Diflu (Korea); Diflucan (Canada, Chile, China, Colombia, Ecuador, Hong Kong, Indonesia, Japan, Korea, Malaysia, Mexico, Peru, Philippines, Taiwan, Thailand); Difnazol (Korea); Flocan (Korea); Flozole (Korea); Flucand (Israel); Flucanol (Israel); Flucazol (Brazil); Flucess (Indonesia); Flucona (Korea); Flucoral (Indonesia); Flucozal (Brazil, Hong Kong); Fludicon (Hong Kong); Fludizol (Thailand); Flukazol (Mexico); Flukezol (Mexico); Flumax (Korea); Flunco (Thailand); Flunizol (Peru); Forcan (India); Fukole (Malaysia); Fulkor (Philippines); Fumay (Taiwan); Funazol (Korea); Funex (Colombia); Fungata (Austria, Germany); Funzela (Philippines); Govazol (Indonesia); Kyrin (Thailand); Medoflucon (China, Singapore); Mutum (Argentina, Peru, Venezuela); Mycorest (Singapore); Nobzol-1 (Colombia); Nobzol-2 (Colombia); Oneflu (Korea); Oxifugol (Mexico); Oxifungol (Mexico); Plunazol (Korea); Prinazole (Korea); Sixanol (Paraguay, Uruguay); Stalene (Hong Kong, Singapore, Thailand); Syscan (India); Tavor (Colombia); Tinazole (Korea); Treflucan (Israel); Triflucan (France, Israel, Turkey); Zemyc (Indonesia); Zoldicam (Mexico)

Drug Class	Antifungals
Indications	Candidiasis, cryptococcal meningitis
Mechanism	Inhibits CYP and C-14 demethylation
Dosage with Qualifiers	Esophageal or oropharyngeal candidiasis—200mg PO/IV ×1, then 100mg PO/IV qd Vaginal candidiasis—150mg PO ×1 Cryptococcal meningitis—400mg PO/IV ×1, then 200mg PO/IV qd • **Contraindications**—hypersensitivity to drug or class, use of astemizole, cisapride, or terfenidine • **Caution**—hepatic or renal dysfunction
Maternal Considerations	There are no adequate reports or well-controlled studies of **fluconazole** in pregnant women. It has been used for the treatment of coccidioidomycosis during pregnancy and *Candida* sepsis postpartum. The systemic antifungal drug with which there has been the most experience is **amphotericin B**. ***Side effects*** include hepatotoxicity, seizures, angioedema, Stevens-Johnson syndrome, agranulocytosis, nausea, vomiting, headache, rash, dizziness, diarrhea, dyspepsia, and taste changes.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **fluconazole** crosses the human placenta. Four children are described with a similar and rare pattern of anomalies. The features include brachycephaly, abnormal facies, abnormal calvarial development, cleft palate, femoral bowing, thin ribs and long bones, arthrogryposis and congenital heart disease. Each was associated with chronic, parenteral use in the 1st trimester. Limited duration oral therapy is unlikely to pose a teratogenic risk. **Fluconazole** does not appear to increase the risks of IUGR or preterm delivery. It has been used for the treatment of congenital candidiasis. Rodent studies conducted at multiples of the MRHD revealed a variety of ossification defects considered consistent with inhibition of estrogen synthesis. There was an increased risk of cleft palate in rats when combined with **phenytoin**. Similar concerns have been reported in humans.
Breastfeeding Safety	There are no adequate reports or well-controlled studies in nursing women. **Fluconazole** enters human breast milk at concentrations similar to maternal plasma. It is generally recommended that breastfeeding be avoided.

Drug Interactions

Clinically significant hypoglycemia may result from the use of **fluconazole** with oral hypoglycemic agents including death. **Fluconazole** reduces the metabolism of **tolbutamide, glyburide,** and **glipizide** and increases the plasma concentration of these agents. When **fluconazole** is used concomitantly with these or other sulfonylurea oral hypoglycemic agents, blood glucose concentrations should be carefully monitored and the dose of the sulfonylurea should be adjusted as necessary.
Prothrombin time may be increased in patients receiving **fluconazole** and **coumarin**-type anticoagulants. Careful monitoring of prothrombin time is recommended.
Increases the plasma concentrations of **phenytoin**. Careful monitoring of **phenytoin** concentrations is recommended.
May significantly increase **cyclosporine** levels in renal transplant patients with or without renal impairment. Careful monitoring of **cyclosporine** concentrations and serum creatinine is recommended.
Rifampin enhances the metabolism of **fluconazole**. Depending on clinical circumstances, consideration should be given to increasing the dose of **fluconazole** when it is administered with **rifampin**.
Increases the serum concentrations of **theophylline**. Careful monitoring of serum theophylline concentrations is recommended.
Cimetidine decreases the **fluconazole** AUC and C_{max}.
Hydrochlorothiazide increases the **fluconazole** AUC and C_{max}
These changes are attributable to a mean ±SD reduction in renal clearance of 30% ± 12%.
Increases the **zidovudine** AUC 20% ± 32% (range: -27 to 104%). The metabolite, GZDV to parent drug ratio significantly decreased after the administration of **fluconazole,** from 7.6 ± 3.6 to 5.7 ± 2.2.

References

Sorensen HT, Nielsen GL, Olesen C, et al. Br J Pharmacol 1999; 48:234-8.
Jick SS. Pharmacotherapy 1999; 19:221-2.
Lee BE, Feinberg M, Abraham JJ, Murthy ARK. Pediatr Infect Dis J 1992; 11:1062-4.
Lopez-Rangel E, Van Allen MI. Birth Defects Res A Clin Mol Teratol 2005;73:919-23.
Nørgaard M, Pederson L, Gislum M, et al. J Antimicrob Chemother 2008; 62:172-6.
Tiboni GM, Iammarrone E, Giampietro F, et al. Teratology 1999; 59:81-7.

Summary

Pregnancy Category: C
Lactation Category: NS (possibly)

- **Fluconazole** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.
- Current evidence suggests it may be a weak teratogen.
- There are alternative agents for which there is more experience during pregnancy and lactation.

Flucytosine—(Ancoban)

International Brand Name—Alcobon (England, Ireland, Israel, New Zealand, South Africa); Ancotil (Australia, Austria, Bulgaria, Czech Republic, Denmark, England, France, Hong Kong, Ireland, Italy, Japan, Malaysia, Netherlands, Norway, Poland, Sweden, Switzerland)

Drug Class	Antifungals
Indications	Severe fungal infection
Mechanism	Unknown
Dosage with Qualifiers	Severe fungal infection—50-150mg/kg PO qd in 4 divided doses • **Contraindications**—hypersensitivity to drug or class • **Caution**—hepatic or renal dysfunction, bone marrow depression
Maternal Considerations	There are no adequate reports or well-controlled studies of **flucytosine** in pregnant women. It has been used during pregnancy for the treatment of cryptococcal meningitis and pneumonia, and *Candida* septicemia. The systemic antifungal drug with which there has been the most experience is **amphotericin B.** ***Side effects*** include cardiac or respiratory arrest, ventricular dysfunction, GI bleeding, renal failure, agranulocytosis, aplastic anemia, thrombocytopenia, N/V, chest pain, dyspepsia, rash, itching, abdominal pain, diarrhea, ataxia, headache, paresthesias, hallucinations, hypoglycemia, hypokalemia, and dizziness.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **flucytosine** crosses the human placenta. While rat studies revealed teratogenicity at doses analogous to human doses, no adverse effects were found in mice, rabbits, and primates.
Breastfeeding Safety	There is no published experience in nursing women. It is unknown whether **flucytosine** enters human breast milk.
Drug Interactions	**Cytarabine,** a cytostatic agent, has been reported to inactivate the antifungal activity of **flucytosine** by competitive inhibition. Drugs that impair glomerular filtration may prolong the biologic t/2 of **flucytosine.**
References	Chen CP, Wang KG. Am J Perinatol 1996; 13:35-6. Ely EW, Peacock JE, Haponik EF, Washburn RG. Medicine (Baltimore) 1998; 77:153-67. Moudgal VV, Sobel JD. Expert Opin Drug Saf 2003; 2:475-83. Schonebeck J, Segerbrand E. Br Med J 1973; 4:337-8.
Summary	**Pregnancy Category: C** **Lactation Category: U** • **Flucytosine** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk. • There are alternative agents for which there is more experience during pregnancy and lactation.

Fludrocortisone—(Florinef)

International Brand Name—Astonin (Spain); Astonin H (Austria, Czech Republic, Germany, Hungary); Cortineff (Bulgaria, Poland); Floricot (India); Florinef (Canada, Chile, Denmark, England, Finland, Greece, Hong Kong, Ireland, Japan, Korea, Malaysia, Netherlands, Norway, Russia, South Africa, Sweden, Switzerland, Taiwan, Thailand); Florinefe (Brazil, Uruguay, Venezuela); Lonikan (Argentina)

Drug Class ..... Corticosteroids

Indications ..... Adrenal insufficiency, postural hypotension

Mechanism ..... Anti-inflammatory, replacement mechanism unknown

Dosage with Qualifiers .....

Adrenal insufficiency—0.1-0.2mg PO qd
Postural hypotension—0.1-1mg PO qd

- **Contraindications**—hypersensitivity to drug or class, systemic fungal infection
- **Caution**—CHF, hepatic or renal dysfunction, diabetes, hypertension, tuberculosis, osteoporosis

Maternal Considerations .....

Fludrocortisone is a synthetic adrenal steroid possessing potent mineralocorticoid and glucocorticoid activities. There are no adequate reports or well-controlled studies of **fludrocortisone** in pregnant women. The published literature consists of cases reports and small series. It has been used without complication for the treatment of adrenal insufficiency during pregnancy. The needed replacement dose often increases and should be guided by serial biochemical measurements. Women treated for salt-losing, congenital adrenal hyperplasia conceive and complete pregnancies successfully. ***Side effects*** include adrenal insufficiency, steroid psychosis, immunosuppression, peptic ulcer disease, N/V, diarrhea, headache, dizziness, insomnia, mood swings, anxiety, hypokalemia, hyperglycemia, acne, cushingoid features, skin atrophy, and poor wound healing.

Fetal Considerations .....

There are no adequate reports or well-controlled studies in human fetuses. Though many corticosteroids in rats have been associated with such anomalies as cleft palate, there is controversy whether corticosteroids are as a class weak teratogens in humans.

Breastfeeding Safety .....

There is no published experience in nursing women. It is unknown whether **fludrocortisone** enters human breast milk, though other corticosteroids are excreted at low concentrations into human breast milk.

Drug Interactions .....

Potassium-sensitive drugs require close monitoring of the potassium level.
May decrease the PT in women taking oral anticoagulants. Monitor prothrombin levels and adjust dosage accordingly.
Decreases the hypoglycemic effect of antidiabetic agents. Monitor for hyperglycemia and adjust the dosage of the antidiabetic drug as necessary.
Increases the ulcerogenic effect and decreases the pharmacologic effect of **aspirin.** Rarely, salicylate toxicity may occur in patients who discontinue steroids.
Barbiturates, **phenytoin,** or **rifampin** each may increase the metabolic clearance of **fludrocortisone** by inducing hepatic enzymes.
May enhance the risk of neurologic complications and inadequate antibody response to vaccines.

Estrogens increase the level of corticosteroid-binding globulin, thus increasing the bound fraction. A reduction in corticosteroid dosage may be required when estrogen is initiated, and increased amounts when estrogen is terminated.

References

Shepard TH, Brent RL, Friedman JM, et al. Teratology 2002; 65:153-61.
Wieacker P, Alexopoulos A, DeGregorio G, Breckwoldt M. Dtsch Med Wochenschr 1989; 114:1117-20.
Zacharin M. J Pediatr Endocrinol Metab 1999; 12:89-94.

Summary

Pregnancy Category: C
Lactation Category: U

- **Fludrocortisone** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Flumazenil—(Marzicon; Romazicon)

International Brand Name—Anexate (Austria, Belgium, Bulgaria, Canada, China, Czech Republic, England, France, Germany, Greece, Hong Kong, Hungary, Indonesia, Ireland, Italy, Japan, Korea, Malaysia, Netherlands, Norway, Poland, Portugal, Spain, Switzerland, Taiwan, Thailand, Turkey); Arsorb (Australia); Lanexat (Argentina, Brazil, Chile, Colombia, Denmark, Ecuador, Finland, Mexico, Paraguay, Peru, Sweden, Uruguay, Venezuela)

Drug Class

Antidotes

Indications

Benzodiazepine overdose

Mechanism

Competitively antagonizes benzodiazepine receptors

Dosage with Qualifiers

Benzodiazepine sedation or overdose reversal—0.2mg IV q min prn; max 5 doses for reversal of sedation, 3mg for overdose

NOTE: watch for re-sedation.

- **Contraindications**—hypersensitivity to drug or class, mixed overdose, TCA overdose
- **Caution**—seizures, alcoholism, psychiatric illness

Maternal Considerations

There are no adequate reports or well-controlled studies of **flumazenil** in pregnant women. The published literature is limited to case reports where it was used successfully for the treatment of benzodiazepine overdose during pregnancy.
Side effects include withdrawal syndrome, seizures, arrhythmias, dizziness, N/V, sweating, blurred vision, headache, bradycardia or tachycardia, anxiety, fatigue, shivering, and confusion.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. Since **flumazenil** can apparently reverse maternally administered **diazepam** in the both the fetus and neonate, it likely crosses the human placenta. Rodent studies reveal no evidence of teratogenicity, but embryotoxicity occurs at high doses. Behavioral changes were noted in rat pups after late pregnancy exposure.

Breastfeeding Safety

There is no published experience in nursing women. It is unknown whether **flumazenil** enters human breast milk. Considering the indication, limited or one-time **flumazenil** use is unlikely to pose a clinically significant risk to the breastfeeding neonate.

Drug Interactions

Caution is necessary when using **flumazenil** in patients with mixed drug overdosage since the toxic effects (e.g., convulsions and cardiac dysrhythmias) of the other drugs (especially cyclic antidepressants) may emerge with the reversal of the benzodiazepine.
Not recommended in epileptic patients who have been receiving chronic benzodiazepine treatment where the abrupt suppression of the protective effect of a benzodiazepine agonist can give rise to convulsions.
The effects of nonbenzodiazepine agonists on the benzodiazepine receptors, such as zopiclone, triazolopyridazines, and others, are also blocked by **flumazenil.**

References

Dixon JC, Speidel BD, Dixon JJ. Acta Paediatr 1998; 87:225-6.
Shibata T, Kubota N, Yokoyama H. Masui 1994; 43:572-4.
Stahl MM, Saldeen P, Vinge E. Br J Obstet Gynaecol 1993; 100:185-8.

Summary

Pregnancy Category: C
Lactation Category: U

- **Flumazenil** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Flunisolide—(AeroBid; Nasalide; Nasarel)

International Brand Name—Bronalide (Canada); Bronilide (France); Flunase (Israel); Flunitec (Argentina, Brazil, Peru, Uruguay); Gibiflu (Italy); Inhacort (Germany); Locasyn (Denmark); Lokilan (Norway); Lokilan Nasal (Finland, Sweden); Lunibron-A (Italy); Lunis (Italy); Nasalide (France); Nasarel (India); Rhinalar (Canada); Sanergal (Slovenia); Synaclyn (Japan); Syntaris (Austria, Bahrain, Belgium, Bulgaria, Czech Republic, England, Germany, Hungary, Ireland, Italy, Kuwait, Netherlands, Poland, Portugal, Puerto Rico, South Africa, Switzerland); Syntaris Nasal Spray (South Africa)

Drug Class

Corticosteroids, inhalation

Indications

Asthma prophylaxis, allergic rhinitis

Mechanism

Unknown

Dosage with Qualifiers

Asthma prophylaxis—2 puffs INH bid (approx 50mcg/puff)
Allergic rhinitis—2 sprays/nostril bid or tid

- **Contraindications**—hypersensitivity to drug or class, status asthmaticus, respiratory infection
- **Caution**—unknown

Maternal Considerations

There is no published experience with **flunisolide** during pregnancy, though inhaled corticosteroids are a cornerstone of asthma therapy. They are used widely during pregnancy without apparent adverse effects.
Side effects include adrenal insufficiency, N/V, diarrhea, headache, sore throat, nasal congestion, dyspepsia, flu-like symptoms, palpitations, abdominal pain, anorexia, peripheral edema, dizziness, cough, eczema, and hypertension.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **flunisolide** crosses the human placenta. In rodents, **flunisolide** is both embryotoxic and teratogenic at 100× the MRHD. Although systemically administered corticosteroids are teratogenic in some rodents, and a weak effect in humans cannot be excluded, the concentration of drug absorbed systemically suggests the risk of a significant fetal effect is low. This conclusion is supported by a recent meta-analysis of inhaled steroid usage during pregnancy.

Breastfeeding Safety	There is no published experience in nursing women. It is unknown whether **flunisolide** enters human breast milk. Considering the concentration and quantity absorbed systemically, it is unlikely the plasma level achieved will be clinically relevant to lactation.
Drug Interactions	No clinically significant interactions identified.
References	Rahimi R, Nikfar S, Abdollahi M. Hum Exp Toxicol 2006; 25:447-52.
Summary	**Pregnancy Category: C** **Lactation Category: U** • **Flunisolide** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Fluocinolone topical—(Synalar)

International Brand Name—Adermina (Chile); Alfabios (Italy); Alvadermo Fuerte (Spain); Aplosyn (Philippines); Capex (Canada); Cervicum (Thailand); Cinolon (Indonesia); Clofeet (Japan); Cortilona (Mexico); Cremisona (Mexico); Cynozet (Philippines); Dermalar (Israel); Dermoflam (Peru); Dermoran (Japan); Esacinone (Israel); Flozet (Philippines); Fluciderm (Thailand); Flucinar (Poland); Flucort (India, Japan, Taiwan); Flulone (Argentina); Flunolone-V (Hong Kong, Singapore); Fluoderm (Canada); Fluonid (Malaysia); Fluquinol (Venezuela); Flusonlen (Taiwan); Fluzon (Japan); Fusalar (Mexico); Inoderm (Indonesia); Jellin (Germany); Luci (India); Radiocin (Israel, South Africa); Supralan (Thailand); Synalar (Canada, New Zealand, Thailand); Synalar 25 (Philippines); Synalar Simple (Mexico, Peru, Uruguay); Syntopic (Philippines)

Drug Class	Corticosteroids; Dermatologics
Indications	Steroid-responsive dermatitis
Mechanism	Unknown
Dosage with Qualifiers	Steroid-responsive dermatitis—apply to affected area bid or qid *NOTE: 0.01% or 0.025% cream, ointment, or salve.* • **Contraindications**—hypersensitivity to drug or class • **Caution**—unknown
Maternal Considerations	There is no published experience with **fluocinolone** during pregnancy. ***Side effects*** include adrenal insufficiency, irritation, burning, itching, dryness, folliculitis, hypertrichosis, acne, hypopigmentation, skin atrophy, and striae.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **fluocinolone** crosses the human placenta. While systemically administered corticosteroids, including **fluocinolone,** are teratogenic in some rodents, and a weak effect in humans cannot be excluded, the concentration of drug absorbed systemically suggests the risk of an adverse fetal effect is low.
Breastfeeding Safety	There are no reports in nursing women. It is unknown whether **fluocinolone** enters human breast milk. However, considering the concentration and quantity absorbed systemically, it is unlikely the plasma level achieved will be clinically relevant to lactation.
Drug Interactions	Topical steroids may increase psoriasis symptoms when combined with **anthralin.**

References

There is no published experience in pregnancy or during lactation.

Summary

Pregnancy Category: C
Lactation Category: U

- **Fluocinolone** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Fluorouracil—(Adrucil)

International Brand Name—Actino-Hermal (Germany); Adrucil (Canada); Efudex (Canada); Efudix (Argentina, Belgium, Bulgaria, Costa Rica, Czech Republic, Dominican Republic, El Salvador, England, France, Germany, Ghana, Guatemala, Honduras, Hong Kong, Ireland, Italy, Japan, Kenya, Mexico, Netherlands, Nicaragua, Panama, Peru, Poland, Puerto Rico, Singapore, South Africa, Spain, Switzerland, Taiwan, Tanzania, Uganda, Uruguay, Zambia); Efurix (Brazil); Fivoflu (Philippines); Fluoxan (Philippines); Fluracedyl (Malaysia); Flurox (Thailand); Ifacil (Mexico); Oncofu (Argentina); Uflahex (Philippines); Utoral (Philippines)

Drug Class

Antimetabolites; Antineoplastics

Indications

Malignancies including breast, colon, basal cell, and gestational trophoblast

Mechanism

Pyrimidine analog that inhibits both DNA and RNA synthesis

Dosage with Qualifiers

Malignancy—Depends on tumor and protocol

NOTE: available in a topical preparation for the treatment of basal cell carcinoma.

- **Contraindications**—hypersensitivity to drug or class, myelosuppression, serious infection, recent surgery
- **Caution**—hepatic or renal dysfunction, prior use of alkylating agents, CAD

Maternal Considerations

There are no adequate reports or well-controlled studies of **fluorouracil** in pregnant women. **Fluorouracil** is most commonly used during pregnancy in the 2nd and 3rd trimesters for the treatment of metastatic breast cancer, where it is often combined with **doxorubicin** and **cyclophosphamide** (FAC). While it should be used only when there is significant risk for the mother's survival, breast cancer can be treated with FAC chemotherapy during the 2nd and 3rd trimesters without significant short-term complications for the majority of children exposed to chemotherapy *in utero.*
Side effects include leukopenia, thrombocytopenia, agranulocytosis, GI bleeding, N/V, diarrhea, anorexia, enteritis, alopecia, dermatitis, photosensitivity, erythema, ulceration, stomatitis, lethargy, malaise, headache, and confusion.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. **Fluorouracil** apparently crosses the human placenta, since maternal administration is associated with fetal immunosuppression. The few published epidemiologic studies support multiple case reports of normal pregnancy outcome after early exposure. Little is known about the long-term effects of intrauterine exposure to **fluorouracil. Fluorouracil** crosses the rodent placenta and produces a variety of defects involving the skeleton and palate. It is embryotoxic to the rodent. The malformations associated with *in utero* exposure to FAC are highly variable, but growth deficiency and anomalies of the

craniofacial region and limbs are most common. The pattern appears to be directly related to the age at and duration of exposure, rather than to the specific drug itself.

Breastfeeding Safety — There is no published experience in nursing women. It is unknown whether **fluorouracil** enters human breast milk.

Drug Interactions — **Leucovorin** may enhance the toxicity of **fluorouracil.**

References

Gwyn KM, Theriault RL. Curr Treat Options Oncol 2000; 3:239-43.
Hahn KM, Johnson PH, Gordon N, et al. Cancer 2006; 107:1219-26.
Inoue T, Horii I. J Toxicol Sci 2002; 27:79-86.

Summary

Pregnancy Category: D
Lactation Category: U

- **Fluorouracil** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Fluoxetine—(Prozac; Sarafem)

International Brand Name—Actan (Chile); Adofen (Spain); Alzac 20 (Guatemala); Andep (India); Ansi (Indonesia); Ansilan (Colombia); ATD 20 (Hong Kong); Auroken (Mexico); Auscap (Australia); Captaton (Argentina); Daforin (Brazil); Depren (Korea); Deprexin (Hong Kong, Korea, Singapore); Deprizac (Philippines); Deproxin (Thailand); Elizac (Indonesia); Floxet (Uruguay); Fluctin (Germany); Fluctine (Austria, Switzerland); Fludac (India); Flufran (India); Fluketin (Singapore); Flunil (India); Fluohexal (Australia); Fluox (Germany); Fluoxac (Mexico); Fluoxeren (Italy); Fluoxil (Dominican Republic); Fluox-Puren (Germany); Fluronin (Taiwan); Flusac (Thailand); Flutin (Colombia, Korea); Flutine (Israel, Thailand); Fluxen (Taiwan); Fluxet (Germany); Fluxetil (Singapore); Fluxetin (Hong Kong, Singapore); Fluxil (Hong Kong, Singapore); Fontex (Denmark, Finland, Norway, Sweden); Foxetin (Korea); Foxtin (Singapore); Fropine (Korea); Fuloren (Korea); Lanclic (Korea); Lorien (South Africa); Lovan (Australia); Magrilan (Israel, Singapore, Thailand); Margrilan (Hong Kong, Israel, Thailand); Modipran (South Africa); Neupax (Peru); Nopres (Indonesia); Nuzak (South Africa); Oxedep (China, India); Plinzene (New Zealand); Pragmaten (Ecuador); Prizma (Israel); Proctin (Korea); Prodep (India); Prozac (Argentina, Belgium, Brazil, Bulgaria, Canada, Chile, China, Colombia, Costa Rica, Czech Republic, Dominican Republic, El Salvador, England, France, Guatemala, Honduras, Hong Kong, Hungary, Ireland, Israel, Italy, Netherlands, Nicaragua, Panama, Paraguay, Peru, Poland, Portugal, Russia, Spain, Thailand, Turkey, Venezuela); Prozac 20 (Korea, Malaysia, Mexico, Philippines, Taiwan, Thailand); Prozac Dispersible (Korea); Qualisac (Hong Kong); Rowexetina (Costa Rica, Dominican Republic, El Salvador, Guatemala, Honduras, Nicaragua, Panama); Sanzur (South Africa); Sinzac (Taiwan); ZAC (Indonesia); Zactin (Australia, Singapore, Taiwan); Zepax (Colombia)

Drug Class — Antidepressants; SSRIs

Indications — Depression, premenstrual dysphoric syndrome, obsessive-compulsive disorder, bulimia, postpartum depression

Mechanism — Selectively inhibits reuptake of serotonin

Dosage with Qualifiers

Depression—begin 20mg PO qd (in AM or PM); increase as needed after several weeks to 60mg qd
Premenstrual dysphoric syndrome—20mg PO qd; max 80mg/d
Obsessive-compulsive disorder—begin 20mg PO qd; increase as needed after several weeks to 80mg
Bulimia—60mg PO qd

- **Contraindications**—hypersensitivity to drug or class, use of an MAOI within 14d
- **Caution**—hepatic or renal dysfunction, seizure history, suicide threat

Maternal Considerations — Depression is common during and after pregnancy, but typically goes unrecognized. Pregnancy is not a reason *a priori* to discontinue psychotropic drugs. A **fluoxetine** dose of 20-40mg/d

results in relatively low trough **fluoxetine**-norfluoxetine concentrations during pregnancy (range, 317-850nmol/L) and the mean norfluoxetine/**fluoxetine** metabolic ratio is 2.4× higher during late pregnancy compared to 2mo postpartum. This suggests increased clearance, which can be explained at least in part by increased demethylation of **fluoxetine** by CYP2D6 and is consistent with the observation that many pregnant women require an increase in their dose to maintain clinical efficacy. **Fluoxetine** is effective treatment for postpartum depression, and is as effective as a course of cognitive-behavioral counseling in the short term.
Side effects include serotonin syndrome, insomnia, nausea, diarrhea, tremor, headache, anorexia, anxiety, dry mouth, decreased libido, delayed or absent orgasm, abnormal dreams, sedation, sweating, and itching.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. **Fluoxetine** crosses the human placenta, achieving F:M ratios approximating 0.9. This is significantly higher than the ratios achieved with either **sertraline** or **paroxetine** and similar to **citalopram.** Maternal doses predict the umbilical cord concentration. Prospectively ascertained pregnancy outcomes after SSRIs, mainly **fluoxetine,** conflict on the potential for a modest teratogenic effect. There are differences in birth weight and acute neonatal outcome between treated and untreated pregnancies. In one study of 20 pregnancies, there was a 4-fold difference in the serotonergic symptom score of newborns during the first 4d of life between treated and control groups. The exposed infants had significantly lower cord blood 5-hydroxyindoleacetic acid (5-HIAA) levels. There was an inverse correlation between the serotonergic symptom score and the umbilical vein 5-HIAA concentrations in the exposed infants. The long-term implications of these findings are unclear. Exposure throughout gestation does not adversely affect cognition, language development, or the temperament of preschool and early school-age children. In sheep, **fluoxetine** has transient effects on fetal behavioral and acid-base status. Rodent studies too are reassuring from the standpoint of structural birth defects, though the rates of IUGR and stillbirth are higher in rats treated with multiples of the MRHD. Prolonged prenatal SSRI exposure in rats is associated with reduced behavioral pain responses and increased parasympathetic cardiac modulation in recovery following an acute neonatal noxious event. However, a recent rodent study found that maternal exposure to **fluoxetine** has transient effects on fetal behavioral and acid-base status during pregnancy and lactation that result in enduring behavioral alterations in the pups throughout life. Others conclude that the behavioral affects are not permanent.

Breastfeeding Safety

Maternal serum and peak breast milk concentrations of **fluoxetine** and its active metabolite, norfluoxetine, predict nursing infant serum norfluoxetine concentrations. The mean estimated infant exposure from the breast milk of women taking 20-40mg/d to **fluoxetine**-norfluoxetine is 2.4% and 3.8% of the maternal weight-adjusted daily dose at 2w and 2mo of age, respectively. Neonatal serum concentrations are typically low in women taking 20mg/d or less. Thus, breastfeeding is not contraindicated.

Drug Interactions

Metabolized by CYP2D6. Some 7% of the population has a mutation causing reduced CYP2D6 activity. Such individuals are termed "poor metabolizers." The pharmacokinetic properties and

relative proportion of metabolites are altered in poor metabolizers. However, the sum of the plasma concentrations of the four active enantiomers of **fluoxetine** is comparable between poor and extensive metabolizers.

Fluoxetine, like other agents metabolized by CYP2D6, also inhibits the activity of this isozyme, and thus may make normal metabolizers resemble poor metabolizers. Medications with a relatively narrow therapeutic index that are metabolized predominantly by the CYP2D6 system should be initiated at the low end of the dose range if a patient is already receiving or has taken **fluoxetine** in the previous 5w. If **fluoxetine** is added to the regimen of a patient already receiving a drug metabolized by CYP2D6, the dose of the original medication may need to be reduced. Drugs with a narrow therapeutic index represent the greatest concern (e.g., **flecainide, vinblastine,** and TCAs). Due to the risk of serious ventricular arrhythmias and sudden death potentially associated with elevated plasma levels of **thioridazine, thioridazine** should not be administered with or within 5w of discontinuing **fluoxetine.**

Patients on stable doses of **phenytoin** and **carbamazepine** may developed elevated plasma levels and clinical anticonvulsant toxicity after the addition of **fluoxetine.**

Some clinical data suggest a possible pharmacodynamic and/or pharmacokinetic interaction between SSRIs and antipsychotics. Elevated levels of **haloperidol** and **clozapine** have been observed in patients also ingesting **fluoxetine.** Clinical studies of **pimozide** with other antidepressants demonstrate an increase in drug interaction or QTc prolongation. The potential for drug interactions or QTc prolongation warrants restricting the concurrent use of **pimozide** and **fluoxetine.**

The t/2 of administered **diazepam** may be prolonged.

Use with **alprazolam** may increase **alprazolam** plasma levels and compromise psychomotor performance decrement.

There are reports of both increased and decreased **lithium** levels when used with **fluoxetine. Lithium** levels should be monitored when these drugs are administered concomitantly.

Previously stable plasma levels of **imipramine** and **desipramine** increased 2- to 10-fold in 2 studies when **fluoxetine** was added. This influence may persist for 3w or longer.

There are rare post-marketing reports describing patients with weakness, hyperreflexia, and incoordination following the use of an SSRI and **sumatriptan.**

Serotonin release by platelets plays an important role in hemostasis. Case-control and cohort design studies reveal an association between the use of drugs that interfere with serotonin reuptake and upper GI bleeding. They also show that concurrent use of an NSAID or **aspirin** potentiates the risk of bleeding. Increased bleeding has been reported when **fluoxetine** was used with **warfarin**.

References

Addis A, Koren G. Psychol Med 2000; 30:89-94.

Bairy KL, Madhyastha S, Ashok KP, et al. Pharmacology 2007; 79:1-11.

Bellantuono C, Migliarese G, Gentile S. Hum Psychopharmacol 2007; 22:121-8.

Calil HM. J Clin Psychiatry 2001; 22(Suppl 62):24-9.

Cohen LS, Heller VL, Bailey JW, et al. Biol Psychiatry 2000; 48:996-1000.

Diav-Citrin O, Shectman S, Weinbaum D, et al. Brit J Clin Pharmacol 2008; Jul 11 (Epub ahead of print).

Heikkinen T, Ekblad U, Palo P, Laine K. Clin Pharmacol Ther 2003; 73:330-7.

Hendrick V, Stowe ZN, Altshuler LL, et al. Am J Psychiatry 2003; 160:993-6.
Hendrick V, Stowe ZN, Altshuler LL, et al. Biol Psychiatry 2001; 50:775-82.
Hoffbrand S, Howard L, Crawley H. Cochrane Database Syst Rev 2001; (2):CD002018.
Laine K, Heikkinen T, Ekblad U, Kero P. Arch Gen Psychiatry 2003; 60:720-6.
Lisboa SF, Oliveira PE, Costa LC, et al. Pharmacology 2007; 80:49-56.
Morrison JL, Chien C, Gruber N, et al. Brain Res Dev Brain Res 2001; 131:47-56.
Morrison JL, Chien C, Riggs KW, et al. Pediatr Res 2002; 51:433-42.
Nulman I, Rovet J, Stewart DE, et al. Am J Psychiatry 2002; 159:1889-95.
Oberlander TF, Eckstein Grunau R, Fitzgerald C, et al. Pediatr Res 2002; 51:443-53.

Summary

Pregnancy Category: C
Lactation Category: S (likely)

- **Fluoxetine** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.
- The clearance of **fluoxetine** is apparently increased during pregnancy.
- There are alternative agents that are less efficiently transferred across the placenta.

Fluoxymesterone—(Alomon; Android-F; Fluoron; Fuloan; Halotestin; Hysterone; Oratestin; Ora-Testryl)

International Brand Name—Halotestin (Denmark, Finland, Greece, Hungary, Japan, Netherlands); Stenox (Mexico)

Drug Class

Androgens; Hormones

Indications

Postpartum breast engorgement, palliative therapy for breast cancer

Mechanism

Binds androgen receptors, producing multiple androgenic and anabolic effects

Dosage with Qualifiers

Postpartum breast engorgement—2.5mg PO ×1 shortly after delivery, then 5-10mg PO qd ×4-5d
Breast cancer, palliation—10-40mg PO qd

- **Contraindications**—hypersensitivity to drug or class, breast cancer, hepatic or renal dysfunction, pregnancy
- **Caution**—unknown

Maternal Considerations

There is no published experience with **fluoxymesterone** during pregnancy. There are no recognized indications for its use during pregnancy.
Side effects include polycythemia, liver tumors, menstrual irregularities, hirsutism, acne, electrolyte imbalance, libido changes, headache, deepened voice, and dyspepsia.

Fetal Considerations

There are no studies in human fetuses. It is unknown whether **fluoxymesterone** specifically or an active metabolite crosses the human placenta. Androgens are recognized human teratogens leading to masculinization of the female fetus.

Breastfeeding Safety

Fluoxymesterone is ineffective for the suppression of lactation and is no longer used. It is unknown whether **fluoxymesterone** enters human breast milk.

Drug Interactions

Androgens may increase sensitivity to oral anticoagulants, necessitating a reduction in order to maintain therapeutic hypoprothrombinemia.
Androgens may increase **oxyphenbutazone** levels.
The metabolic effects of androgens may decrease blood glucose in diabetic patients and, therefore, decrease insulin requirements.

References

No current relevant references.

Summary

Pregnancy Category: X
Lactation Category: U
- Contraindicated during pregnancy and lactation.

Fluphenazine decanoate—(Permitil, Prolixin)

International Brand Name—Anatensol (India, Netherlands, Peru); Anatensol Decanoato (Peru); Dapatum D25 (Germany); Dapotum d (Hungary); Dapotum D (Hungary, Switzerland); Dapotum Depot (Austria); Deca (China, Malaysia, Thailand); Decafen (South Africa); Flucan (Taiwan); Fludecasine (Japan); Fludecate (Chile, Israel); Fludecate Multidose (South Africa); Mirenil (Poland); Modecate (Canada, China, England, France, Hong Kong, Indonesia, Ireland, Puerto Rico, Singapore, Spain, Uruguay); Moditen (Czech Republic); Moditen Depot (Hungary); Phenazine (Thailand); Phlufdek (Philippines); Prolixin-D (Colombia); Siqualone (Finland, Norway, Sweden); Sydepres (Philippines)

Drug Class

Antipsychotics; Phenothiazines

Indications

Psychosis (e.g., chronic schizophrenia)

Mechanism

Unclear; postsynaptic D_1 and D_2 (dopamine) receptor antagonist

Dosage with Qualifiers

Psychosis—begin 12.5-25mg IM; response within 12-96h, dose q2-4w

NOTE: also available as fluphenazine enanthate, which has an even longer duration of action.

- **Contraindications**—hypersensitivity to drug or class, CNS depression, bone marrow depression, severe hypotension, pheochromocytoma
- **Caution**—hepatic dysfunction, seizure disorder, myasthenia gravis, Parkinson's disease, severe CV disease

Maternal Considerations

Fluphenazine is a long-acting parenteral antipsychotic typically used in institutional settings. There are no adequate reports or well-controlled studies in pregnant women. Consistent with its biochemistry, **fluphenazine** increases maternal prolactin.
Side effects include seizures, neuroleptic malignant syndrome, aplastic anemia, agranulocytosis, cholestatic jaundice, nausea, anorexia, headache, depression, leukopenia, hyperprolactinemia, tardive dyskinesia, sedation, pseudo-parkinsonism, drowsiness, blurred vision, dry mouth, constipation, photosensitivity, and urinary retention.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **fluphenazine** crosses the human placenta. Rodent studies reveal bone and CNS malformations. The incidence of these malformations increases significantly when diphenylhydantoin is administered concurrently. Peroxidative bioactivation of phenothiazines to their

cation radical by human placental peroxidase may be one mechanism of developmental toxicity.

Breastfeeding Safety

There is no published experience in nursing women. It is unknown whether **fluphenazine** enters human breast milk.

Drug Interactions

Antacids decrease absorption and should be taken at least 2h before or 2h after.
β-Blockers, barbiturates, **orphenadrine,** and **bromocriptine** each may lower the serum level of **fluphenazine.**
Antimalarial drugs may increase the serum level of **fluphenazine.**
Combination with TCA lowers the concentrations of both drugs.
Inhibits the BP-lowering effects of **guanadrel.**
Levodopa is less effective when combined with **fluphenazine.**
Combination with **meperidine** can cause very low BP and significant depression of the CNS.
May increase the effects of other drugs that cause drowsiness, including antidepressants, alcohol, antihistamines, sedatives, pain relievers, anxiety medicines, and muscle relaxants.

References

Abdel-Hamid HA, Abdel-Rahman MS, Abdel-Rahman SA. J Appl Toxicol 1996; 16:221-5.
Yang X, Kulkarni AP. Teratog Carcinog Mutagen 1997; 17:139-51.

Summary

Pregnancy Category: C
Lactation Category: U
- **Fluphenazine** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Flurandrenolide topical—(Cordan; Haelan)

International Brand Name—Drenison (Brazil, Canada, Spain); Drenison 1 4 (Canada); Haelan (England, Ireland)

Drug Class

Corticosteroids, topical; Dermatologics

Indications

Steroid-responsive dermatitis

Mechanism

Anti-inflammatory mechanism unknown

Dosage with Qualifiers

Steroid-responsive dermatitis—apply to affected area qd/qid

NOTE: available as 0.025% or 0.05% in cream, ointment, or lotion; may be combined with ***neomycin.***

- **Contraindications**—hypersensitivity to drug or class
- **Caution**—unknown

Maternal Considerations

There are reports of **flurandrenolide** use during pregnancy. ***Side effects*** include adrenal suppression, burning, itching, dryness, acne, hypopigmentation, hypertrichosis, and contact dermatitis.

Fetal Considerations

There are no reports or well-controlled studies of **flurandrenolide** in human fetuses. Rodent teratogenicity studies have apparently not been performed. While systemically administered corticosteroids are teratogenic in some rodents, and a weak effect in humans cannot be excluded, the concentration of drug absorbed systemically if applied to a small area suggests the risk of a significant fetal effect is low.

Breastfeeding Safety	There is no published experience in nursing women. It is unknown whether **flurandrenolide** enters human breast milk. It is unlikely the limited systemic concentration achieved after application to a small area is clinically relevant to lactation.
Drug Interactions	Topical steroids may increase psoriasis symptoms when combined with **anthralin.**
References	No current relevant references.
Summary	**Pregnancy Category: C** **Lactation Category: S** (likely) • **Flurandrenolide** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Flurazepam—(Dalmane; Fluleep; Midorm; Niotal; Paxane)

International Brand Name—Apo-Flurazepam (Canada); Benozil (Japan); Dalmadorm (Denmark, Germany, Ghana, Guatemala, Hong Kong, Italy, Kenya, Korea, Malaysia, Netherlands, Portugal, South Africa, Switzerland, Taiwan, Tanzania, Thailand, Uganda, Zambia); Dalmane (Canada, England, Ghana, Ireland, Kenya, Philippines, Tanzania, Uganda, Zambia); Dalmate (Japan); Dormodor (South Africa, Spain); Felison (Italy); Flunox (Italy); Fluralema (Venezuela); Fluraz (India); Fluzepam (Slovenia); Fordrim (Argentina); Insumin (Japan); Irdal (Ireland); Manlsum (Taiwan); Midorm AR (Italy); Natam (Argentina); Nergart (Japan); Nindral (India); Remdue (Italy); Somlan (Argentina); Staurodorm (Austria, Belgium, Czech Republic, Germany, Israel, Taiwan); Valdorm (Italy)

Drug Class	Benzodiazepines; Hypnotics; Sedatives
Indications	Insomnia, short-term relief
Mechanism	Binds to benzodiazepine receptors
Dosage with Qualifiers	Insomnia—15-30mg PO qh • **Contraindications**—hypersensitivity to drug or class, pregnancy • **Caution**—hepatic or pulmonary dysfunction, sleep apnea
Maternal Considerations	There are no adequate reports or well-controlled studies of **flurazepam** in pregnant women. There are other hypnotics on the market with better pharmacologic and safety profiles, such as **zolpidem.** Prolonged use of hypnotics is not advised. ***Side effects*** include coma, dependence, sedation, dizziness, ataxia, confusion, headache, nausea, and elevated LFTs.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. **Flurazepam** crosses the human placenta, though the kinetics remain to be elucidated. Benzodiazepines such as **diazepam** and **chlordiazepoxide** may be associated with an increased risk of malformations after 1st trimester exposure. Rodent teratogenicity studies with **flurazepam** specifically have not apparently been performed. Neonatal depression was reported in a neonate of a woman taking **flurazepam** for the 10d preceding delivery. The long-term neurologic effects of *in utero* exposure are unknown.
Breastfeeding Safety	There are no adequate reports or well-controlled studies in nursing women. Older abstracts suggest **flurazepam** enters human breast milk.

Drug Interactions

Phenothiazines, narcotics, barbiturates, MAOIs, and other antidepressants may potentiate the action of **flurazepam.**
Cimetidine may delay **flurazepam** clearance.
Valproate may potentiate the CNS-depressant effects.
In vitro studies of human liver suggest CYP2CI9 and CYP3A4 are the principal isozymes involved in the initial oxidative metabolism of **flurazepam.** Potential inhibitors of CYP2CI9 (e.g., **cimetidine, quinidine, tranylcypromine**) and CYP3A4 (e.g., **clotrimazole, ketoconazole, troleandomycin**) may decrease **flurazepam** elimination, while inducers of CYP2CI9 (e.g., **rifampin**) and CYP3A4 (e.g., **carbamazepine, dexamethasone, phenobarbital, phenytoin**) may increase the rate of elimination. It is possible **flurazepam** could interfere with the metabolism of CYP2CI9 (e.g., **imipramine, omeprazole, propranolol**) and CYP3A4 (e.g., **cyclosporine, paclitaxel, terfenadine, theophylline, warfarin**) substrates.

References

No current relevant references

Summary

Pregnancy Category: X
Lactation Category: U

- There are no indications that require the use of **flurazepam** during pregnancy.
- There are other hypnotics on the market, such as **zolpidem** and escopiclone, with better pharmacologic and safety profiles.

Flurbiprofen—(Ansaid)

International Brand Name—None identified.

Drug Class

Analgesics, non-narcotic; NSAIDs; Ophthalmics

Indications

Dysmenorrhea, osteoarthritis, analgesia (mild to moderate pain), antipyretic

Mechanism

Inhibits cyclooxygenases and lipoxygenase; reduces prostaglandin synthesis

Dosage with Qualifiers

Dysmenorrhea—begin 100mg PO ×1, then 50-100mg PO bid or tid
Osteoarthritis—50-100mg PO bid or tid
Analgesia (mild to moderate pain)—begin 100mg PO ×1, then 50-100mg PO bid or tid

- **Contraindications**—hypersensitivity to drug or class, ASA/NSAID-induced asthma
- **Caution**—hypertension, history of GI bleeding, CHF, nasal polyps

Maternal Considerations

Flurbiprofen is a nonselective COX inhibitor with analgesic, antipyretic, and anti-inflammatory activities. There are no adequate reports or well-controlled studies of **flurbiprofen** in pregnant women. It is equivalent to **aspirin** and superior to **codeine** as an analgesic for postpartum uterine pain. It is unknown whether **flurbiprofen** offers any advantage over other, similar NSAIDs. **Flurbiprofen** prolongs rat parturition, as do most NSAIDs.
Side effects include GI bleeding, acute renal failure, bronchospasm, thrombocytopenia, interstitial nephritis,

hepatotoxicity, agranulocytosis, dyspepsia, nausea, abdominal pain, dizziness, headache, rash, urticaria, increased LFTs, fluid retention, tinnitus, and drowsiness.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. **Flurbiprofen** crosses the human placenta. Other NSAIDs cause ductus arteriosus constriction and oligohydramnios secondary to fetal oliguria. **Flurbiprofen** is known to do so in rats. Rodent studies are generally reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than that used clinically. High doses in the rodent are associated with embryotoxicity and increased perinatal mortality secondary to delayed parturition.

Breastfeeding Safety

The elimination half-life of **flurbiprofen** during early lactation is slightly prolonged (mean 4.8h) compared to adult males. The peak plasma concentrations are comparable to those reported for healthy volunteers. In 10 of 12 women (3-5d postpartum), the **flurbiprofen** concentration in breast milk was less than 0.050mcg/ml. The remaining women did not exceed 0.07mcg/ml. This concentration is insufficient to pose a risk to the breastfeeding neonate.

Drug Interactions

NSAIDs may decrease the antihypertensive effect of ACEIs.
NSAIDs enhance the risk patients taking **warfarin** will suffer serious bleeding.
Aspirin lowers serum **flurbiprofen.** The clinical significance of this interaction is not known.
Attenuates the hypotensive effect of **propranolol** but not **atenolol;** the underlying mechanism is unknown.
NSAIDs can reduce the natriuretic effect of **furosemide** and thiazides in some patients by inhibiting renal prostaglandin synthesis.
NSAIDs can increase plasma **lithium** levels by reducing renal **lithium** clearance. Subjects should be observed carefully for signs of **lithium** toxicity.
NSAIDs competitively inhibit **methotrexate** accumulation in rabbit renal slices. This may indicate they could enhance the **methotrexate** toxicity.

References

Bloomfield SS, Mitchell J, Cissell G, Barden TP. Am J Med 1986; 80:65-70.
Smith IJ, Hinson JL, Johnson VA, et al. J Clin Pharmacol 1989; 29:174-84.

Summary

Pregnancy Category: B (1st and 2nd trimesters), **D** (3rd trimester)
Lactation Category: S

- An NSAID for which there is little experience regarding use during pregnancy.
- Popular in many countries for postpartum analgesia.
- **Flurbiprofen** offers no clear advantage over other NSAIDs for which there is more experience.

Fluticasone—(Cutivate; Flonase; Flonase Aq; Flovent; Flunase; Zoflut)

International Brand Name—Allegro (Israel); Atemur Mite (Germany); Beconase Allergy 24 Hour (Australia); Cutivat (Denmark); Cutivate (Argentina, Austria, Belgium, Bulgaria, Colombia, Costa Rica, Czech Republic, Dominican Republic, Ecuador, El Salvador, England, Guatemala, Honduras, Hong Kong, Hungary, Indonesia, Ireland, Korea, Mexico, Netherlands, Nicaragua, Panama, Paraguay, Peru, Philippines, Singapore, South Africa, Taiwan, Uruguay, Venezuela); Flixonase (Austria, Belgium, Brazil, Bulgaria, Chile, Colombia, Costa Rica, Czech Republic, Denmark, Dominican Republic, Ecuador, El Salvador, England, Finland, France, Guatemala, Honduras, Hong Kong, Hungary, Indonesia, Ireland, Israel, Italy, Korea, Malaysia, Mexico, Netherlands, Nicaragua, Panama, Paraguay, Peru, Poland, Russia, Singapore, Taiwan, Thailand, Turkey, Uruguay, Venezuela); Flixonase 24 hour (New Zealand); Flixonase Nasal Spray (New Zealand); Flixotide (Austria, Bulgaria, China, Czech Republic, Denmark, England, Finland, France, Hong Kong, Hungary, Indonesia, Ireland, Israel, Italy, Korea, Mexico, Netherlands, Peru, Philippines, Russia, Singapore, South Africa, Taiwan, Thailand, Turkey); Flixotide Disk (China, New Zealand); Flixotide Disks (Australia); Flixotide Inhaler (Australia); Flixovate (France); Flonase (Canada); Flunase (Japan); Flutide (Germany, Japan); Flutivate (Germany, Norway); Zoflut (India)

Drug Class ..... Corticosteroids, inhalation; Corticosteroids, topical; Dermatologics

Indications ..... Asthma prophylaxis

Mechanism ..... Anti-inflammatory mechanism unknown

Dosage with Qualifiers .....

Asthma prophylaxis—begin 88mcg bid if on bronchodilator alone; max 880mcg bid, taper to lowest effective dose

NOTE: available as 44-, 110-, 220mcg/puff; also available for IN and topical use; may be combined with ***salmeterol,*** *a β-mimetic agent.*

- **Contraindications**—hypersensitivity to drug or class, acute asthma, status asthmaticus
- **Caution**—unknown

Maternal Considerations .....

There are no adequate reports or well-controlled studies of **fluticasone** in pregnant women. **Fluticasone** is a popular agent in women with asthma and commonly encountered during pregnancy. Case series are reassuring. It is not effective for the treatment of pregnancy rhinitis. Once-daily **budesonide** nasal spray, **fluticasone** nasal spray, **mometasone** furoate nasal spray, and **triamcinolone** aqueous nasal spray have similar efficacy and safety profiles for treatment of allergic rhinitis in adults. Differences in sensory attributes, experience during pregnancy, and cost may contribute to better patient acceptance of one versus another. A recent meta-analysis concluded that inhaled or nasal corticosteroids do not increase the rates of adverse obstetric outcomes.
Side effects include adrenal suppression, bronchospasm, glaucoma, cataracts, cushingoid features, headache, nasal congestion, sinusitis, and pharyngitis.

Fetal Considerations .....

There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **fluticasone** crosses the human placenta. However, inhaled or nasal corticosteroids alone do not adversely affect fetal growth or placental function. While systemically administered corticosteroids, including **fluticasone,** are teratogenic in some rodents and a weak effect in humans cannot be excluded, the concentration of drug absorbed suggests the risk of an adverse fetal effect is low. There are no documented epidemiologic studies with IN corticosteroids during pregnancy; however, inhaled corticosteroids have not been incriminated as teratogens and are commonly used by pregnant

women who have asthma. Less than 0.1% of an inhaled dose crosses the rodent placenta.

Breastfeeding Safety

There are no adequate reports or well-controlled studies in nursing women. It is unknown whether **fluticasone** enters human breast milk. Measurable but small amounts enter rat breast milk. However, considering the concentration and quantity absorbed systemically, it is unlikely the plasma level achieved will be clinically relevant to lactation.

Drug Interactions

Metabolized by CYP3A4. **Ritonavir,** a highly potent CYP3A4 inhibitor, may significantly increase plasma **fluticasone** levels, significantly reducing serum cortisol concentrations and even generating systemic corticosteroid effects, including Cushing's syndrome and adrenal suppression.
Ketoconazole, another potent CYP3A4 inhibitor, increases mean plasma **fluticasone** and reduces the plasma cortisol AUC.

References

Clifton VL, Rennie N, Murphy VE. Aust N Z J Obstet Gynaecol 2006; 46:136-40.
Ellegard EK, Hellgren M, Karlsson NG. Clin Otolaryngol 2001; 26:394-400.
Herman H. Am J Rhinol 2007; 21:70-9.
Mazzotta P, Loebstein R, Koren G. Drug Saf 1999; 20:361-75.
Murphy VE, Fittock RJ, Zarzycki PK, et al. Placenta 2007; 28:39-46.
Rahimi R, Nikfar S, Abdollahi M. Hum Exp Toxicol 2006; 25:447-52.

Summary

Pregnancy Category: C
Lactation Category: S
- **Fluticasone** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Fluvastatin—(Lescol; Lescol XL)

International Brand Name—Canef (Mexico); Cranoc (Germany); Fractal (France); Fractal LP (France); Lescol (Argentina, Australia, Austria, Belgium, Brazil, Bulgaria, Canada, China, Colombia, Costa Rica, Czech Republic, Denmark, Dominican Republic, Ecuador, El Salvador, England, France, Guatemala, Honduras, Hong Kong, Hungary, Indonesia, Ireland, Italy, Korea, Malaysia, Mexico, Netherlands, Nicaragua, Norway, Panama, Peru, Philippines, Poland, Russia, Singapore, South Africa, Sweden, Switzerland, Taiwan, Thailand, Turkey, Venezuela); Lescol LP (France); Lescol XL (England, Philippines, Singapore, Thailand); Leucol (Chile); Locol (Germany)

Drug Class

Antihyperlipidemics; HMG-CoA reductase inhibitors

Indications

Hypercholesterolemia, mixed dyslipidemia, secondary prevention of cardiac events

Mechanism

HMG-CoA reductase competitive inhibitor

Dosage with Qualifiers

Hypercholesterolemia—begin 20mg PO qh; max 40mg bid
Mixed dyslipidemia—begin 20mg PO qh; max 40mg bid
Secondary prevention of cardiac events—begin 20mg PO qh; max 40mg bid

NOTE: check LFTs after 3mo or upon increasing dose.

- **Contraindications**—hypersensitivity to drug or class, active hepatic disease
- **Caution**—hepatic or renal disease, alcohol abuse

■ Maternal Considerations

Fluvastatin is a competitive inhibitor of the enzyme responsible for the conversion of HMG-CoA to mevalonate, a precursor of cholesterol. There are no adequate reports or well-controlled studies of **fluvastatin** in pregnant women. Hyperlipidemia is a chronic illness, and discontinuing treatment during pregnancy is unlikely to compromise patient care. Published experience is confined to a case report. However, there is an unexpected high maternal mortality rate in rats during lactation. Supplementation with mevalonic acid completely blocks and/or ameliorates death, cardiac myopathy, and other adverse effects. Thus, the adverse maternal effects result from exaggerated pharmacologic activity at the dose levels administered (i.e., inhibition of the enzyme HMG-CoA reductase, its immediate product mevalonic acid, and cholesterol biosynthesis). It is not known whether pregnancy enhances the toxicity of **fluvastatin** in humans.
Side effects include pancreatitis, hepatic toxicity, rhabdomyolysis, constipation, dyspepsia, flatulence, nausea, diarrhea, abdominal pain, myalgias, muscle weakness, and elevated CPK or LFTs.

■ Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. It is not known whether **fluvastatin** crosses the placenta. While **lovastatin, simvastatin,** and **atorvastatin** are inhibitors for P-glycoprotein and may be substrates for this transporter, **fluvastatin** and **pravastatin** consistently demonstrate no significant inhibition of P-glycoprotein. In rodents, **fluvastatin** is associated with delayed and abnormal skeletal development. There is one report of VATER in the child of a woman who took **fluvastatin** during the 1st trimester. Similar-class drugs are associated with rare reports of malformations.

■ Breastfeeding Safety

There are no adequate reports or well-controlled studies in nursing women. **Fluvastatin** apparently enters human breast milk, as the manufacturer reports an M:P ratio of 2.0. The affect on the breastfeeding neonate is unknown.

■ Drug Interactions

CYP2C9 is primarily responsible for **fluvastatin** metabolism (~75%), while CYP2C8 and CYP3A4 isozymes are involved to a much lesser extent (i.e., ~5% and ~20%, respectively). If one pathway is inhibited, other pathways may compensate. CYP3A4 inhibitors/substrates such as **cyclosporine, erythromycin,** and **itraconazole** have minimal effect on the pharmacokinetics, confirming minor involvement of CYP3A4. In contrast, the administration of **fluvastatin** with **phenytoin** increases both **phenytoin** and **fluvastatin** levels, suggesting CYP2C9 involvement.
Use with or up to 4h after **cholestyramine** decreases the **fluvastatin** AUC by more than 50% and the C_{max} by 50-80%. However, use 4h after **cholestyramine** produces a clinically significant additive effect compared to either drug alone.
Cyclosporine increases the **fluvastatin** AUC 1.9-fold and C_{max} 1.3-fold compared to historical controls.
A single morning dose of **phenytoin** increases the steady-state **fluvastatin** C_{max} by 27% and AUC by 40%, whereas **fluvastatin** increases the mean **phenytoin** C_{max} by 5% and AUC by 20%. **Phenytoin** levels should to be monitored closely when **fluvastatin** is initiated or its dosage changed.
Increases the mean C_{max} and AUC of **diclofenac** by 60% and 25%, respectively.
Increases the mean C_{max}, AUC, and t/2 of **glibenclamide** in NIDDM patients by some 50%, 69%, and 121%, respectively. **Glibenclamide** increases the mean C_{max} and AUC of **fluvastatin** by 44% and 51%, respectively. Patients on concomitant therapy

with **glibenclamide** (or **glyburide**) and **fluvastatin** should continue to be monitored appropriately when their **fluvastatin** dose is increased to 40mg bid.
Cimetidine, ranitidine, and **omeprazole** increased the **fluvastatin** C_{max} (43%, 70%, and 50%, respectively) and AUC (24-33%) while reducing plasma clearance by 18-23%.
Reduces the C_{max} (59%) and AUC (51%) of **rifampicin** with a large increase (95%) in plasma clearance.

References

Holtzman CW, Wiggins BS, Spinler SA. Pharmacotherapy 2006; 26:1601-7.
Hrab RV, Hartman HA, Cox RH Jr. Teratology 1994; 50:19-26.
Seguin J, Samuels P. Obstet Gynecol 1999; 93:847.

Summary

Pregnancy Category: X
Lactation Category: NS (possibly)
- **Fluvastatin** is presently considered contraindicated during pregnancy.

Fluvoxamine—(Floxyfral; Luvox)

International Brand Name—Anwu (Taiwan); Dumirox (Korea, Spain, Uruguay); Dumyrox (Greece, Portugal); Faverin (Australia, England, Hong Kong, Ireland, Israel, Philippines, Singapore, Thailand, Turkey); Favoxil (Israel); Fevarin (Bulgaria, Czech Republic, Denmark, Finland, Germany, Hungary, Italy, Netherlands, Norway, Poland, Russia, Sweden, Turkey); Floxyfral (Austria, Belgium, France, Switzerland); Fluvohexal (Germany); Fluvoxin (India); Lote (Taiwan); Luvox (Argentina, Australia, Brazil, Canada, Costa Rica, El Salvador, Guatemala, Honduras, Indonesia, Malaysia, Nicaragua, Panama, Peru, South Africa, Taiwan, Venezuela); Movox (Australia); Voxamin (Colombia)

Drug Class

Antidepressants

Indications

Obsessive-compulsive disorder

Mechanism

Selectively inhibits serotonin reuptake

Dosage with Qualifiers

Obsessive-compulsive disorder—begin at 50mg PO qh; increase by 50mg q3-4d; max 300mg/d

NOTE: taper gradually if discontinued.

- **Contraindications**—hypersensitivity to drug or class, concurrent or recent use of **astemizole, cisapride, terfenidine,** or an MAOI within 14d
- **Caution**—CV disease, suicide risk, seizure disorder

Maternal Considerations

There are no adequate reports or well-controlled studies of **fluvoxamine** in pregnant women. It is chemically unrelated to the other SSRIs. The few published case reports suggest no adverse effects when used at recommended doses.
Side effects include seizures, bradycardia, hepatic toxicity, toxic epidermal necrosis, withdrawal syndrome, N/V, constipation, agitation, headache, sweating, flatulence, and palpitations.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. Though the kinetics need further clarification, about one third of the maternal **fluvoxamine** dose crosses the human placenta and is excreted into the AF. This is about half of the placental transfer of **fluoxetine**. There is no evidence of teratogenicity or any other adverse effect in humans after 1st trimester exposure. A recent meta-analysis concluded that SSRIs do not increase the risk of major, CV, and minor

malformations but do increase the risk of spontaneous abortion. However, newborns exposed to SSRI antidepressants toward the end of pregnancy can show signs of agitation, altered muscle tone, and breathing. These neonatal symptoms have been noted with **citalopram, fluoxetine, fluvoxamine, paroxetine,** and **sertraline.** An estimated 20-30% of newborns exposed to an SSRI toward the end of pregnancy are affected. The symptoms are variously attributed to withdrawal or to the drug itself. There is no consensus on the treatment of affected newborns, but close monitoring is mandatory. SSRI antidepressants are not teratogenic in animals. Prolonged prenatal SSRI exposure in rats is associated with reduced behavioral pain responses and increased parasympathetic cardiac modulation in recovery following an acute neonatal noxious event. However, a recent rodent study found that maternal exposure to **fluoxetine** has transient effects on fetal behavioral and acid-base status during pregnancy and lactation that resulted in enduring behavioral alterations in the pups throughout life. At higher doses, many pups died from a dilated cardiomyopathy. Others conclude that the behavioral affects are not permanent.

Breastfeeding Safety

There are no adequate reports or well-controlled studies in nursing women. **Fluvoxamine** is excreted in low concentrations into human breast milk, but the resulting neonatal levels are below the limit of detection.

Drug Interactions

Smokers have a 25% increase in the metabolism of **fluvoxamine** compared to nonsmokers.

Inhibits the following CYP isozymes known to be involved in the metabolism of the following drugs:

CYP1A2: **Warfarin, theophylline,** and **propranolol.**

CYP2C9: **Warfarin.**

CYP3A4: **Alprazolam.**

Approximately 7% of the population has a genetic defect causing reduced activity of CYP2D6. These individuals are termed ''poor metabolizers'' of drugs such as **debrisoquin, dextromethorphan,** and TCAs. While none of those studied for drug interactions significantly affect the pharmacokinetics of **fluvoxamine,** an *in vivo* study of **fluvoxamine** single-dose pharmacokinetics in 13 poor metabolizers demonstrated increased mean C_{max}, AUC, and t/2 for **fluvoxamine** by 52%, 200%, and 62%, respectively, compared to ''extensive metabolizers.'' Caution is indicated in patients known to have reduced CYP2D6 activity and those taking drugs known to inhibit this isozyme (e.g., **quinidine**).

A clinically significant **fluvoxamine** interaction is possible with drugs having a narrow therapeutic ratio such as **terfenadine, astemizole, cisapride, pimozide, warfarin, theophylline,** certain benzodiazepines, and **phenytoin.** Plasma levels and/or pharmacodynamic effects of the latter drug should be monitored closely, at least until steady-state conditions are reached.

Increased **carbamazepine** levels and symptoms of toxicity are reported with **fluvoxamine** use.

May increase serum **clozapine** levels**,** increasing the risk of adverse events

As with other serotonergic drugs, **lithium** may enhance the serotonergic effects of **fluvoxamine.** Seizures have been reported. The combination should be used with caution.

Increases **methadone** levels, with symptoms of opioid intoxication reported in 1 patient. Opioid withdrawal symptoms were reported after **fluvoxamine** discontinuation in another patient.

Rare post-marketing reports describe weakness, hyperreflexia, and incoordination after using an SSRI and **sumatriptan.** Appropriate

observation of the patient is advised if treatment with **sumatriptan** and an SSRI (e.g., **fluoxetine, fluvoxamine, paroxetine, sertraline**) is clinically indicated.
In one study, a single 40mg dose of **tacrine** added to **fluvoxamine** 100mg/d administered at steady state was associated with 5- and 8-fold increases in **tacrine** C_{max} and AUC, respectively. Several subjects experienced N/V, sweating, and diarrhea after co-administration, consistent with the cholinergic effects of **tacrine.**
Increased TCA levels occur after the co-administration of **fluvoxamine** with either **amitriptyline, clomipramine,** or **imipramine.** Caution is indicated, and the dose of TCA may need to be reduced.
Tryptophan may enhance the serotonergic effects of **fluvoxamine,** and the combination should therefore be used with caution. Severe vomiting has been reported.
Bradycardia has been reported when used with **diltiazem.**
Use of **fluvoxamine** and **propranolol** resulted in a mean 5-fold increase (range 2-17) in minimum **propranolol** plasma concentrations. One case of bradycardia and hypotension and a second case of orthostatic hypotension are reported with the co-administration of **fluvoxamine** maleate and **metoprolol.** A reduction in the initial β-blocker dose and more cautious dose titration is recommended if **propranolol** or **metoprolol** is to be used with **fluvoxamine.**

References

Bairy KL, Madhyastha S, Ashok KP, et al. Pharmacology 2007; 79:1-11.
Bellantuono C, Migliarese G, Gentile S. Hum Psychopharmacol 2007; 22:121-8.
Hendrick V, Fukuchi A, Altshuler L, et al. Br J Psychiatry 2001; 179:163-6.
Hostetter A, Ritchie JC, Stowe ZN. Biol Psychiatry 2000; 48:1032-4.
Kristensen JH, Hackett LP, Kohan R, et al. J Hum Lact 2002; 18:139-43.
Kulin NA, Pastuszak A, Sage SR, et al. JAMA 1998; 279:609-10.
Lisboa SF, Oliveira PE, Costa LC, et al. Pharmacology 2007; 80:49-56.
[No author]. Prescrire Int 1999; 8:157-9.
[No author]. Prescrire Int 2004; 13:103-4.
Noorlander CW, Ververs FT, Nikkels PGJ, et al. PLoS ONE 2008; 3:e2782.
Rahimi R, Nikfar S, Abdollahi M. Reprod Toxicol 2006; 22:571-5.

Summary

Pregnancy Category: C
Lactation Category: S (likely)

- **Fluvoxamine** should be used during pregnancy only if the benefit justifies the potential perinatal risk.
- The risk to the neonate is real, and doctors should be aware when considering antidepressant treatment for women in the 3rd trimester.

Folic acid—(Acido; Folasic; Folicet; Folico; Folvite; Nifolin; Renal Multivit Form Forte Zinc)

International Brand Name—Acfol (Spain); Acide Folique CCD (France); Acido Folico (Colombia, Ecuador, Peru); Apo-Folic (Canada, New Zealand); Filicine (Greece); Folacin (Sweden); Folart (Philippines); Foliamin (Hong Kong, Thailand); Folic Acid DHA (Malaysia); Folicid (Korea); Folina (Italy); Folinsyre (Denmark, Norway); Folitab (Mexico); Folivit (Thailand); Folsan (Austria, Germany, Hungary); Folverlan (Germany); Folvite (Finland, Switzerland); Gravi-Fol (Germany); Ingafol (India); Lexpec (England, Ireland); Megafol (Australia); RubieFol (Germany)

Drug Class ..... Hematinics; Vitamins/minerals

Indications ..... Pregnancy supplementation, prevention of recurrent NTDs, megaloblastic anemia

Mechanism ..... Required for erythropoiesis and DNA synthesis

Dosage with Qualifiers .....

Pregnancy supplementation—0.8-1mg PO qd
Prevention of recurrent NTDs—5mg PO qd prior to conception
Megaloblastic anemia—0.4mg PO qd ×4-5d; max 1mg/d

NOTE: available in PO or parenteral forms.

- **Contraindications**—undiagnosed anemia
- **Caution**—unknown

Maternal Considerations .....

Suboptimal preconception folate and vitamin B_6 reserves, especially when combined, may increase the risk of spontaneous abortion. Women who become pregnant before folate restoration is complete have an increased risk of folate insufficiency at conception and during pregnancy. As a consequence, they may be at increased risk of preterm birth. Recent epidemiologic investigation suggests a reduction in the rates of preterm birth and low birth weight since the introduction of widespread food fortification. Women with HIV also show improved pregnancy outcomes when supplemented with folate.
Side effects include N/V, anorexia, flatulence, irritability, altered sleep pattern, erythema, rash, and itching.

Fetal Considerations .....

NTDs and other pregnancy complications are linked to impaired *MTHFR* function. Each doubling of the serum folate concentration roughly halves the risk of an NTD. It is suggested that high levels of folate supplementation might blunt the negative impact of antiepileptic drugs. More recently, evidence has emerged that vitamin B_{12} deficiency also increases the risk of a child with an NTD. Placental folate transfer is not compromised in IUGR pregnancies. Knockout of folate receptors in mice, and knock-down of folate receptors by antisense oligonucleotides at day 8, or antibodies to folate receptor, results in profound developmental abnormalities ranging from NTDs to neurocristopathies such as cleft lip and cleft palate, cardiac septal defects, and eye defects. These abnormalities can be prevented by supplying folate into cells via alternative pathways. The high prevalence of mutated *MTHFR* genotypes in spontaneously aborted embryos supports the potentially protective role of periconceptional folic acid supplementation.

Breastfeeding Safety ..... Maternal folate stores are depleted during lactation without supplementation. Supplementation minimizes maternal loss and significantly increases the concentration of folate in milk.

Drug Interactions ..... No clinically relevant interactions identified.

■ **References**

Antony AC. Am J Clin Nutr 2007; 85:598S-603S.
Bisseling TM, Steegers EA, van den Heuvel JJ, et al. Placenta 2004; 25:588-93.
Lumley J, Watson L, Watson M, Bower C. Cochrane Database Syst Rev 2001; (3):CD001056.
Mackey AD, Picciano MF. Am J Clin Nutr 1999; 69:285-92.
Ray JG, Wyatt PR, Thompson MD, et al. Epidemiology 2007; 18:362-6.
Ronnenberg AG, Goldman MB, Chen D, et al. Obstet Gynecol 2002; 100:107-13.
Schwahn B, Rozen R. Am J Pharmacogenomics 2001; 1:189-201.
Shaw GM, Carmichael SL, Nelson V, et al. Public Health Rep 2004; 119:170-3.
Wald NJ, Law MR, Morris JK, Wald DS. Lancet 2001; 358:2069-73.
Zetterberg H, Regland B, Palmer M, et al. Eur J Hum Genet 2002; 10:113-8.

■ **Summary**

Pregnancy Category: A
Lactation Category: S

- Preconception folate supplementation reduces the incidence of NTDs and possibly other birth defects.
- Preconception folate supplementation may reduce the incidence of spontaneous abortion in couples that are each carriers of an *MTHFR* mutation.
- Folate should be provided to every pregnant woman.

Fomepizole—(Antizol)

International Brand Name—Antizol (Israel)

■ **Drug Class** — Antidotes; Toxicology

■ **Indications** — Ethylene glycol or methanol toxicity

■ **Mechanism** — Inhibits alcohol dehydrogenase

■ **Dosage with Qualifiers**

Ethylene glycol toxicity—begin 15mg/kg IV q12h; then 10mg/kg q12h ×4, then 15mg/kg q12h until ethylene glycol level below 20mg/dl and pH normal
Methanol toxicity—begin 15mg/kg IV q12h; then 10mg/kg q12h ×4, then 15mg/kg q12h until methanol level below 20mg/dl and pH normal

- **Contraindications**—hypersensitivity to drug or class
- **Caution**—unknown

■ **Maternal Considerations**

There are no adequate reports or well-controlled studies of **fomepizole** in pregnant women. The published experience consists of several case reports. However, the risks of ethylene or methanol toxicity to mother and fetus outweigh any theoretic risk of the drug. ***Side effects*** include seizures, N/V, headache, dizziness, metallic taste, abnormal smell, and rash.

■ **Fetal Considerations**

There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **fomepizole** crosses the placenta. However, both methanol and ethylene glycol do cross the human placenta. Animal reproduction studies have not been performed.

■ **Breastfeeding Safety**

There are no adequate reports or well-controlled studies in nursing women. It is unknown whether **fomepizole** enters human

breast milk. However, it is unlikely a patient requiring treatment will breastfeed during that period.

Drug Interactions

Oral doses of **fomepizole** (10-20mg/kg), via alcohol dehydrogenase inhibition, significantly reduced the rate of elimination of ethanol (by approximately 40%) given to healthy volunteers in moderate doses. Similarly, ethanol decreased the rate of elimination of **fomepizole** (by approximately 50%) by the same mechanism. Reciprocal interactions may occur with concomitant use of **fomepizole** and drugs that increase or inhibit the CYP system (e.g., **carbamazepine, cimetidine, ketoconazole, phenytoin**), though this has not been studied.

References

Velez LI, Kulstad E, Shepherd G, Roth B. Vet Hum Toxicol 2003; 45:28-30.

Summary

Pregnancy Category: C
Lactation Category: S

- **Fomepizole** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Fondaparinux—(Arixtra)

International Brand Name—Arixtra (Australia, Colombia, Malaysia, Mexico, Singapore, Thailand)

Drug Class

Anticoagulants

Indications

DVT prophylaxis for hip or knee replacement, or surgery for hip fracture

Mechanism

Selectively binds ATIII, potentiating factor Xa neutralization and inhibiting thrombin formation

Dosage with Qualifiers

DVT prophylaxis for hip replacement—2.5mg SC qd for 5-10d beginning 6-8h postsurgery
DVT prophylaxis for knee replacement—2.5mg SC qd for 5-10d beginning 6-8h postsurgery
DVT prophylaxis after hip fracture surgery—2.5mg SC qd for 5-10d beginning 6-8h postsurgery

NOTE: monitor renal function and CBC; avoid regional anesthesia within 24h.

- **Contraindications**—hypersensitivity to drug or class, active bleeding, weight <50kg, CrCl <30ml/min, thrombocytopenia associated with antiplatelet antibodies, IM administration, bacterial endocarditis, neuraxial analgesia
- **Caution**—renal dysfunction, history of GI bleeding, hemorrhagic stroke, heparin-induced thrombocytopenia, active or recent peptic ulcer disease, and diabetic retinopathy

Maternal Considerations

Fondaparinux is the first in a new class of heparinoid antithrombotic agents developed for the prevention and treatment of VTE. It inhibits thrombin generation by selectively inhibiting factor Xa. **Fondaparinux** is rapidly absorbed, reaching its maximum concentration in approximately 2h. The terminal t/2 of 13-21h permits once-daily dosing. **Fondaparinux's** reproducible linear pharmacokinetic profile suggests individual dose adjustments will not be required for the vast majority of the nonpregnant population and that there will be no need for

routine hemostatic monitoring. At therapeutic concentrations (>2mg/L), **fondaparinux** exhibits >94% binding to its target protein, antithrombin. The current experience in pregnancy, though encouraging, is confined to a series of case reports. It is unknown whether pregnancy alters clearance of **fondaparinux**. Though conceptually superior, there is inadequate clinical study to favor its use over LMWH or unfractionated **heparin.**
Side effects include hemorrhage, thrombocytopenia, epidural or spinal hematoma, paralysis, injection site response, and increased LFTs.

Fetal Considerations ..... There are no adequate reports or well-controlled studies in human fetuses. *In vitro*, **fondaparinux** does not cross the human placenta, suggesting the fetus is not directly at risk.

Breastfeeding Safety ..... There are no adequate reports or well-controlled studies in nursing women. It is unknown whether **fondaparinux** enters human breast milk.

Drug Interactions ..... The concomitant use of oral anticoagulants (e.g., **warfarin**), platelet inhibitors (e.g., **aspirin**), NSAIDs (e.g., **piroxicam**), and **digoxin** did not significantly affect the pharmacokinetics/pharmacodynamics of **fondaparinux.**

References .....

Gerhardt A, Zotz RB, Stockschlaeder M, Scharf RE. Thromb Haemost 2007; 97:496-7.
Harenberg J. Thromb Res 2007; 119:385-8.
Lagrang F, Vergnes C, Brun JL, et al. Thromb Haemost 2002; 87:831-5.
Mazzolai L, Hohlfeld P, Spertini F, et al. Blood 2006; 108:1569-70.
Wijesiriwardana A, Lees DA, Lush C. Blood Coagul Fibrinolysis 2006; 17:147-9.

Summary .....

Pregnancy Category: B
Lactation Category: U

- Though there is no published experience during pregnancy, **fondaparinux** remains an attractive possibility for DVT prophylaxis during pregnancy.
- Though conceptually superior, there is inadequate clinical study to favor its use over LMWH or unfractionated **heparin.**
- There are alternative agents for which there is more experience during pregnancy and lactation.

Formoterol, inhaled—(Foradil Aerolizer)

International Brand Name—Asto (Korea); Atock (China, Japan, Korea, Philippines, Taiwan); Bronteral (Korea); Fomerol (Korea); Foradil (Austria, Belgium, Brazil, Bulgaria, Canada, Colombia, Costa Rica, Czech Republic, Denmark, Dominican Republic, El Salvador, Finland, France, Greece, Guatemala, Honduras, Hong Kong, Hungary, Ireland, Italy, Mexico, Netherlands, New Zealand, Nicaragua, Panama, Peru, Philippines, Russia, Singapore, Spain, Sweden, Switzerland, Turkey, Uruguay, Venezuela); Foradil Aerolizer (New Zealand); Foradile (Australia); Foradil P (Germany); Fordilen (Argentina); Formoclean (Korea); Forterol (Korea); Lexoma (Korea); Newtock (Korea); Oxis (Germany, Indonesia, Ireland, Korea, Malaysia, Netherlands, Philippines, Singapore, Sweden, Thailand); Sortel (Korea); Tempus (Paraguay)

Drug Class ..... Adrenergic agonists; Bronchodilators

Indications ..... Asthma prophylaxis, treatment of exercise-induced asthma; COPD maintenance

Mechanism ..... β_2-Agonist

Dosage with Qualifiers

Asthma prophylaxis—12mcg INH q12h
Treatment of exercise-induced asthma—12mcg INH 15-30min prior to exercise; may repeat q12h prn, max 24mcg/d
COPD maintenance—12mcg INH q12h; max 24mcg/d

- **Contraindications**—hypersensitivity to drug or class, acute asthma
- **Caution**—arrhythmia, CV disease, hypertension, diabetes mellitus, hypokalemia, seizure disorder

Maternal Considerations

Formoterol is a long-acting β-mimetic agent used for asthma prophylaxis. It is not for acute treatment. There are no adequate reports or well-controlled studies of **formoterol** in pregnant women. Only 33 pregnant women were reported to have used **formoterol** in a post-marketing survey. No adverse effects were noted. There is some reduction in rodent myometrial contractility when studied *in vitro*. In one rodent study of lipopolysaccharide (LPS)-triggered preterm labor, **formoterol** reduced the cytokine response to LPS.
Side effects include arrhythmia, paradoxical bronchospasm, hypokalemia, nervousness, tremor, headache, dry mouth, nausea, dizziness, insomnia, chest pain, muscle cramps, dyspepsia, and dysphonia.

Fetal Considerations

There are no adequate reports or well-controlled studies of **formoterol** in human fetuses. Rodent studies are reassuring, revealing delayed ossification, IUGR, and increased perinatal mortality only at doses >2000× the MRHD.

Breastfeeding Safety

There is no published experience in nursing women. It is unknown whether **formoterol** enters human breast milk. The transfer of similar agents, such as **terbutaline,** is very low.

Drug Interactions

Additional adrenergic drugs are may potentiate the sympathetic effects of **formoterol.**
Use with xanthine derivatives, steroids, or diuretics may potentiate any hypokalemic effect of adrenergic agonists.
Formoterol, as with other β_2-agonists, should be given with great caution to women being treated with MAOIs, TCAs, or drugs known to prolong the QTc interval since the action of adrenergic agonists on the CV system may be potentiated by these agents. Drugs known to prolong the QTc interval have an increased risk of ventricular arrhythmias.
β-Blockers and **formoterol** may inhibit each other if administered concurrently. β-Blockers not only block the therapeutic effects of β-agonists, but may produce severe bronchospasm in asthmatic patients. Under certain circumstances (e.g., as prophylaxis after MI), there may be no acceptable alternative but to use a β-blocker in a patient with asthma. In this setting, cardioselective β-blockers could be considered, although administered with caution.

References

Bardou M, Cortijo J, Loustalot C, et al. Naunyn Schmiedebergs Arch Pharmacol 1999; 360:457-63.
Shinkai N, Takasuna K, Takayama S. Reproduction 2003; 125:199-203.
Shinkai N, Takayama S. J Pharm Pharmacol 2000; 52:1417-23.
Wilton LV, Shakir SA. Drug Saf 2002; 25:213-23.

Summary

Pregnancy Category: C
Lactation Category: U

- **Formoterol** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Foscarnet—(Foscavir)

International Brand Name—Foscavir (Austria, Belgium, Brazil, Czech Republic, England, Finland, France, Greece, Hungary, Ireland, Israel, Italy, Netherlands, Norway, Spain, Sweden, Switzerland); Foscovir (Denmark)

Drug Class	Antivirals
Indications	Acyclovir-resistant HSV, CMV retinitis, AIDS
Mechanism	Selectively inhibits viral DNA polymerase
Dosage with Qualifiers	Acyclovir-resistant HSV—40mg/kg IV given over 1h q8h for 2-3w CMV retinitis, AIDS—begin at 60mg/kg IV given over 1h q8h; administer maintenance dose ×2-3w *NOTE: renal dosing.* • **Contraindications**—hypersensitivity to drug or class • **Caution**—renal dysfunction, malnutrition, CNS disorders
Maternal Considerations	**Foscarnet** exerts its antiviral activity by a selective inhibition at the pyrophosphate binding site on virus-specific DNA polymerases. There are no adequate reports or well-controlled studies of **foscarnet** in pregnant women, and the indications are limited. **Foscarnet** was used successfully during pregnancy in 1 woman with AIDS for the treatment of genital **acyclovir**-resistant HSV type 2, and in another HIV-infected woman with myeloradiculitis. ***Side effects*** include renal failure, anemia, pancreatitis, bone marrow suppression, thrombocytopenia, leukopenia, agranulocytopenia, bronchospasm, seizures, N/V, diarrhea, fever, headache, weakness, hypocalcemia, hypophosphatemia, and hypomagnesemia.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **foscarnet** crosses the human placenta. Rodent studies were for the most part reassuring, revealing a modest increase in minor skeletal abnormalities.
Breastfeeding Safety	There is no published experience in nursing women. It is unknown whether **foscarnet** enters human breast milk. However, it is concentrated in rat breast milk.
Drug Interactions	A possible drug interaction of **foscarnet** and **pentamidine** has been described. Concomitant treatment may have caused hypocalcemia resulting in a death. Since **foscarnet** decreases serum ionized calcium, concurrent treatment with other drugs known to influence serum calcium concentrations should be used with particular caution.
References	Alla P, de Jaureguiberry JP, Legier HP, et al. Rev Med Interne 1999; 20:514-6. Alvarez-McLeod A, Havlik J, Drew KE. Clin Infect Dis 1999; 29:937-8.
Summary	**Pregnancy Category: C** **Lactation Category: U** • **Foscarnet** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Fosfomycin tromethamine—(Monurol)

International Brand Name—Monuril (Colombia, France, Germany); Monuril Pediatrico (Colombia); Uridoz (France)

Drug Class

Antibiotics, miscellaneous; Antiseptics, urinary tract

Indications

Acute cystitis with susceptible strains

Mechanism

Bactericidal

Dosage with Qualifiers

Acute cystitis—3g PO ×1

- **Contraindications**—sensitivity to drug or class
- **Caution**—hepatic dysfunction

Maternal Considerations

Fosfomycin is an orally active, broad-spectrum bactericidal agent that has the advantage of single-dose administration. In several controlled trials conducted in pregnant women, it was similar in efficacy to other commonly used agents.
Side effects include diarrhea, vaginitis, N/V, headache, weakness, dizziness, and dyspepsia.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. **Fosfomycin** crosses the human placenta, though the kinetics remain to be clarified. It does not reach an F:M ratio of unity. Rodent studies are reassuring; fetal toxicity is seen only when the dose used produced maternal toxicity.

Breastfeeding Safety

There is no published experience in nursing women. It is unknown whether **fosfomycin** enters human breast milk.

Drug Interactions

Metoclopramide, which increases GI motility, lowers the serum concentration and urinary excretion of **fosfomycin.** Other drugs that increase GI motility may produce similar effects.

References

Ferreres L, Paz M, Martin G, Gobernado M. Chemotherapy 1977; 23(Suppl 1):175-9.
Krcmery S, Hromec J, Demesova D. Int J Antimicrob Agents 2001; 17:279-82.
Reeves DS. Infection 1992; 20(Suppl 4):S313-6.

Summary

Pregnancy Category: B
Lactation Category: U

- **Fosfomycin** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.
- As an agent for routine use, it offers no advantage over more commonly used compounds.
- There are other agents available for which there is greater experience during pregnancy and lactation.

Fosinopril—(Monopril)

International Brand Name—Acenor-M (Indonesia); BPNorm (Philippines); Dynacil (Germany); Fosinil (Belgium); Fosinorm (Germany); Fosipres (Italy); Fositen (Portugal, Switzerland); Fositens (Austria, Spain); Fovas (India); Fozitec (France); Monopril (Australia, Brazil, Canada, Chile, China, Colombia, Costa Rica, Denmark, Ecuador, El Salvador, Greece, Guatemala, Honduras, Hong Kong, Hungary, Korea, Malaysia, Mexico, Nicaragua, Panama, Peru, Poland, Russia, South Africa, Taiwan, Thailand, Turkey, Venezuela); Newace (Netherlands); Sapril (Philippines); Staril (England); Vasopril (Israel)

Drug Class	ACEI/A2R-antagonists
Indications	Hypertension, CHF, acute MI, nephropathy
Mechanism	ACE inhibitor
Dosage with Qualifiers	Hypertension—begin 10mg PO qd; max 80mg/d; lower dose required with diuretic CHF—begin 10mg PO qd; max 80mg/d Acute MI—10-20mg PO qd Nephropathy—20mg PO qd *NOTE: renal dosing; may also be combined with* ***hydrochlorothiazide.*** • **Contraindications**—hypersensitivity to drug or class, hereditary or ACE-related angioedema, pregnancy • **Caution**—renal artery stenosis, severe CHF, renal dysfunction, connective tissue disease, volume depletion, hyponatremia
Maternal Considerations	There is no published experience with **fosinopril,** a long-acting ACEI, during pregnancy. **Fosinopril** is rarely if ever necessary during pregnancy. ***Side effects*** include angioedema, hypotension, acute renal failure, hepatic toxicity, agranulocytosis, pancreatitis, cough, dizziness, fatigue, hyperkalemia, N/V, elevated BUN/Cr, musculoskeletal pain, and URI symptoms.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **fosinopril** crosses the human placenta. However, this class of drugs is known to have adverse human fetal renal effects leading to disability or death and should be considered contraindicated during pregnancy. Similar effects occur with **fosinopril** in rodents.
Breastfeeding Safety	There is no published experience in nursing women. The manufacturer reports low levels of **fosinopril** in human breast milk.
Drug Interactions	Patients on diuretics, especially those with intravascular volume depletion, may occasionally experience an excessive reduction of BP after initiation of therapy with **fosinopril.** May attenuate potassium loss caused by thiazide diuretics. Potassium-sparing diuretics (e.g., **amiloride, spironolactone, triamterene**) or potassium supplements can increase the risk of hyperkalemia. Increased serum **lithium** and symptoms of **lithium** toxicity have been reported in patients receiving ACEIs during therapy with **lithium.** These drugs should be co-administered with caution. If a diuretic is also used, the risk of **lithium** toxicity may be increased. Antacids may reduce **fosinopril** serum levels and urinary excretion. Therefore, if concomitant administration of these agents is indicated, dosing should be separated by 2h.

■ **References** ····· Grove KL, Mayo RJ, Forsyth CS, et al. Toxicol Lett 1995; 80:85-95.

■ **Summary** ·····

Pregnancy Category: D (2nd trimester), **C** (1st trimester)
Lactation Category: U

- ACEI and A2R-antagonists should be avoided during pregnancy unless there are no alternatives.
- Should an ACEI/A2R-antagonist be required, **fosinopril** is a poor selection during pregnancy because of its long t/2.
- There are alternative agents for which there is more experience during pregnancy and lactation.

Fosphenytoin—(Cerebyx)

International Brand Name—Prodilantin (France)

■ **Drug Class** ····· Anticonvulsants; Hydantoins

■ **Indications** ····· Status epilepticus, seizure disorder, seizure prevention prior to neurosurgery

■ **Mechanism** ····· See **Phenytoin**

■ **Dosage with Qualifiers** ·····

Status epilepticus—15-20mg **phenytoin** equivalents/kg IV ×1
Seizure disorder—load 10-20mg **phenytoin** equivalents/kg IV/IM, then 4-6mg **phenytoin** equivalents/kg IV/IM
Seizure prophylaxis before neurosurgery—load 10-20mg **phenytoin** equivalents/kg IV/IM, then 4-6mg **phenytoin** equivalents/kg IV/IM

NOTE: therapeutic level 10-20mcg/ml.

- **Contraindications**—hypersensitivity to drug or class, sinus bradycardia, 2nd or 3rd degree AV block, SA block
- **Caution**—hypotension, hepatic or renal dysfunction, CV disease, diabetes mellitus, porphyria

■ **Maternal Considerations** ····· **Fosphenytoin** is converted *in vivo* to **phenytoin.** There are no adequate reports or well-controlled studies of **fosphenytoin** in pregnant women, but the risks should be similar to **phenytoin.** The risk of seizure during pregnancy may rise because of increased clearance. Maternal serum levels should be monitored throughout gestation.
Side effects include CV collapse, hypotension, bradycardia, arrhythmias, Stevens-Johnson syndrome, toxic delirium, pancytopenia, thrombocytopenia, leukopenia, agranulocytosis, hepatic toxicity, anemia, dizziness, nystagmus, itching, paresthesias, headache, somnolence, N/V, ataxia, tremor, dry mouth, blurred vision, fever, constipation, and electrolyte change.

■ **Fetal Considerations** ····· There are no adequate reports or well-controlled studies in human fetuses. Its risk profile should be similar to **phenytoin**.

■ **Breastfeeding Safety** ····· There is no published experience in nursing women. It is unknown whether **fosphenytoin** enters human breast milk. Its profile should be similar to **phenytoin**.

■ **Drug Interactions** ····· Drugs highly bound to albumin could increase the unbound fraction of **fosphenytoin.**

The most significant drug interactions following administration of **fosphenytoin** are expected to occur with drugs that interact with phenytoin (see **phenytoin**).
Monitoring of plasma **phenytoin** concentrations may be helpful when possible drug interactions are suspected.

References ..... There is no published experience in pregnancy or during lactation. (See **phenytoin.**)

Summary .....

Pregnancy Category: D
Lactation Category: NS

- Functionally equivalent to **phenytoin.**
- **Fosphenytoin** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Frovatriptan—(Froval)

International Brand Name—Allegro (Germany); Migard (England, Ireland)

Drug Class ..... Migraines

Indications ..... Migraine

Mechanism ..... Selective 5-HT_1 agonist

Dosage with Qualifiers .....

Migraine—2.5mg PO ×1, may repeat after 2h; max 7.5mg/24h

- **Contraindications**—hypersensitivity to drug or class, CAD, CV disease, PVD, ischemic bowel disease, uncontrolled hypertension, hemiplegic or basilar migraine, use of an ergot or 5-HT_1 agonist within 24h.
- **Caution**—cardiac risk factors

Maternal Considerations .....

There is no published experience with **frovatriptan** during pregnancy.
Side effects include acute MI, coronary vasospasm, arrhythmias, subarachnoid hemorrhage, hypertensive crisis, stroke, bowel ischemia, dizziness, fatigue, flushing, paresthesias, dry mouth, bone pain, dyspepsia, neck or jaw tightness, and chest pressure.

Fetal Considerations ..... There are no adequate reports or well-controlled studies of **frovatriptan** in human fetuses.

Breastfeeding Safety .....

There is no published experience in nursing women. It is unknown whether **frovatriptan** enters human breast milk. Considering the limited dosing regimen and the safety of similar-class agents, **frovatriptan** is likely compatible with breastfeeding. If desired, the patient may pump her breasts for 24h and then resume breastfeeding.

Drug Interactions .....

Ergot-containing drugs may cause prolonged vasospastic reactions.
Concomitant use of other 5-$HT_{1B/1D}$ agonists within 24h of **frovatriptan** is not recommended.
SSRIs (e.g., **fluoxetine, fluvoxamine, paroxetine, sertraline**) have been reported, rarely, to cause weakness, hyperreflexia, and incoordination when co-administered with 5-HT_1 agonists.
If concomitant treatment with **frovatriptan** and an SSRI is

clinically warranted, appropriate observation of the patient is advised.

References — There is no published experience in pregnancy or during lactation.

Summary

Pregnancy Category: C
Lactation Category: U
- **Frovatriptan** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Furazolidone—(Furoxone)

International Brand Name—Enterocodil (Brazil); Furapill (Ecuador); Furion (Thailand); Furoxona (Chile, Colombia, Mexico, Peru, Venezuela); Furoxone (Philippines); Giardil (Argentina)

Drug Class — Antibiotics; Antiprotozoals; Nitrofurans

Indications — Bacterial infection

Mechanism — Interferes with enzyme systems

Dosage with Qualifiers

Bacterial infection—100mg PO qid ×5-10d
- **Contraindications**—hypersensitivity to drug or class, use of an MAOI within 2w, alcohol use
- **Caution**—G6PD deficiency

Maternal Considerations — **Furazolidone** is a metabolite of **nitrofurantoin** and should have a similar degree of safety during pregnancy. It is an alternative treatment for giardiasis. There are no adequate reports or well-controlled studies in pregnant women. (See **nitrofurantoin.**) ***Side effects*** include hypertension, hemolytic anemia, hypoglycemia, N/V, abdominal pain, headache, rash, urticaria, fever, and arthralgia.

Fetal Considerations — There are no adequate reports or well-controlled studies of **furazolidone** in human fetuses (see **nitrofurantoin**).

Breastfeeding Safety — There is no published experience in nursing women. **Furazolidone** is excreted into rodent breast milk. (See **nitrofurantoin.**)

Drug Interactions — See **nitrofurantoin.**

References — There is no published experience in pregnancy or during lactation.

Summary

Pregnancy Category: C
Lactation Category: S
- **Furazolidone** is a metabolite of **nitrofurantoin** and should have a similar degree of safety during pregnancy.
- **Furazolidone** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Furosemide—(Lasix)

International Brand Name—Aldic (Thailand); Anfuramaide (Taiwan); Apo-Frusemide (New Zealand); Apo-Furosemide (Canada); Aquarid (South Africa); Arasemide (Japan); Cetasix (Indonesia); Classic (Indonesia); Desal (Poland); Dirine (Malaysia); Diural (Denmark, Norway, Sweden, Switzerland); Diuresal (Taiwan); Diurin (New Zealand); Diurolasa (Spain); Diusemide (South Africa); Diuspec (Philippines); Dryptal (England, Ireland); Durafurid (Germany); Edenol (Mexico); Errolon (Argentina); Eutensin (Japan); Franyl (Japan); Fretic (Philippines); Frumid (Malaysia); Frusehexal (Australia); Frusema (Philippines); Frusid (Australia, Hong Kong); Furanthril (Czech Republic); Furanturil (Bulgaria); Furesin (Brazil); Furetic (Thailand); Furix (Norway, Sweden); Furmid (Malaysia); Furo-Basan (Switzerland); Furomen (Finland); Furomex (Czech Republic); Furomin (Finland); Furo-Puren (Germany); Furorese (Germany); Furoscan (Philippines); Furosix (Indonesia); Furovite (Israel); Fusid (Germany, Israel); Fusimex (Philippines); Hissuflux (Colombia); Hydrex (South Africa); Impugan (Denmark, Indonesia, Sweden, Switzerland, Thailand); Jufurix (Germany); Kofuzon (Taiwan); Kutrix (Japan); Lasiletten (Netherlands); Lasilix (France, Morocco); Lasix (Austria, Belgium, Brazil, Bulgaria, Canada, Chile, Costa Rica, Czech Republic, Denmark, Dominican Republic, Ecuador, El Salvador, England, Finland, Germany, Greece, Guatemala, Honduras, Hong Kong, India, Indonesia, Ireland, Italy, Korea, Malaysia, Mexico, Netherlands, Nicaragua, Norway, Panama, Paraguay, Peru, Philippines, Portugal, Russia, Singapore, Sweden, Switzerland, Taiwan, Thailand, Turkey, Uruguay, Venezuela); Lasix Retard (Denmark, Netherlands, Norway, Portugal, Sweden); Laxur (Chile); Marsemide (Philippines); Naclex (Indonesia); Nephron (Argentina); Odemase (Germany); Odemex (Costa Rica, Dominican Republic, Ecuador, El Salvador, Guatemala, Honduras, Nicaragua, Panama); Oedemex (Switzerland); Pharmix (Philippines); Promedes (Japan); Rasitol (Malaysia); Retep (Argentina); Seguril (Spain); Selectofur (Mexico); Urenil (Japan); Uresix (Indonesia); Urex (Hong Kong); Zafurida (Mexico)

Drug Class	Diuretics, loop
Indications	Pulmonary or peripheral edema, hypertension, hypercalcemia
Mechanism	Inhibits the reabsorption of sodium and chloride in the Loop of Henle
Dosage with Qualifiers	Pulmonary edema—begin at 40mg IV ×1 slowly, assess response; may increase to 80mg IV q1h prn Peripheral edema—20-80mg PO qd to bid; max 600mg qd Hypertension—40mg PO bid; max 600mg qd Hypercalcemia—80-100mg IV q1-2h, or 120mg PO qd • **Contraindications**—hypersensitivity to drug or class, hypersensitivity to sulfonamides, anuria, hepatic coma, electrolyte imbalance • **Caution**—severe renal disease, acute MI, diabetes mellitus, SLE, history of pancreatitis, combined with ototoxic drugs
Maternal Considerations	There are no adequate reports or well-controlled studies of **furosemide** in pregnant women. It is one of the drugs of choice for the treatment of CHF and/or pulmonary edema during pregnancy. High concentrations of **furosemide** dilate the capacitance vessels and assist the reduction in preload. The long clinical experience for the noted indications is reassuring. In one study of women with preeclampsia, **furosemide** caused a significant decrease in the intervillous blood flow. This likely reflects an already contracted intravascular volume. In another study of women with hyperdynamic cardiac outputs (COs), **furosemide** initiated at 22w gestation decreased CO and stroke volume (1.2±0.2L/min and 17±3ml, respectively), whereas total pulmonary resistance increased (101±26 dyne.sec.cm^{-5}; p <.001 for all) after 2.9±1.4w. However, the hemodynamic improvement did not approach that expected for pregnancy. Thus, while **furosemide** improved the hyperdynamic circulation, it neither lowered BP nor caused clinically significant vasoconstriction. In rabbit studies, a high dose of **furosemide** was associated with unexplained maternal deaths. ***Side effects*** include hypokalemia, metabolic alkalosis, orthostatic hypotension, ototoxicity, leukopenia, thrombocytopenia,

pancreatitis, jaundice, SLE exacerbation, vasculitis, erythema multiforme, hemolytic anemia, dizziness, N/V, weakness, cramps, hyperuricemia, hyperglycemia, tinnitus, paresthesias, and photosensitivity.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. **Furosemide** crosses the human placenta, achieving an F:M ratio approximating unity after 8-10h. It is unclear, however, how responsive the fetal kidney is to it, and the impact of gestational age on that response. Direct administration of **furosemide** for fetal therapy, typically in association with hydrops, has been frequently reported. However, no corresponding diuresis has been documented. In rodents, an effect on newborn urine concentrating ability is reported after *in utero* exposure. An increased prevalence was also noted in one mouse study. Though fetal sheep absorb it from AF presumably via a transmembrane mechanism, direct administration fails to generate a fetal diuresis. In addition, there is no fetal diuresis after administration to the gravid ewe. In summary, the impact of **furosemide** on the fetus is unclear and likely small.

Breastfeeding Safety

There are no adequate reports or well-controlled studies in nursing women. **Furosemide** does enter human breast milk, but the kinetics remain to be elucidated. It is unlikely one-time or limited use would cause harm during lactation.

Drug Interactions

May increase the ototoxicity of aminoglycoside antibiotics, especially in the presence of impaired renal function. Avoid this combination except in life-threatening situations.
Should not be used concomitantly with **ethacrynic acid** because of the possibility of ototoxicity.
Patients receiving high doses of salicylates, as in rheumatic disease, may experience salicylate toxicity at lower doses because of competitive renal excretory sites.
May antagonize the skeletal muscle relaxing effect of **tubocurarine** and potentiate the action of **succinylcholine.**
Lithium generally should not be given with diuretics because they reduce **lithium's** renal clearance and add a high risk of **lithium** toxicity.
May add to or potentiate the therapeutic effect of other antihypertensive drugs. Potentiation occurs with ganglionic or peripheral adrenergic blocking drugs.
May decrease arterial responsiveness to NE. However, NE may still be used effectively.
Simultaneous administration of **sucralfate** may reduce the natriuretic and antihypertensive effects of **furosemide.** Patients receiving both drugs should be observed closely. The intake of **furosemide** and **sucralfate** should be separated by at least 2h.
Indomethacin may reduce the natriuretic and antihypertensive effects of **furosemide** in some patients by inhibiting prostaglandin synthesis.

References

Anandakumar C, Biswas A, Chua TM, et al. Ultrasound Obstet Gynecol 1999; 13:263-5.
Beermann B, Groschinsky-Grind M, Fahraeus L, Lindstrom B. Clin Pharmacol Ther 1978; 24:560-2.
Carr DB, Gavrila D, Brateng D, Easterling TR. Hypertens Pregnancy 2007; 26:173-8.
Chamberlain PF, Cumming M, Torchia MG, et al. Am J Obstet Gynecol 1985; 151:815-9.
Gilbert WM, Newman PS, Brace RA. Am J Obstet Gynecol 1995; 172:1471-6.

Ross MG, Ervin MG, Leake RD. Am J Obstet Gynecol 1985; 152:1107.
Mallie JP, Boudzoumou P. Pediatr Nephrol 1996; 10:458-60.
Suonio S, Saarikoski S, Tahvanainen K, et al. Am J Obstet Gynecol 1986; 155:122-5.

Summary

Pregnancy Category: C
Lactation Category: S (likely)

- **Furosemide** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.
- The long clinical experience for the noted indications is reassuring.

Gabapentin—(Neurontin)

International Brand Name—Dineurin (Chile); Gabatin (Korea); Gantin (Australia); Kaptin (Colombia); Neurontin (Austria, Belgium, Canada, Czech Republic, England, Finland, France, Germany, Greece, Hong Kong, Hungary, India, Indonesia, Ireland, Italy, Kenya, Korea, Malaysia, Norway, Philippines, Poland, Singapore, South Africa, Spain, Sweden, Switzerland, Taiwan, Thailand, Uruguay, Venezuela); Nupentin (Australia); Pendine (Australia)

Drug Class ..... Anticonvulsants

Indications ..... Seizures (partial), postherpetic neuralgia, neuropathic pain

Mechanism ..... Unknown

Dosage with Qualifiers .....

Seizures (partial)—begin 300mg PO qd ×1d, then bid ×1d, then tid; usual maintenance 1800-2400mg qd; max 3600mg/d
Postherpetic neuralgia—begin 300mg PO qd ×1d, then bid ×1d, then tid; max 1800mg/d
Neuropathic pain—begin 300mg PO qd ×1d, then bid ×1d, then tid; max 3600mg/d

NOTE: renal dosing.

- **Contraindications**—hypersensitivity to drug or class
- **Caution**—renal dysfunction, abrupt withdrawal

Maternal Considerations .....

Gabapentin is a 2nd-generation anticonvulsant used mainly as an adjunct. While there is little published experience during pregnancy and lactation, the limited study available suggests a higher safety margin relative to 1st-generation agents. The impact of pregnancy upon **gabapentin** metabolism apparently has not been studied. The dose may require adjustment during pregnancy, and should be based on both serum concentration and clinical symptoms. **Gabapentin** has been used for chronic headache during early pregnancy. While a relationship between hormones and seizure activity exists in many women, good options for catamenial epilepsy remain elusive. And while interactions between enzyme-inducing anticonvulsants and contraceptives are well documented, this is not true for **gabapentin.** Patients should be counseled to plan pregnancy, and informed of the value of folate supplementation, the importance of medication adherence, and the risk of teratogenicity.
Gabapentin has been given for Restless Leg Syndrome, a disorder reportedly increased during pregnancy, and appears to reduce both the frequency and the severity of hot flashes in postmenopausal women in a dose-dependent manner.
Side effects include leukopenia, dizziness, somnolence, fatigue, ataxia, tremor, blurred vision, N/V, nervousness, dysarthria, weight gain, and dyspepsia.

Fetal Considerations .....

There are no adequate reports or well-controlled studies in human fetuses. **Gabapentin** crosses the human placenta, achieving a F:M ratio of 1.7 (range 1.3-2.1). Limited observations suggest active transport of **gabapentin,** with accumulation in the fetus. This suggests the presence of L-type amino acid transporter 1 in the placenta. There was no evidence of human teratogenicity in a small post-marketing study. Rodent studies reveal fetotoxicity and an increased prevalence of minor malformations, including skeletal abnormalities (skull, spine, and limbs) and hydronephrosis.

Breastfeeding Safety .....

There are no adequate reports or well-controlled studies in nursing women. **Gabapentin** is excreted into human breast milk.

In one series, the M:P ratio was 1.0 (range, 0.7-1.3) from 2w to 3mo. The infant dose was estimated at 0.2-1.3mg/kg/day, equivalent to 1.3-3.8% of the weight-normalized dose received by the mother. Thus, the drug is absorbed by the neonate. The plasma concentration in the breastfed infants was approximately 12% of the mother's plasma level, but no adverse effects were observed. Absent a larger experience, the infant should be monitored for possible adverse effects, the drug given at the lowest effective dose, and breastfeeding avoided at times of peak drug levels.

Drug Interactions

Naproxen appears to increase **gabapentin** absorption by 12-15%.
Gabapentin decreases **hydrocodone** C_{max} and AUC values in a dose-dependent manner.
Morphine may increase the mean **gabapentin** AUC.
Cimetidine appears to modestly decrease the oral clearance of **gabapentin** by altering renal excretion of both **gabapentin** and creatinine.
The C_{max} of **norethindrone** is 13% higher when given with **gabapentin,** though this interaction is not expected to be of clinical importance.
Antiacids reduce the bioavailability of **gabapentin** by about 20%. It is recommended that **gabapentin** be taken at least 2h after antiacid use.

References

Bar-Oz B, Nulman I, Koren G, Ito S. Paediatr Drugs 2000; 2:113-26.
Crawford P. CNS Drugs 2002; 16:263-72.
Djokanovic N, Garcia-Bournissen F, Koren G. J Obstet Gynaecol Can 2008; 30:505-7.
Gustus T, Kurlan R, McDermott MP, Kieburtz K. Obstet Gynecol 2003; 101:337-45.
Lowe SA. Best Pract Res Clin Obstet Gynaecol 2001; 15:863-76.
Marcus DA. Expert Opin Pharmacother 2002; 3:389-93.
McAuley JW, Anderson GD. Clin Pharmacokinet 2002; 41:559-79.
Ohman I, Vitols S, Tomson T. Epilepsia 2005; 46:1621-4.
Wilton LV, Shakir S. Epilepsia 2002; 43:983-92.

Summary

Pregnancy Category: C
Lactation Category: S (likely)
- Limited study suggests a higher safety margin relative to 1st-generation anticonvulsants.

Gadoversetamide—(Optimark)

International Brand Name—OptiMARK (Argentina)

Drug Class

Diagnostics, nonradioactive

Indications

MRI

Mechanism

A component, gadolinium, is paramagnetic

Dosage with Qualifiers

MRI—0.2ml/kg at 1-2ml/sec (alternatively 0.1 mmol/kg)

- **Contraindications**—hypersensitivity to drug or class
- **Caution**—hemolytic anemia, renal insufficiency

Maternal Considerations

There is no published experience with **gadoversetamide** during pregnancy.

Side effects include body discomfort, headache, abdominal pain, asthenia, back pain, flushing, N/V, diarrhea, dyspepsia, dizziness, paresthesias, rhinitis, and taste alteration.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **gadoversetamide** crosses the human placenta. It does cross the rodent placenta. Limited rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR.

Breastfeeding Safety

There is no published experience in nursing women. It is unknown whether **gadoversetamide** enters human breast milk. It is excreted in rat breast milk. Breastfeeding women should consider discarding their milk after injection for the first 72h after the MRI.

Drug Interactions

Drug interactions with other contrast agents and other drugs have not been studied.

References

Wible JH, Troup CM, Hynes MR, et al. Invest Radiol 2001; 36:401-12.

Summary

Pregnancy Category: C
Lactation Category: U

- **Gadoversetamide** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Galantamine—(Reminyl)

International Brand Name—Nivalin (Austria, Bulgaria, Germany, Hungary, Poland, Russia); Reminyl (England, France, Germany, Hong Kong, Ireland, Israel, Korea, Malaysia, Philippines, Singapore, Taiwan, Thailand)

Drug Class

Alzheimer's disease agents; Cholinesterase inhibitors

Indications

Alzheimer's dementia

Mechanism

Cholinesterase inhibitor

Dosage with Qualifiers

Alzheimer's dementia—begin 4mg PO bid; increase by 4mg bid q4w to a max of 12mg bid

NOTE: renal and hepatic dosing.

- **Contraindications**—hypersensitivity to drug or class
- **Caution**—peptic ulcer disease, cardiac conduction defects, seizure disorder, asthma, COPD, hepatic or renal dysfunction

Maternal Considerations

There is no published experience in pregnancy. In light of the natural history of Alzheimer's disease, **galantamine** is unlikely to be required during pregnancy.
Side effects include AV block, bradycardia, arrhythmias, seizures, urinary obstruction, N/V, diarrhea, anorexia, dizziness, dyspepsia, fatigue, depression, insomnia, abdominal pain, rhinitis, tremor, syncope, and hematuria.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **galantamine** crosses the human placenta. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses

higher than those used clinically. **Galantamine** has the therapeutic potential to protect the brain from glutamate toxicity.

Breastfeeding Safety — There is no published experience in nursing women. It is unknown whether **galantamine** enters human breast milk.

Drug Interactions — **Galantamine** could interfere with the activity of anticholinergic medications. A synergistic effect is expected when cholinesterase inhibitors are given with **succinylcholine,** other cholinesterase inhibitors, and similar neuromuscular blocking agents or cholinergic agonists such as **bethanechol.**
Principally metabolized by CYP3A4 and CYP2D6. **Ketoconazole,** a strong inhibitor of CYP3A4 and an inhibitor of CYP2D6, increases the AUC of **galantamine** by about 30%. **Paroxetine,** a strong inhibitor of CYP2D6, increases the oral bioavailability of **galantamine** by about 40%.

References

Takada-Takatori Y, Kume T, Sugimoto M, et al. Eur J Pharmacol 2006; 549:19-26.

Summary

Pregnancy Category: B
Lactation Category: U
- **Galantamine** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Ganciclovir—(Cytovene)

International Brand Name—Cymevan (France); Cymeven (Germany); Cymevene (Argentina, Bangladesh, Brazil, Chile, Colombia, Ecuador, France, Germany, India, Ireland, Japan, Malaysia, Mexico, Pakistan, Paraguay, Peru, Poland, Puerto Rico, Slovenia, Uruguay, Venezuela); Cytovene (Canada); Denosine (Japan); Virgan (England, France, Ireland, Korea, Philippines)

Drug Class — Antivirals

Indications — CMV retinitis

Mechanism — Inhibits viral DNA polymerase

Dosage with Qualifiers — CMV retinitis—5mg/kg IV over 1h q12h ×14-21d; then 5mg/kg IV qd, then 1000mg PO qd

NOTE: renal dosing.

- **Contraindications**—hypersensitivity to drug or class, bone marrow depression
- **Caution**—renal dysfunction

Maternal Considerations — There are no adequate reports or well-controlled studies in pregnant women. Case reports include **ganciclovir** use during the 1st trimester in 1 woman with a liver transplant and another with a kidney transplant, and in a third with CMV hepatitis.
Side effects include seizures, coma, thrombocytopenia, neutropenia, anemia, nephrotoxicity, fever, diarrhea, N/V, sweating, chills, pruritus, neuropathy, paresthesias, and elevated LFTs.

Fetal Considerations — There are no adequate reports or well-controlled studies in human fetuses. **Ganciclovir** crosses the human placenta by passive diffusion. It has been administered directly to CMV-infected fetuses with sonographically detected sequelae

and no clear success: the viral load declined but the fetus died. It also has been used to treat an infected fetus who developed primary CMV after maternal primary infection associated with a renal transplant. In this instance, the fetal CMV was reportedly erradicated. Postnatally, **ganciclovir** remains the drug of choice for the treatment of symptomatic neonatal CMV; it is not curative, but rather ameliorates sequelae. **Ganciclovir** is embryotoxic in rats and mice. In rabbits, it is associated with cleft palate, micropthalmia, renal agenesis, and hydrocephaly.

Breastfeeding Safety

There are no adequate reports or well-controlled studies in nursing women. Fetuses with brain or abdominal findings have the worst prognoses and are potential candidates for fetal therapy. It is unknown whether **ganciclovir** enters human breast milk. **Ganciclovir** enters rat breast milk by passive diffusion, reaching near-maternal serum levels. However, it is usually considered compatible with breastfeeding considering its neonatal application.

Drug Interactions

Increased the steady-state **didanosine** AUC 111 ± 114%. The steady-state **ganciclovir** AUC decreased 21 ± 17% when **didanosine** was administered 2h prior to **ganciclovir.**
The **ganciclovir** AUC was not affected by the presence of **didanosine** when the 2 drugs were given together.
AUC decreased 17 ± 25% in the presence of **zidovudine.**
Steady-state **zidovudine** AUC increased 19 ± 27% in the presence of **ganciclovir.** Since both **zidovudine** and **ganciclovir** have the potential to cause neutropenia and anemia, some patients may not tolerate concomitant therapy at full dosage.
AUC increased 53 ± 91% in the presence of **probenecid.** Renal clearance of **ganciclovir** decreased 22 ± 20%, which is consistent competition for renal tubular secretion.
Generalized seizures have been reported in patients who received **ganciclovir** and **imipenem-cilastatin.** These drugs should not be used concomitantly unless the potential benefits outweigh the risks.
Drugs that inhibit replication of rapidly dividing cell populations such as bone marrow, spermatogonia, and germinal layers of skin and GI mucosa (e.g., **amphotericin B, dapsone, doxorubicin, flucytosine, pentamidine, trimethoprim-sulfamethoxazole** combinations, **vinblastine, vincristine,** or other nucleoside analogs) may have additive toxicity when administered with **ganciclovir.** The combined use should be considered only if the potential benefits outweigh the risks.
Increases in serum creatinine have occurred in patients also treated with **cyclosporine** or **amphotericin B,** drugs with known nephrotoxicity potential.

References

Alcorn J, McNamara PJ. Antimicrob Agents Chemother 2002; 46:1831-6.
Bale JF, Miner L, Petheram SJ. Curr Treat Options Neurol 2002; 4:225-30.
Henderson GI, Hu ZQ, Yang Y, et al. Am J Med Sci 1993; 306:151-6.
Manuyama Y, Sameshina H, Kamitomo M, et al. J Obstet Gynaecol Res 2007; 33:619-23.
Miguelez M, Gonzalez A, Perez F. Scand J Infect Dis 1998; 30:304-5.
Miller BW, Howard TK, Goss JA, et al. Transplantation 1995; 60:1353-4.
Pescovitz MD. Transplantation 1999; 15:758-9.
Puliyanda DP, Silverman NS, Lehman D, et al. Transpl Infect Dis 2005; 7:71-4.

Summary

Pregnancy Category: C
Lactation Category: S (likely)
- **Ganciclovir** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Gatifloxacin—(Tequin)

International Brand Name—Bonoq (Germany); Bonoq-Uro (Germany); Gaticin (Indonesia); Gatiflo (Korea); Starox (Chile); Tequin (Argentina, Brazil, Canada, Indonesia, Malaysia, Mexico, Philippines, Singapore, South Africa, Thailand); Zymar (Singapore, Thailand); Zyquin (India)

Drug Class

Antibiotics; Quinolones

Indications

Bacterial infection; uncomplicated gonorrhea

Mechanism

Bactericidal—inhibits DNA gyrase and topoisomerase IV

Dosage with Qualifiers

Bacterial infections—200-400mg PO/IV (infuse over 60min) qd ×7-10d
Uncomplicated gonorrhea—400mg PO ×1

NOTE: renal dosing.

- **Contraindications**—hypersensitivity to drug or class, prolonged QT interval
- **Caution**—CV disease, proarrhythmic condition, concurrent class IA, III antiarrhythmic agents

Maternal Considerations

Gatifloxacin is a well-absorbed oral quinolone. There is no published experience with **gatifloxacin** during pregnancy.
Side effects include pseudomembranous colitis, superinfection, vaginitis, increased ICP, seizures, tendinitis, toxic psychosis, N/V, diarrhea, abdominal pain, headache, dyspepsia, dizziness, lightheadedness, insomnia, rash, anxiety, confusion, increased LFTs, agitation, and photosensitivity.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **gatifloxacin** crosses the human placenta. Rodent studies using multiples of the MRHD reveal an increased risk of skeletal abnormalities and neonatal death rate.

Breastfeeding Safety

There is no published experience in nursing women. It is unknown whether **gatifloxacin** enters human breast milk. **Gatifloxacin** does enter rat milk, and caution is recommended during lactation.

Drug Interactions

Hypoglycemia has been reported after **gatifloxacin** in patients taking **glyburide**.
An increase in **digoxin** concentrations was observed in about ⅓ of subjects after beginning **gatifloxacin.** Patients taking **digoxin** should be monitored for signs and/or symptoms of toxicity.
Probenecid significantly increased **gatifloxacin** levels.
The concomitant administration of NSAIDs with a quinolone may increase the risks of CNS stimulation and convulsions.

References

There is no published experience in pregnancy or during lactation.

Summary

Pregnancy Category: C
Lactation Category: U

- **Gatifloxacin** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.
- There are other agents with more experience and a higher safety profile during pregnancy and lactation.

Gemfibrozil—(Lopid; Tripid)

International Brand Name—Apo-Gemfibrozil (New Zealand); Ausgem (Australia); Bolutol (Spain); Brozil (Malaysia); Chlorestrol (Thailand); Cholespid (Philippines); Clearol (Taiwan); Decrelip (Spain); Detrichol (Indonesia); Elmogan (Hong Kong); Fetinor (Indonesia); Fibralip (Indonesia); Fibrocit (Italy); Gedum (Argentina); Gemd (Taiwan); Gemfi (Germany); Gemfibril (Thailand); Gemfibromax (Australia); Gemizol (New Zealand); Gemlipid (Italy, Turkey); Gemnpid (Taiwan); Gemzil (Hong Kong); Gevilon (Czech Republic, Finland, Germany, Hungary, Poland, Switzerland); Gevilon Uno (Germany); Gozid (Thailand); Grifogemzilo (Peru); Hidil (Thailand); Hipolixan (Ecuador); Ipolipid (Hong Kong, Malaysia); Lanaterom (Indonesia); Lifibron (Indonesia); Lipazil (Australia); Lipidys (Thailand); Lipigem (India, Philippines); Lipira (Indonesia); Lipison (Hong Kong); Lipistorol (Hong Kong); Lipizyl (India); Lipofor (Hong Kong); Lipolo (Thailand); Lipostorol (Malaysia); Lipozid (Philippines); Lipozil (Dominican Republic, El Salvador, Guatemala); Lipur (France); Lopid (Australia, Belgium, Brazil, Canada, Chile, China, Colombia, Denmark, Ecuador, England, Finland, Greece, Hong Kong, Indonesia, Ireland, Italy, Malaysia, Mexico, Netherlands, Peru, Philippines, Portugal, South Africa, Spain, Sweden, Taiwan, Thailand, Turkey, Uruguay, Venezuela); Lopid O.D. (Philippines); Lowin (Hong Kong); Manobrozil (Thailand); Mariston (Malaysia); Mersikol (Indonesia); Normolip (India); Panazil (Taiwan); Polyxit (Thailand); Progemzal (Indonesia); Recozil (Singapore); Reducel (Philippines); Synbrozil (Hong Kong); Triglizil (Colombia); Uragem (China); Zilop (Colombia, Indonesia)

Drug Class

Antihyperlipidemics

Indications

Hypertriglyceridemia, hypercholesterolemia (high LDL, triglycerides; low HDL)

Mechanism

Decreases hepatic free fatty acid extraction, inhibits synthesis and increases clearance of the VLDL carrier apolipoprotein B, inhibits peripheral lipolysis.

Dosage with Qualifiers

Hypertriglyceridemia—600mg PO bid 30min ac
Hypercholesterolemia—600mg PO bid 30min ac

- **Contraindications**—hypersensitivity to drug or class, gallbladder disease, **cerivastatin** use, hepatic dysfunction
- **Caution**—renal dysfunction, use with other statins-class agents

Maternal Considerations

There are no adequate reports or well-controlled studies of **gemfibrozil** in pregnant women. Hyperlipidemia is a chronic illness. Discontinuation of therapy during pregnancy is in most instances unlikely to alter the long-term outcome. Case reports document uncomplicated use of **gemfibrozil** in pregnant women with either hypertriglyceridemia or familial chylomicronemia or complications there of.
Side effects include myositis, cholelithiasis, cholestatic jaundice, thrombocytopenia, anemia, rhabdomyolysis, acute appendicitis, atrial fibrillation, increased LFTs, elevated CPK, N/V, dyspepsia, abdominal pain, diarrhea, and fatigue.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. Based on a single case report, **gemfibrozil** crosses the human placenta. The level of **gemfibrozil** in the fetal venous and arterial cord blood was within the expected therapeutic range for adults. Despite extremely low fat in the maternal diet, the levels of essential fatty acids measured in the mother and in the

fetal blood immediately postpartum were normal. Rodent studies reveal a dose-related increase in skeletal abnormalities at twice the MRHD.

Breastfeeding Safety

There are no adequate reports or well-controlled studies in nursing women. It is unknown whether **gemfibrozil** enters human breast milk. The offspring of treated rodents have reduced weight during neonatal and weaning periods.

Drug Interactions

The risk of myopathy and rhabdomyolysis is increased when combined with HMG-CoA reductase inhibitors. Myopathy or rhabdomyolysis with or without acute renal failure have been reported as early as 3w after the initiation of combined therapy. There is no assurance that periodic monitoring of CK will prevent the occurrence of severe myopathy and kidney damage. Caution should be exercised when anticoagulants are combined with **gemfibrozil.** The dose of the anticoagulant should be reduced to maintain the protime at the desired level.
Use with **repaglinide** causes a significant increase in **repaglinide** levels. Patients taking **repaglinide** should not start **gemfibrozil;** patients taking **gemfibrozil** should not start taking **repaglinide.** Concomitant use may enhance and prolong the hypoglycemic effect of **repaglinide,** and blood glucose levels should be monitored and **repaglinide** dose adjustments made as needed. Rare post-marketing events of serious hypoglycemia are reported in patients taking **repaglinide** and **gemfibrozil** together. In addition, **gemfibrozil** and **itraconazole** have a synergistic metabolic inhibitory effect on **repaglinide.** Patients taking **repaglinide** and **gemfibrozil** should not take **itraconazole.**

References

Al-Shali K, Wang J, Fellows F, et al. Clin Biochem 2002; 35:125-30.
Fitzgerald JE, Petrere JA, de la Iglesia FA. Fundam Appl Toxicol 1987; 8:454-64.
Keilson LM, Vary CP, Sprecher DL, Renfrew R. Ann Intern Med 1987; 124:425-8.
Perronne G, Critelli C. Minerva Ginecol 1996; 48:573-6.
Tsai EC, Brown JA, Veldee MY, et al. BMC Pregnancy Childbirth 2004; 4:27.

Summary

Pregnancy Category: C
Lactation Category: U

- **Gemfibrozil** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Gentamicin—(Garamycin; Genoptic; Gentacidin; Gentak; G-Myticin; Ocu-Mycin)

International Brand Name—Adelanin (Philippines); Alcomicin (Belgium, Canada, Indonesia, Israel, South Africa, Thailand); Apigent (Israel); Azupel (Paraguay); Bactiderm (Philippines); Biogaracin (India); Cidomycin (England, Ireland, Israel, Malaysia, Puerto Rico, South Africa); Danigen (Indonesia); Dermogen (Malaysia); Diakarmon (Greece, Israel, South Africa); Dispagent (Uruguay); Epigent (Israel); Fermentmycin (South Africa); Garabiotic (Indonesia); Garalone (Portugal); Garamicin (Thailand); Garamicina (Brazil, Colombia, Costa Rica, Dominican Republic, Ecuador, El Salvador, Guatemala, Honduras, Mexico, Nicaragua, Panama); Garamicina Cream (Colombia); Garamicina Crema (Ecuador, Mexico); Garamicina Oftalmica (Colombia, Costa Rica, Dominican Republic, Ecuador, El Salvador, Guatemala, Honduras, Mexico, Nicaragua, Panama); Garamycin (Australia, Bulgaria, Canada, Czech Republic, Denmark, Greece, Hong Kong, Hungary, India, Indonesia, Malaysia, Netherlands, Norway, Philippines, Poland, Russia, Sweden, Switzerland, Taiwan, Thailand, Turkey); Garbilocin (Greece); Gencin (South Africa); Gendril (Philippines); Genoptic (Hong Kong, New Zealand, South Africa, Taiwan); Genrex (Mexico); Gensumycin (Denmark, Finland, Norway, Sweden); Gentabiotic (Costa Rica, Dominican Republic, El Salvador, Guatemala, Honduras, Nicaragua, Panama, Peru); Gentabiox (Peru); Gentac (Taiwan); Gentacin (Hong Kong, Japan, Korea); Gentacor (Philippines); Gentacyl (Indonesia); Gentagram (Peru); Genta Grin (Mexico); Gental (Thailand); Gentalline (France); Gentalol (Japan); Gentalyn (Chile, Italy, Peru, Venezuela); Gentalyn Oftalmico-Otico (Peru); Gentamax (Ecuador); Gentame (Malaysia); Gentamedical (Spain); Gentamen (Israel); Gentamerck (Indonesia); Gentamina (Argentina, Paraguay, Uruguay); Gentamytrex (Germany, Hungary, Netherlands, Philippines, Poland); Gentamytrex Ophthiole (Malaysia); Gentarad (Israel); Gentasil (Peru); Gentasporin (India); Gentatrim (Israel); Genticin (England, Ireland, Israel, South Africa); Genticina (Spain); Genticyn (India); Gentiderm (Indonesia); Genum (Philippines); Geomycine (Belgium); Gevramycin (Spain); G-Mycin (Korea); Grammicin (Thailand); Hexamycin (Denmark); Konigen (Indonesia); Lacromycin (Israel); Lisagent (Taiwan); Migenta (Uruguay); Miragenta (Colombia); Miramycin (Hong Kong, Malaysia, Singapore, Taiwan, Thailand); Nichogencin (Indonesia); Obogen (Philippines); Ocugenta (Korea); Oftagen (Peru); Ophtagram (Belgium, Germany, Philippines, Switzerland); Opthagen (Philippines); Optigen (Hong Kong, Malaysia); Opti-Genta (Israel); Optimycin (South Africa); Ottogenta (Indonesia); Pyogenta (Indonesia); Refobacin (Austria, Germany); Rigaminol (Peru); Rocy Gen (Philippines); Rovixida (Argentina); Rupegen (Argentina); Sagestam eye drops (Indonesia); Sedanazin (Japan); Servigenta (Malaysia); Skinfect (Thailand); Sulmycin (Germany); Tangyn (Philippines); Terramycin N Augensalbe (Germany); Terramycin N Augentropfen (Germany); Versigen (Thailand); Yectamicina (Mexico)

Drug Class	Aminoglycosides; Antibiotics; Dermatologics; Ophthalmics; Otics
Indications	Bacterial infection, endocarditis prophylaxis
Mechanism	Bactericidal—inhibits protein synthesis by binding the bacterial 30S ribosomal subunit
Dosage with Qualifiers	Bacterial infection—1-3mg/kg/d in 3 divided doses to achieve a peak 5-10mcg/ml and trough <2mcg/ml Endocarditis prophylaxis—1.5mg/kg IV 30-60min prior to the procedure *NOTE: renal dosing; available for parenteral, topical, or ophthalmic administration.* • **Contraindications**—hypersensitivity to drug or class • **Caution**—renal dysfunction, nephrotoxic agents, cochlear implant, myasthenia gravis
Maternal Considerations	**Gentamicin** is commonly used in obstetric patients for the treatment of infections such as pyelonephritis. Though its clearance is increased during pregnancy and in the puerperium, routine monitoring of peak and trough levels is not required in otherwise healthy women with normal renal function. Coupled with **clindamycin,** it remains standard for the treatment of puerperal endomyometritis. Once-daily treatment postpartum (5mg/kg) with **clindamycin** is as effective as and cheaper than tid dosing. Once the endometritis has resolved on IV therapy, there is no need for further oral therapy. ***Side effects*** include nephro- and ototoxicity, thrombocytopenia, agranulocytosis, neurotoxicity, enterocolitis, pseudotumor cerebri,

N/V, rash, pruritus, weakness, tremor, muscle cramps, anorexia, edema, headache, diarrhea, dyspepsia, tinnitus, and elevated BUN/Cr.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. **Gentamicin** crosses the human placenta, reaching an F:M ratio approximating unity. In rodents, placental transfer is greater early than late gestation. **Gentamicin** interferes with renal protein reabsorption in fetal rats, and depresses body weights, kidney weights, and median glomerular counts in newborn rats when administered systemically at multiples of the MRHD. However, the evidence for human fetal **gentamicin** toxicity is weak. *In utero* exposure to **gentamicin** does not appear to cause increase the risk of audiologic impairment. There is no evidence to support the practice in some locales of using **gentamicin** for ophthalmia neonatorum prophylaxis.

Breastfeeding Safety

Gentamicin enters human breast milk. In one study, the mean M:P **gentamicin** ratios were 0.11 and 0.44 at 1 and 7h, respectively., However, only trace amounts are absorbed by the breastfeeding child.

Drug Interactions

Drugs that decrease renal clearance increase the risk of **gentamicin** toxicity.

References

Briggs GG, Ambrose P, Nageotte MP. Am J Obstet Gynecol 1989; 160:309-13.
Celiloglu M, Celiker S, Guven H, et al. Obstet Gynecol 1994; 84:263-5.
Czeizel AE, Rockenbauer M, Olsen J, Sorensen HT. Scand J Infect Dis 2000; 32:309-13.
French LM, Smaill FM. Cochrane Database Syst Rev 2002; (1):CD001067.
Kirkwood A, Harris C, Timar N, Koren G. J Obstet Gynaecol Can 2007; 29:140-5.
Livingston JC, Llata E, Rinehart E, et al. Am J Obstet Gynecol 2003; 188:149-52.
Mitra AG, Whitten MK, Laurent SL, Anderson WE. Am J Obstet Gynecol 1997; 177:786-92.
Nichoga LA, Skosyreva AM, Voropareva SD. Antibiotiki 1982; 27:46-50.
Popović J, Grujić Z, Sabo A. J Clin Pharm Ther 2007; 32:595-602.
Smaoui H, Schaeverbeke M, Mallie JP, Schaeverbeke J. Pediatr Nephrol 1994; 8:447-50.

Summary

Pregnancy Category: C
Lactation Category: S

- **Gentamicin** is widely used during pregnancy and lactation without evidence of excess toxicity to mother or fetus.

Glatiramer acetate—(Copaxone)

International Brand Name—None identified.

Drug Class	Immunomodulators
Indications	Relapsing MS
Mechanism	Unknown
Dosage with Qualifiers	Relapsing MS—20mg SC qd • **Contraindications**—hypersensitivity to drug or class, hypersensitivity to **mannitol** • **Caution**—immunosuppression
Maternal Considerations	There is no published experience with **glatiramer** during pregnancy. As a result, most "experts" recommend discontinuing **glatiramer** prior to conception. ***Side effects*** include injection site reactions, transient chest pain, back pain, flu-like symptoms, erythema, infection, asthenia, itching, anxiety, N/V, insomnia, hypertonus, dyspnea, rash, sweating, and palpitations.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **glatiramer** crosses the human placenta. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically.
Breastfeeding Safety	There is no published experience in nursing women. It is unknown whether **glatiramer** enters human breast milk.
Drug Interactions	No clinically relevant interactions identified.
References	There is no published experience in pregnancy or during lactation.
Summary	**Pregnancy Category: B** **Lactation Category: U** • **Glatiramer** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Glimepiride—(Amaryl)

International Brand Name—Euglim (India); Glimerid (Colombia); Solosa (Philippines)

Drug Class	Hypoglycemics; Sulfonylureas
Indications	Diabetes mellitus, type 2
Mechanism	Stimulates pancreatic beta cell release of insulin
Dosage with Qualifiers	Diabetes mellitus, type 2—begin 1-2mg PO with first main meal of the day; max 8mg qd • **Contraindications**—hypersensitivity to drug or class, DKA • **Caution**—hypersensitivity to sulfonamides

Maternal Considerations

There are no adequate reports or well-controlled studies of **glimepiride** in pregnant women. The published experience is limited to case reports.
Side effects include hypoglycemia, pancytopenia, thrombocytopenia, aplastic anemia, dizziness, asthenia, nausea, and headache.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **glimepiride** crosses the human placenta. There is evidence suggesting other 2nd-generation sulfonylureas cross poorly. However, there is a case report of a newborn with persistent hyperinsulinemic hypoglycemia after long-term *in utero* exposure to **glimepiride.** Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically. Fetal losses occurred at doses approximating 4000× the MRHD.

Breastfeeding Safety

There are no adequate reports or well-controlled studies in nursing women. It is unknown whether **glimepiride** enters human breast milk.

Drug Interactions

NSAIDs and other drugs that are highly protein bound (e.g., salicylates, sulfonamides, **chloramphenicol,** coumarins, **probenecid,** MAOIs, and β-blockers) may potentiate the hypoglycemic action of sulfonylureas. Observe closely for hypoglycemia when these drugs are administered with **glimepiride.**
Drugs that tend to produce hyperglycemia may worsen glucose control. These include thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, **phenytoin,** nicotinic acid, sympathomimetics, and **isoniazid.**
Aspirin decreases the **glimepiride** AUC by about ⅓, though blood glucose and serum C-peptide concentrations are unaffected and no hypoglycemic symptoms have been reported.
Propranolol increases the C_{max}, AUC, and t/2 of **glimepiride** by 23%, 22%, and 15%, respectively. However, pooled data from clinical trials in patients with NIDDM revealed no evidence of clinically significant adverse interactions with uncontrolled use of β-blockers.
A potential interaction between **miconazole** and oral hypoglycemic agents leading to severe hypoglycemia has been reported. Whether this interaction also occurs with the IV, topical, or vaginal preparations of **miconazole** is not known.
There is a potential interaction of **glimepiride** with inhibitors (e.g., **fluconazole**) and inducers (e.g., **rifampicin**) of CYP2C9.

References

Balaguer Santamaria JA, Feliu Rovira A, Escribano Subias J, et al. Rev Clin Esp 2000; 200:399-400.
Elliott BD, Schenker S, Langer O, et al. Am J Obstet Gynecol 1994; 171:653-60.
Kalyoncu NI, Yaris F, Kadioglu M, et al. Saudi Med J 2005; 497-9.

Summary

Pregnancy Category: C
Lactation Category: U

- **Glimepiride** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.
- A better-studied 2nd-generation agent, such as **glyburide,** is a preferable alternative if an oral hypoglycemic is necessary.

Glipizide—(Glucotrol; Glucotrol XL; Minidab)

International Brand Name—Aldiab (Indonesia); Apamid (Thailand); Beapizide (Singapore); Decose (Taiwan); Depizide (Thailand); Diabes (Taiwan); Diasef (Hong Kong, Singapore); Dibizide (Malaysia); Digrin (Korea); Dipazide (Thailand); Gipzide (Thailand); Glibenese (Austria, Belgium, Denmark, Finland, France, Germany, Greece, Netherlands, Russia, Spain, Sweden, Switzerland); Glibetin (Taiwan); Glican (El Salvador); Glidiab (China, Taiwan); Glipicontin (India); Glipid (New Zealand); Glix (Malaysia); Glizide (Thailand); Glucodiab (Thailand); Glucolip (India); Gluconil (Philippines); Gluco-Rite (Israel); Glucotrol XL (China, Hong Kong, Indonesia); Glucozide (Taiwan); Glupitel (Mexico); Glupizide (Taiwan); Glutrol (China); Glyde (India); Glygen (Thailand); Glynase (India); Glyzid (Indonesia); Glyzip (India); Melizid (Finland); Melizide (Australia, Finland, Singapore); Mindiab (Denmark, Finland, Hong Kong, Norway, Russia, Sweden); Minidiab (Austria, Belgium, Brazil, Bulgaria, Chile, China, Czech Republic, Denmark, France, Hong Kong, Hungary, Indonesia, Italy, Malaysia, Philippines, Poland, Portugal, Taiwan, Thailand, Turkey, Venezuela); Minodiab (Argentina, Costa Rica, Dominican Republic, El Salvador, England, Greece, Honduras, Ireland, Mexico, Nicaragua, Panama, Spain); Napizide (Taiwan); Ozidia (France); Pezide (Thailand); Sunglucon (Hong Kong); Xeltic (Thailand)

Drug Class ..... Hypoglycemics; Sulfonylureas

Indications ..... Diabetes mellitus, type 2

Mechanism ..... Stimulates pancreatic beta cell release of insulin

Dosage with Qualifiers .....

Diabetes mellitus, type 2—begin 5mg PO 30min prior to first main meal of the day; doses above 15mg/d, give in 2 divided doses 30min ac, max 40mg qd

NOTE: available in XL preparation (max dose 20mg/d).

- **Contraindications**—hypersensitivity to drug or class, diabetic ketoacidosis, IDDM
- **Caution**—hypersensitivity to sulfonamides

Maternal Considerations .....

There is no published experience with **glipizide** during pregnancy. Some oral hypoglycemic agents are potentially attractive for the treatment of gestational or type 2 diabetes mellitus during pregnancy. However, their use at the present time should probably be confined to formal protocols.
Side effects include hypoglycemia, pancytopenia, thrombocytopenia, aplastic anemia, dizziness, asthenia, nausea, and headache.

Fetal Considerations .....

There are no adequate reports or well-controlled studies in human fetuses. About 6% of the maternal dose of **glipizide** crosses the isolated human placenta. Only **glyburide** transport is lower. No teratogenic effects were found in rodents, though fetal loss occurs across a range of doses.

Breastfeeding Safety .....

There is no published experience in nursing women. It is unknown whether **glipizide** enters human breast milk.

Drug Interactions .....

NSAIDs and other drugs that are highly protein bound (e.g., salicylates, sulfonamides, **chloramphenicol,** coumarins, **probenecid,** MAOIs, and β-blockers) may potentiate the hypoglycemic action of sulfonylureas. Observe closely for hypoglycemia when these drugs are administered to a patient receiving **glipizide.**
Drugs that tend to produce hyperglycemia may worsen glucose control. These include thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, **phenytoin,** nicotinic acid, sympathomimetics, and **isoniazid.**
A potential interaction between **miconazole** and oral hypoglycemic agents leading to severe hypoglycemia has been reported. Whether this interaction also occurs with the IV,

topical, or vaginal preparations of **miconazole** is not known. There is also a potential interaction of **glipizide** with inhibitors (e.g., **fluconazole**) and inducers (e.g., **rifampicin**) of CYP2C9. The effect of **fluconazole** was demonstrated in a placebo-controlled crossover study of normal volunteers. The increase in the **glipizide** AUC after **fluconazole** was 56.9%.

References

Elliott BD, Schenker S, Langer O, et al. Am J Obstet Gynecol 1994; 171:653-60.

Summary

Pregnancy Category: C
Lactation Category: U

- **Glipizide** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.
- A better-studied 2nd-generation agent such as **glyburide** is a preferable alternative if an oral hypoglycemic is indicated.

Glucagon—(GlucaGen [rDNA origin])

International Brand Name—Glucagen (Argentina, Belgium, Brazil, Chile, China, Colombia, Denmark, France, Germany, Greece, Hong Kong, India, Ireland, Italy, Malaysia, Paraguay, Poland, South Africa, Switzerland, Thailand, Uruguay); Glucagen Novo (Hong Kong)

Drug Class

Antihypoglycemics; Hormones

Indications

Hypoglycemia, severe

Mechanism

Converts hepatic glycogen to glucose

Dosage with Qualifiers

Hypoglycemia, severe—0.5-1mg IV/IM/SC ×1; may repeat in 25min

- **Contraindications**—hypersensitivity
- **Caution**—insulinoma, pheochromocytoma

Maternal Considerations

There are no adequate reports or well-controlled studies in pregnant women. There is, however, a long, reassuring clinical experience of **glucagon** use during pregnancy, typically in diabetic women with insulin-induced severe hypoglycemia.
Side effects include hyperglycemia, hypotension, N/V, urticaria, and ARDS.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. **Glucagon** does not appear to cross the human placenta. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically.

Breastfeeding Safety

There is no published experience with **glucagon** in nursing women. It is unknown whether it is excreted in human breast milk. However, **glucagon** is not active when ingested, as it is destroyed in the GI tract before absorption.

Drug Interactions

No clinically relevant interactions identified.

References

Spellacy WN, Buhi WC. Obstet Gynecol 1976; 47:291-4.

Summary

Pregnancy Category: B
Lactation Category: S

- **Glucagon** is indicated for the treatment of severe hypoglycemia during pregnancy and lactation.

Glyburide—(DiaBeta; Micronase)

International Brand Name—Amecladin (Philippines); Apo-Glibenclamide (New Zealand); Benclamin (Thailand); Calabren (Czech Republic); Clamide (Hong Kong); Cytagon (Thailand); Dangbinol (Korea); Daonil (Bangladesh, Belgium, Bolivia, Brazil, Canada, Chile, Colombia, England, France, Greece, Israel, Italy, Morocco, Netherlands, New Zealand, Pakistan, Paraguay, Russia, Spain, Switzerland, Uruguay, Venezuela); Daono (Thailand); Debtan (Thailand); Diabet (Korea); Dibelet (Malaysia, Thailand); Euglucan (France); Euglucon (Austria, Bangladesh, Belgium, Bolivia, Brazil, Chile, Costa Rica, Czech Republic, Dominican Republic, El Salvador, England, Germany, Greece, Guatemala, Honduras, Italy, Netherlands, Nicaragua, Pakistan, Panama, Paraguay, Russia, South Africa, Spain, Switzerland, Uruguay, Venezuela); G.B.N. (Singapore); Gilemal (Austria, Bulgaria, China, Hungary); Glencamide (Thailand); Glibemid (Singapore); Gliben (Hong Kong, Italy, New Zealand, Taiwan); Glibenhexal (China); Glibenil (Mexico); Glibens (Colombia); Glibesyn (Malaysia); Glibet (India); Glibetic (Israel); Glicem (Ecuador); Glidiabet (Peru); Glikeyer (Mexico); Glimel (Hong Kong); Glimide (Malaysia); Glisulin (Korea); Glitisol (Taiwan); Gluben (Israel); Glucal (Mexico); Glucolon (Spain); Glucomid (South Africa); Gluconic (Indonesia); Glyamid (Indonesia); Glyben (South Africa); Glycomin (South Africa); Hemi-Daonil (Argentina, France, Morocco, Netherlands); Humedia (Germany); Insol (Philippines); Locose (Thailand); Lodulce (Philippines); Manoglucon (Thailand); Med-Glionil (Thailand); Melix (South Africa); Miglucan (France); Norboral (Mexico); Orabetic (Philippines); Pira (Argentina); Prodiabet (Indonesia); Renabetic (Indonesia); Semi-Daonil (Argentina, England, Hong Kong, Indonesia, Ireland, Morocco, New Zealand, Switzerland); Semi-Euglucon (Argentina, Austria, Hong Kong, India, Indonesia, Netherlands, Philippines, Switzerland, Thailand); Sugril (Thailand); Suraben (Korea); Tiabet (Indonesia); Trodeb (Indonesia); Xeltic (Hong Kong)

Drug Class	Hypoglycemics; Sulfonylureas
Indications	Diabetes mellitus, type 2
Mechanism	Stimulates beta cell release of insulin
Dosage with Qualifiers	Diabetes mellitus, type 2—begin 2.5-5mg PO with first main meal of the day; usual maintenance dose 2.5-5.0 mg/d; max 20mg qd (micronized 1.5-3.0mg/d; usual maintenance dose 0.75-1.25mg/d) *NOTE: may be combined with* ***metformin.*** • **Contraindications**—hypersensitivity to drug or class, DKA, IDDM, CrCl <50 • **Caution**—hepatic or renal dysfunction, hypersensitivity to sulfonamides, thyroid disease, adrenal insufficiency
Maternal Considerations	A growing body of investigation indicates that **glyburide** is an effective alternative to insulin in women with either gestational or Type II diabetes, where it is more cost-effective than insulin. ***Side effects*** include hypoglycemia, pancytopenia, thrombocytopenia, leukopenia, aplastic or hemolytic anemia, hepatitis, nausea, epigastric pain, dizziness, blurred vision, dyspepsia, elevated LFTs, rash, photosensitivity, hyponatremia, and headache.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. Less than 2% of the maternal **glyburide** dose crosses the isolated perfused human placenta, findings confirmed *in vivo*. Back transport by BCRP appears to be the principle mechanism limiting **glyburide** efflux across the placenta. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically.
Breastfeeding Safety	There is no published experience in nursing women. It is unknown whether **glyburide** enters human breast milk.
Drug Interactions	The hypoglycemic action of sulfonylureas may be potentiated by certain drugs, including NSAIDs and other drugs that are highly protein bound (e.g., salicylates, sulfonamides, **chloramphenicol, probenecid,** coumarins, MAOIs, and β-adrenergic blocking agents). When such drugs are administered to a patient receiving

glyburide, the patient should be observed closely for hypoglycemia. The patient should be observed closely for loss of control after withdrawal of such drugs.
Certain drugs tend to produce hyperglycemia and may lead to loss of control. These drugs include the thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, **phenytoin,** nicotinic acid, sympathomimetics, calcium channel blocking drugs, and **isoniazid.** When such drugs are administered to a patient receiving **glyburide,** the patient should be closely observed for loss of control. When such drugs are withdrawn from a patient receiving **glyburide,** the patient should be observed closely for hypoglycemia.
A possible interaction between **glyburide** and **ciprofloxacin,** a fluoroquinolone antibiotic, has been reported, resulting in a potentiation of the hypoglycemic action of **glyburide.** The mechanism of action for this interaction is not known.
A potential interaction between oral **miconazole** and oral hypoglycemic agents leading to severe hypoglycemia has been reported. Whether this interaction also occurs with the IV, topical, or vaginal preparations of **miconazole** is not known.
Metformin: In a single-dose interaction study in NIDDM subjects, decreases in **glyburide** AUC and C_{max} were observed, but were highly variable. The single-dose nature of this study, and the lack of correlation between **glyburide** blood levels and pharmacodynamic effects, makes the clinical significance of this interaction uncertain. Co-administration of **glyburide** and **metformin** did not result in any changes in either **metformin** pharmacokinetics or pharmacodynamics.

References

Elliott BD, Schenker S, Langer O, et al. Am J Obstet Gynecol 1994; 171:653-60.
Goetzl L, Wilkins I. J Perinatol 2002; 22:403-6.
Langer O, Conway DL, Berkus MD, et al. N Engl J Med 2000; 343:1134-8.
Lim JM, Tayob Y O'Brien PM, Shaw RW. Med J Malaysia 1997; 52:377-81.
Morretti ME, Rezuani M, Koren G. Ann Pharmacother 2008; 42:483-90.
Polex E, Lubetsky A, Koren G. Placenta 2008; Aug 29(8):743-7. Epub 2008 Jun 16.

Summary

Pregnancy Category: B
Lactation Category: U

- A potentially attractive alternative or supplement to insulin for the treatment of type 2 diabetes mellitus during pregnancy and gestational diabetes characterized by hyperglycemia.

Glycerin

Drug Class ..... Laxatives

Indications ..... Constipation

Mechanism ..... Irritates mucosa, increasing peristalsis and stool water content

Dosage with Qualifiers

Constipation—1 adult suppository PR prn

- **Contraindications**—hypersensitivity to drug or class, anuria, hypovolemia, pulmonary edema
- **Caution**—abdominal pain, hepatic or renal dysfunction

Maternal Considerations

There are no adequate reports or well-controlled studies of **glycerin** in pregnant women. Maternal risks are related to abuse of the product.
Side effects include diarrhea, headache, nausea, and rectal irritation.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. However, maternal systemic absorption of **glycerin** is low.

Breastfeeding Safety

There is no published experience in nursing women. However, maternal systemic absorption of **glycerin** is low, suggesting the risk to the breastfeeding neonate is minimal.

Drug Interactions

No clinically relevant interactions identified.

References

There is no published experience in pregnancy or during lactation.

Summary

Pregnancy Category: C
Lactation Category: S

- Traditional remedy for constipation.

Glycopyrrolate—(Robinul)

International Brand Name—Gastrodyn Inj (Finland); Glycopyrrolate Inj (India); Mobinul (Korea); Robinul (Japan, South Africa, Taiwan); Robinul Forte (Canada); Robinul Inj. (Austria, Belgium, Denmark, England, Finland, Germany, Ireland, Netherlands, Norway, Sweden, Switzerland); Sroton (Japan); Strodin (Korea)

Drug Class

Anesthetics, adjunct; Anticholinergics; Gastrointestinals

Indications

Peptic ulcer disease, anesthesia adjunct, neuromuscular blockade reversal

Mechanism

Antagonizes ACh receptors

Dosage with Qualifiers

Peptic ulcer disease—1-2mg PO bid or tid; alternative 0.1-2mg IV/IM tid or qid
Anesthesia adjunct—begin 0.004mg/kg IM 30-60min before anesthesia
Neuromuscular blockade reversal—0.01mg/kg, max 1mg IV for each 1mg (0.07mg/kg; max 5mg at a time) of **neostigmine**

- **Contraindications**—hypersensitivity to drug or class, glaucoma, GI obstruction, ileus, myasthenia gravis, ulcerative colitis, unstable CV system
- **Caution**—hepatic dysfunction

Maternal Considerations

Glycopyrrolate reduces nausea after spinal anesthesia in pregnant women. It also reduces the prevalence of hypotension after epidural anesthesia in women with normal HRs to a similar degree as **ephedrine.** It may increase the risk of significant tachycardia when given with a β-mimetic agent.
Side effects include orthostatic hypotension, constipation, dry mouth, mydriasis, blurred vision, urinary retention, nausea,

	insomnia, weakness, palpitations, dizziness, headache, confusion, and abdominal pain.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **glycopyrrolate** crosses the human placenta. Transfer is limited in the ewe, achieving a peak F:M ratio of 0.13. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically.
Breastfeeding Safety	There is no published experience in nursing women. It is unknown whether **glycopyrrolate** enters human breast milk.
Drug Interactions	Injection with other anticholinergics or medications with anticholinergic activity, such as phenothiazines, antiparkinson drugs, or TCAs, may intensify the antimuscarinic effects and may result in an increase in anticholinergic side effects. Concomitant administration of **glycopyrrolate** injection and **potassium chloride** in a wax matrix may increase the severity of **potassium chloride**–induced GI lesions as a result of a slower GI transit time. There are no known drug interactions with the tablet form.
References	Murad SH, Conklin KA, Tabsh KM, et al. Anesth Analg 1981; 60:710-4. Rucklidge MW, Durbridge J, Barnes PK, Yentis SM. Anaesthesia 2002; 57:4-8. Ure D, James KS, McNeill M, Booth JV. Br J Anaesth 1999; 82:277-9.
Summary	**Pregnancy Category: B** **Lactation Category: U** • **Glycopyrrolate** is commonly used during pregnancy and lactation as an adjunct to anesthesia without apparent adverse effect.

Gold sodium thiomalate—(Aurolate; Myochrysine)

International Brand Name—Allochrysine (Belgium); Auromyose (Netherlands); Aurothio (Korea); Miocrin (Colombia, Costa Rica, Dominican Republic, El Salvador, Panama, Singapore, Spain); Myochrysine (Canada); Myocrisin (Denmark, England, Finland, Hong Kong, Hungary, Ireland, Israel, Norway, Puerto Rico, South Africa, Sweden, Thailand); Shiosol (Japan); Tauredon (Austria, Czech Republic, Germany, Hungary, Poland, Portugal, Russia, Switzerland)

Drug Class	Antiarthritics; Gold compounds
Indications	Rheumatoid arthritis
Mechanism	Unknown
Dosage with Qualifiers	Rheumatoid arthritis—begin 10mg IM qw ×1, 25mg IM qw ×1, then 25-50mg IM for an additional 10w • **Contraindications**—hypersensitivity to drug or class, concurrent **penicillamine** use • **Caution**—granulocytopenia or anemia secondary to drug reaction, skin rash, hepatic or renal dysfunction, moderate to severe hypertension, compromised CV or cerebral circulations

Maternal Considerations	There are no adequate reports or well-controlled studies of **gold sodium thiomalate** in pregnant women. It is important to perform a urinalysis before each injection because of the risk of maternal renal toxicity. ***Side effects*** include pruritus, exfoliative dermatitis, oral pharyngeal ulcers, metallic taste, renal toxicity, granulocytopenia, thrombocytopenia, aplastic anemia, flushing, fainting, dizziness, bradycardia, shock, and tongue swelling.
Fetal Considerations	There are no adequate reports or well-controlled studies of **gold sodium thiomalate** in human fetuses. Gold does cross the human placenta to a limited degree, and scant deposition occurs in the fetal liver. Rodent studies reveal an increased prevalence of multiple defects involving the CNS, abdominal wall, and limbs.
Breastfeeding Safety	There are no adequate reports or well-controlled studies in nursing women. **Gold sodium thiomalate** enters human breast milk, and the slow maternal clearance of gold must be remembered. Gold was found in the serum and RBCs of a nursing infant. In one study, the estimated weight-adjusted dose to the infant exceeded that received by the mother.
Drug Interactions	No clinically relevant interactions identified.
References	Bennett PN, Humphries SJ, Osborne JP, et al. Br J Pharmacol 1990; 29:777-9. Moller-Madsen B, Danscher G, Uldbjerg N, Allen JG. Rheumatol Int 1987; 7:47-8.
Summary	**Pregnancy Category: C** **Lactation Category: NS** (possibly) • **Gold sodium thiomalate** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk. • It would be reasonable to seek an alternative therapy during breastfeeding.

Granisetron hydrochloride—(Kytril)

International Brand Name—Granicip (India); Kevatril (Germany); Kytril (Argentina, Canada, Chile, China, Colombia, Ecuador, Hong Kong, Indonesia, Japan, Korea, Mexico, Philippines, Taiwan, Thailand, Uruguay); Setron (Israel)

Drug Class	Antiemetics; Antivertigo agents; Serotonin receptor antagonists
Indications	Severe N/V secondary to chemotherapy, radiation, or spinal anesthesia
Mechanism	Selective 5-HT_3 antagonist
Dosage with Qualifiers	Severe N/V of chemotherapy—10mcg/kg IV over 5min, or 2mg PO qd Severe N/V of radiation therapy—2mg PO qd beginning within 30min of therapy Prophylaxis for postoperative N/V—2-4mg IV • **Contraindications**—hypersensitivity to drug or class • **Caution**—unknown

Maternal Considerations

N/V after spinal anesthesia is common and distressing. **Granisetron** may be superior to both **droperidol** and **metoclopramide** for its prevention but controversy continues. The addition of **dexamethasone** (8mg) further enhances its efficacy. There are several case reports of its use during pregnancy in women receiving chemotherapy.
Side effects include anemia, thrombocytopenia, leukopenia, headache, weakness, somnolence, diarrhea, constipation, fever, rash, hypertension, taste changes, alopecia, and elevated LFTs.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **granisetron** crosses the placenta. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically.

Breastfeeding Safety

There is no published experience in nursing women. It is unknown whether **granisetron** enters human breast milk.

Drug Interactions

Because **granisetron** is metabolized by hepatic CYP drug-metabolizing enzymes, inducers or inhibitors of these enzymes may change the clearance and, hence, the half-life of **granisetron.** No specific interaction studies have been conducted in anesthetized patients.
In *in vitro* human microsomal studies, **ketoconazole** inhibited the ring oxidation of **granisetron;** the clinical significance is not known. In a human pharmacokinetic study, hepatic enzyme induction with **phenobarbital** resulted in a 25% increase in total plasma clearance of IV **granisetron.** The clinical significance of this change is not known.

References

Balki M, Kasodekae S, Dhumne S, Carvalho JC. Anesth Analg 2007; 104:679-83.
Fujii Y, Saitoh Y, Tanaka H, Toyooka H. Anesth Analg 1999; 88:1346-50.
Fujii Y, Tanaka H, Toyooka H. Acta Anaesthesiol Scand 1998; 42:921-5.
Merimsky O, Le Chevalier T, Missenard G, et al. Ann Oncol 1999; 10:345-50.

Summary

Pregnancy Category: B
Lactation Category: S

- An effective antiemetic during pregnancy, especially for women undergoing cancer therapy or receiving a spinal anesthetic.
- There are cheaper, often as effective, agents available for the treatment of hyperemesis.

Griseofulvin—(Brofulin; Fulvicin U/F; Fulvina; Grifulin; Grifulvin V; Grisactin; Grisactin Ultra; Griseofulvin Ultramicrosize; Gris-Peg; Microfulvin; Microgris; Sporostatin; Taidin/Fulvicin P/G; Ultragris; Ultramicrosize Griseofulvin)

International Brand Name—Fulcin (Brazil, Bulgaria, Ecuador, Peru); Fulcin Forte (Mexico); Fungin (Thailand); Grisefuline (France); Grisenova (Greece); Griseofulvine (Netherlands); Griseofulvin Prafa (Indonesia); Grisflavin (Thailand); Grisfulvin V (Philippines); Grisovin (Israel, Mexico, New Zealand, Peru); Grisovin-FP (India, Malaysia, Mexico); Grisuvin (Malaysia); Grivin (Malaysia); Krisovin (Malaysia); Likuden M (Germany); Microfulvin-500 (Indonesia); Myconil (Malaysia); Mycostop (Indonesia); Pongyl-V (Korea)

Drug Class

Antifungals

Indications

Tinea corporis, tinea capitis, tinea cruris, tinea pedis, tinea unguium

Mechanism

Deposited in the keratin of precursor cells, enhancing resistance to fungal invasion

Dosage with Qualifiers

Tinea corporis—500mg PO qd
Tinea capitis—500mg PO qd
Tinea cruris—500mg PO qd
Tinea pedis—750-1000mg PO in 2 divided doses
Tinea unguium—750-1000mg PO in 2 divided doses

NOTE: micronized dose listed, 500mg = 330mg ultramicronized; avoid prolonged exposure to sunlight.

- **Contraindications**—hypersensitivity to drug or class, porphyria
- **Caution**—penicillin allergy, hepatic dysfunction

Maternal Considerations

There are no adequate reports or well-controlled studies in pregnant women. Plasma concentrations of contraceptive steroids are decreased by **griseofulvin,** which stimulates their hepatic metabolism. **Griseofulvin** inhibits chromosomal distribution during cell division. Thus, men are cautioned to delay fathering children for 6mo after completing therapy, and women planning conception should wait at least 1mo.
Side effects include hepatic toxicity, granulocytopenia, nausea, headache, rash, urticaria, photosensitivity, lupus-like syndrome, oral candidasis, paresthesias, dizziness, fatigue, insomnia, proteinuria, flatulence, and diarrhea.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **griseofulvin** crosses the human placenta. Epidemiologic studies are limited but reassuring. While teratogenicity is suggested in horses and cats, rodent studies indicating teratogenicity were not confirmed after repetition. There are unsubstantiated reports of an association with conjoined twinning in humans.

Breastfeeding Safety

There are no adequate reports or well-controlled studies of **griseofulvin** in nursing women. It is unknown whether this drug is excreted in human breast milk.

Drug Interactions

Patients on **warfarin**-type anticoagulant therapy may require dosage adjustment of the anticoagulant during and after **griseofulvin** therapy. Concomitant use of barbiturates usually

depresses **griseofulvin** activity and may necessitate raising the dosage.
May reduce the efficacy of oral contraceptives and increase the incidence of breakthrough bleeding.
The effect of alcohol may be potentiated by **griseofulvin,** producing such effects as tachycardia and flushing.

References

Czeizel AE, Metneki J, Kazy Z, Puho E. Acta Obstet Gynecol Scand 2004; 83:827-31.
King CT, Rogers PD, Cleary JD, Chapman SW. Clin Infect Dis 1998; 27:1151-60.
Schutte JG, van den Ingh TS. Vet Q 1997; 19:58-60.
Scott FW, LaHunta A, Schultz RD, et al. Teratology 1975; 11:79-86.

Summary

Pregnancy Category: C
Lactation Category: U
- **Griseofulvin** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Guaifenesin—(Fenesin; Fenex La; Humibid L.A.; Mucobid-L.A.; Muco-Fen LA; Organidin Nr; Pneumomist; Prolex; Touro Ex; Tussin)

International Brand Name—44 Exp (Mexico); Balminil Expectorant (Canada); Bronchocal (Israel); Codimal (Philippines); Cofen (Singapore); Desbly (France); Dextricyl (Philippines); Ecolate (Thailand); Excaugh 100 (Hong Kong); Expectorin Cough (Philippines); Fagusan N Losung (Germany); Fenatussin (Korea); Flemonex (Philippines); Gufensin (Hong Kong); Pharmachem (Philippines); Probat (Indonesia); Resyl (Austria, Bulgaria, Ecuador, Switzerland); Resyl S (Finland, Sweden); Robitessin (Venezuela); Robitussin (Argentina, Australia, Canada, Colombia, England, Finland, Hong Kong, Ireland, Italy, Malaysia, Mexico, Philippines, Puerto Rico, Spain, Sweden, Taiwan, Thailand); Robitussin jarabe (Ecuador); Sipla (Indonesia); Suprekof (Philippines); Tintus (Finland); Transpulmin G (Philippines)

Drug Class

Antitussives; Expectorants

Indications

Cough suppression, expectorant

Mechanism

Increases the quantity and decreases the viscosity of respiratory tract secretions

Dosage with Qualifiers

Cough suppression—600-1200mg PO qd; max 2400mg/d
Expectorant—200-400mg PO q4h; max 2400mg/d

NOTE: available in tablet or syrup, and may be combined with ***hydrocodone, phenylephrine,*** *or* ***pseudoephedrine.***

- **Contraindications**—hypersensitivity to drug or class
- **Caution**—unknown

Maternal Considerations

Guaifenesin is a common component in many over-the-counter cough remedies. There are no adequate reports or well-controlled studies in pregnant women. Animal reproduction studies have not been conducted.
Side effects include drowsiness, N/V, rash, and headache.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **guaifenesin** crosses the

	human placenta. Unfortunately, limited epidemiologic study provides no help in estimating the risk of **guaifenesin.** Rodent teratogenicity studies have not been performed.
Breastfeeding Safety	There is no published experience with **guaifenesin** in nursing women. It is unknown whether this drug is excreted in human breast milk.
Drug Interactions	No clinically relevant interactions identified.
References	Shaw GM, Todoroff K, Velie EM, Lammer EJ. Teratology 1998; 57:1-7. Werler MM, Mitchell AA, Hernandez-Diaz S, Honein MA. Am J Obstet Gynecol 2005; 193:771-7.
Summary	**Pregnancy Category: C** **Lactation Category: U** • **Guaifenesin** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Guanabenz acetate—(Wytensin)

International Brand Name—Rexitene (Austria); Wytens (Japan)

Drug Class	Adrenergic antagonists, central; Antihypertensives
Indications	Hypertension
Mechanism	Centrally acting α_2-agonist
Dosage with Qualifiers	Hypertension—begin 2-4mg PO bid; increase by 4-8mg/d q1-2w; max 32mg PO bid • **Contraindications**—hypersensitivity to drug or class • **Caution**—hepatic or renal dysfunction
Maternal Considerations	There is no published experience with **guanabenz** during pregnancy. ***Side effects*** include sedation, arrhythmias, AV block, rebound hypertension, dizziness, weakness, headache, N/V, diarrhea, constipation, chest pain, bradycardia, edema, and rash.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **guanabenz** crosses the placenta. Rodent studies are generally reassuring, with only minor ossification abnormalities noted at doses many multiples of the MRHD.
Breastfeeding Safety	There is no published experience in nursing women. It is unknown whether **guanabenz** enters human breast milk.
Drug Interactions	There is potential for increased sedation when **guanabenz** is administered concomitantly with CNS-depressant drugs.
References	No current relevant references identified.

Summary	**Pregnancy Category: C** **Lactation Category: U** • **Guanabenz** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk. • There are many other antihypertensive agents for which there is a large body of experience during pregnancy and lactation.

Guanadrel sulfate—(Hylorel)

International Brand Name—None identified.

Drug Class	Adrenergic antagonists, peripheral; Antihypertensives
Indications	Hypertension
Mechanism	Inhibits NE release from neuronal storage sites
Dosage with Qualifiers	Hypertension—begin 5mg PO bid; adjust dose weekly until a max of 400mg/d *NOTE: renal dosing; tolerance may develop after chronic use, requiring an increased dose.* • **Contraindications**—hypersensitivity to drug or class, suspected pheochromocytoma, recent or current use of an MAOI, CHF • **Caution**—asthma, anticipated major surgery, peptic ulcer disease, renal dysfunction
Maternal Considerations	**Guanadrel** is an orally active antihypertensive that lowers both systolic and diastolic pressure. It is typically employed as a second-line agent following a diuretic. There is no published experience with **guanadrel** during pregnancy. ***Side effects*** include orthostatic hypotension, fatigue, drowsiness, headache, visual disturbances, paresthesias, constipation, nocturia, edema, and weight gain.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **guanadrel** crosses the placenta. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically.
Breastfeeding Safety	There is no published experience in nursing women. It is unknown whether **guanadrel** enters human breast milk.
Drug Interactions	No clinically relevant interactions identified.
References	There is no published experience in pregnancy or during lactation.
Summary	**Pregnancy Category: B** **Lactation Category: U** • **Guanadrel** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk. • There are alternative agents for which there is more experience during pregnancy and lactation.

Guanethidine monosulfate—(Antipres; Declindin; Ingadine; Ismelin; Normalin; Sanotensin)

International Brand Name—Ismeline (Australia, Austria, Belgium, England, Ireland, Japan)

Drug Class	Adrenergic antagonists, peripheral; Antihypertensives
Indications	Hypertension, moderate to severe, including that secondary to renal disease
Mechanism	Inhibits or interferes with catecholamine release at the neuroeffector junction, depletes NE
Dosage with Qualifiers	Hypertension, moderate to severe: Ambulatory—begin 10mg PO qd, increase q2-5d to achieve desired control Hospitalized—begin 25-50mg PO qd, increasing by 25-50mg qd prn *NOTE: renal dosing; may be combined with **hydralazine** or thiazide diuretics.* • **Contraindications**—hypersensitivity to drug or class, pheochromocytoma, CHF not secondary to hypertension, concurrent use of MAOIs • **Caution**—surgery, fever, chronic use (may need to reduce dose), renal dysfunction, peptic ulcer disease, recent MI, CAD
Maternal Considerations	This ganglionic blocker is rarely used during pregnancy, as there are other agents with fewer side effects available. Hypotension is a major concern. ***Side effects*** include hypotension, chest pain, dyspnea, diarrhea, N/V, dry mouth, depression, tremor, blurred vision, weakness, myalgia, dermatitis, weight gain, and increased BUN.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **guanethidine** crosses the human placenta.
Breastfeeding Safety	There are no adequate reports or well-controlled studies in nursing women. **Guanethidine** does enter human breast milk at very low concentrations.
Drug Interactions	Use with rauwolfia derivatives may cause excessive postural hypotension and mental depression. Thiazides may enhance the hypotensive effect. Amphetamines, TCA, phenothiazines and oral contraceptives may reduce the hypotensive effect. MAOI should be discontinued at least 1 week before initiation.
References	No current relevant references identified.
Summary	**Pregnancy Category: C** **Lactation Category: S** (likely) • There are alternative agents for which there is more experience during pregnancy and lactation.

Guanfacine hydrochloride—(Entulic; Tenex)

International Brand Name—Estulic (Belgium, Czech Republic, Ecuador, France, Germany, Hungary, Indonesia, Japan, Netherlands, Philippines, Poland, Russia, South Africa, Spain, Turkey)

Drug Class	Adrenergic antagonists, central; Antihypertensives
Indications	Hypertension, migraine headache, heroin withdrawal
Mechanism	Centrally acting α_2-agonist
Dosage with Qualifiers	Hypertension—1-3mg PO qhs Migraine headache—1mg PO qd ×12w Heroin withdrawal—0.03-1.5mg PO qd *NOTE: renal dosing.* • **Contraindications**—hypersensitivity to drug or class • **Caution**—hepatic dysfunction, CAD, recent MI
Maternal Considerations	There are no well-controlled trials of **guanfacine** during pregnancy. It is not generally recommended for the treatment of preeclamptic hypertension, in part because of its slow onset. There is one report of 30 preeclamptic women in which only 24 responded. ***Side effects*** include fatigue, weakness, somnolence, dizziness, constipation, and headache.
Fetal Considerations	There are no adequate reports or well-controlled studies of **guanfacine** in human fetuses.
Breastfeeding Safety	There is no published experience in nursing women. It is unknown whether **guanfacine** enters human breast milk.
Drug Interactions	The potential for increased sedation when given with other CNS-depressant drugs should be appreciated. Use with a known microsomal enzyme inducer (**phenobarbital** or **phenytoin**) in patients with renal impairment may cause significant reductions in elimination t/2 and plasma concentration. More frequent dosing may be required to achieve or maintain the desired hypotensive response. Further, if **guanfacine** is to be discontinued in such patients, careful tapering of the dosage may be necessary in order to avoid rebound phenomena.
References	Philipp E. Br J Clin Pharmacol 1980; 10:137S-40S.
Summary	**Pregnancy Category: B** **Lactation Category: U** • There are alternative agents for which there is more experience during pregnancy and lactation. • Not recommended for use in women with preeclampsia.

Haemophilus influenzae vaccine—(ActHIB; HibTITER; OmniHIB; PedvaxHIB; ProHIBIT)

International Brand Name—Act-HIB (Brazil, Canada, Chile, Ecuador, Korea, Paraguay, Peru, Uruguay); HIBest (France, India); HibTITER (Austria, Belgium, Denmark, England, Germany, Ireland, Italy, New Zealand, South Africa, Switzerland); Pedvax HIB (Brazil, Canada)

Drug Class

Vaccines

Indications

Maternal susceptibility

Mechanism

Immunization to capsular polysaccharides

Dosage with Qualifiers

Haemophilus influenzae B susceptibility—0.5mg IM ×1

- **Contraindications**—hypersensitivity to drug or class, hypersensitivity to diphtheria vaccine or thimerosal, acute febrile illness
- **Caution**—immunosuppression

Maternal Considerations

***Haemophilus influenzae* conjugate vaccine** is a combination of capsular polysaccharides purified from HIB; it protects only against the B strain. There are no adequate reports or well-controlled studies in pregnant women. Maternal immunization does not interfere with subsequent neonatal immunization. ***Haemophilus influenzae* conjugate vaccine** is not contraindicated in women with HIV.
Side effects include erythema, allergic reaction, and fever.

Fetal Considerations

There are no adequate reports or well-controlled studies of ***H. influenzae* conjugate vaccine** in human fetuses. The *H. influenzae* antibodies generated cross the placenta and provide passive immunity. In two studies, it effectively produced passive immunity in the newborn after administration to women during the 3rd trimester. Maternal malnutrition may reduce placental transfer. While animal studies have not been conducted, there is no evidence the vaccine components either cross the placenta or pose a risk to the human fetus.

Breastfeeding Safety

There is no published experience with ***H. influenzae* conjugate vaccine** in nursing women. It is certainly possible *H. influenzae* antibodies enter human breast milk. It is unknown whether they convey any protection to the nursing newborn.

Drug Interactions

No impairment of antibody response to the individual antigens of ***H. influenzae* conjugate vaccine** was demonstrated in children 2-20mo of age given the vaccine at the same time but at separate sites as DTP plus OPV.

References

Baril L, Briles DE, Crozier P, et al. Clin Exp Immunol 2004; 135:474-7.
Calvalcante RS, Kopelman BI, Costa-Carvalho BT. Braz J Infect Dis 2008; 12:47-51.
Nahm MH, Glezen P, Englund J. Vaccine 2003; 21:3393-7.
Yamauchi K, Hotomi M, Billal DS, et al. Vaccine 2006; 24:5294-9.

Summary

Pregnancy Category: C
Lactation Category: U

- A successful tool for the reduction of neonatal *H. influenzae* infections in some populations.

Halcinonide topical—(Dermalog; Halog; Halog-E)

International Brand Name—Adcortin (Japan); Berodan (Korea); Cortilate (India); Dermalog Simple Al (Mexico); Halciderm (Costa Rica, El Salvador, England, Guatemala, Honduras, Ireland, Italy, Nicaragua, Panama, Peru, Switzerland); Halciderm Crema Al (Costa Rica, Dominican Republic, El Salvador, Guatemala, Honduras, Nicaragua, Panama); Halcimat (Germany); Halog (Austria, Brazil, Canada, Denmark, France, Hong Kong, India, Indonesia, Norway, Venezuela); Volog (Israel, South Africa, Turkey)

Drug Class	Corticosteroids, topical; Dermatologics
Indications	Steroid-responsive dermatitis
Mechanism	Unknown
Dosage with Qualifiers	Steroid-responsive dermatitis—apply to affected area bid or tid *NOTE: available in cream, ointment, salve, 0.25% and 0.1%.* • **Contraindications**—hypersensitivity to drug or class • **Caution**—unknown
Maternal Considerations	There is no published experience with **halcinonide** during pregnancy. **Halcinonide** reduces scar formation. ***Side effects*** include adrenal suppression, burning, itching, contact dermatitis, folliculitis, dry skin, acne, perioral dermatitis, infection, and skin atrophy.
Fetal Considerations	While there are no adequate reports or well-controlled studies in human fetuses, the quantity of **halcinonide** absorbed systemically is unlikely to pose a risk to the fetus even if it does cross the placenta. Though some corticosteroids are teratogens in some rodents, there is no substantative evidence they act as teratogens in humans.
Breastfeeding Safety	There is no published experience in nursing women. It is unknown whether **halcinonide** enters human breast milk. Some nonfluoridated and fluoridated corticosteroids enter human breast milk with M:P ratios ranging between 0.05 and 0.25.
Drug Interactions	No clinically relevant interactions identified.
References	There is no published experience in pregnancy or during lactation.
Summary	**Pregnancy Category: C** **Lactation Category: S** (likely) • **Halcinonide** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Halobetasol topical—(Ultravate)

International Brand Name—Ultravate (Canada)

Drug Class	Corticosteroids
Indications	Steroid-responsive dermatitis, psoriasis
Mechanism	Unknown
Dosage with Qualifiers	Steroid-responsive dermatitis—apply qd or bid; max 50g/w *NOTE: available in cream or ointment.* • **Contraindications**—hypersensitivity to drug or class • **Caution**—unknown
Maternal Considerations	There is no published experience with **halobetasol** during pregnancy. Human and animal studies indicate approximately 2% of the applied cream dose (3% ointment) enters the circulation within 96h of topical administration. ***Side effects*** include adrenal suppression, burning, itching, contact dermatitis, folliculitis, dry skin, acne, perioral dermatitis, infection, and skin atrophy.
Fetal Considerations	While there are no adequate reports or well-controlled studies in human fetuses, the quantity of **halobetasol** absorbed systemically is unlikely to pose a risk to the fetus even if it does cross the placenta. Though some corticosteroids are teratogens in rodents, there is no substantative evidence they act as teratogens in humans. When given systemically to rodents at doses that are multiples of the MRHD, **halobetasol** is associated with embryotoxicity, cleft palate, and abdominal wall defects.
Breastfeeding Safety	There is no published experience in nursing women. It is unknown whether **halobetasol** enters human breast milk. Considering the dose and route, it is unlikely the milk concentration will reach a clinically relevant level. Some nonfluoridated and fluoridated corticosteroids enter human breast milk with M:P ratios ranging between 0.05 and 0.25.
Drug Interactions	No clinically relevant interactions identified.
References	There is no published experience in pregnancy or during lactation.
Summary	**Pregnancy Category: C** **Lactation Category: S** (likely) • **Halobetasol** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Haloperidol—(Einalon; Haldol; Haloperidol Lactate; Pacedol; Pericate; Seranase)

International Brand Name—Alased (Greece); Aloperidin (Greece); Apo-Haloperidol (Canada, Malaysia); Avant (Taiwan); Binison (Taiwan); Brotopon (Japan); Cereen (South Africa); Cizoren (India); Depidol (India); Dores (Indonesia); Dozic (England); Duraperidol (Germany); Einalon S (Japan); Govotil (Indonesia); Haldol (Austria, Belgium, Brazil, Bulgaria, Chile, Costa Rica, Denmark, Dominican Republic, Ecuador, El Salvador, England, France, Germany, Guatemala, Honduras, Hong Kong, Indonesia, Ireland, Mexico, Netherlands, New Zealand, Nicaragua, Norway, Panama, Paraguay, Peru, Philippines, Poland, Portugal, Sweden, Switzerland, Taiwan, Thailand); Halidol (India, Israel); Halojust (Japan); Halomed (Thailand); Halo-P (Thailand); Haloper (Czech Republic, Germany, Russia); Haloperil (Mexico); Haloperin (Finland); Halopidol (Argentina, Colombia); Halopol (Thailand); Halosten (Japan); Haricon (Thailand); Haridol-D (China); Inin (Taiwan); Linton (Japan); Lodomer-2 (Indonesia); Mixidol (Japan); Motivan (Malaysia); Novoperidol (Canada); Peluces (Japan); Perida (Thailand); Peridol (Canada, China, Korea); Peridor (Israel); Selezyme (Japan); Seranace (England, South Africa); Serenace (Bangladesh, Indonesia, Ireland, Korea, Pakistan, South Africa, Thailand); Serenase (Belgium, Denmark, Finland, Italy); Serenelfi (Portugal); Sigaperidol (Germany, Switzerland); Trancodol-5 (India); Trancodol-10 (India)

Drug Class	Antipsychotics
Indications	Psychosis, Tourette's syndrome
Mechanism	Unknown
Dosage with Qualifiers	Psychosis—0.5-5mg PO bid or tid; max 100mg/d; or 2.5mg IV/IM q4-8h Acute psychosis—0.5-50mg IV (slow, at 5mg/min) Tourette's syndrome—begin 0.5-1.5mg PO tid, increase 2mg/d prn; typically 9mg/d *NOTE: available in a depot form (**haloperidol decanoate**), 50-100mg IM qmo.* • **Contraindications**—hypersensitivity to drug or class, CNS depression, coma, Parkinson's disease • **Caution**—hepatic dysfunction, seizure disorder, thyrotoxicosis, CV disease
Maternal Considerations	There are no adequate reports or well-controlled studies of **haloperidol** in pregnant women. There is, however, a large body of experience during pregnancy suggesting a wide margin of safety. There is 1 case report of an overdose at 34w treated symptomatically without detectable adverse effect. There is another case report of neuroleptic malignant syndrome during pregnancy treated successfully with **dantrolene** and **bromocriptine.** **Haloperidol** has also been used to treat chorea gravidarum. It is similar to **olanzapine** for the treatment of schizophrenia in terms of compliance, symptoms, extrapyramidal symptoms, and overall quality of life, but **haloperidol** costs significantly less. ***Side effects*** include arrhythmias, seizures, neuroleptic malignant syndrome, tardive dyskinesia, extrapyramidal effects, dystonia, pneumonia, fever, jaundice, insomnia, drowsiness, anxiety, menstrual irregularities, and galactorrhea.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. **Haloperidol** crosses the human placenta (65% of the maternal dose) and can be recovered from neonatal hair. In a series of 188 women who consulted a drug information service after exposure to **haloperidol** (plus 27 exposed to a similar agent), there was no increase in birth defects, though the preterm birth rate was double that of the matched controls. Two exposed neonates had a limb abnormality. After maternal overdose, the

fetus had an abnormal biophysical profile for 5d. **Haloperidol** is teratogenic in some rodents. In hamsters, it produces a variety of spinal abnormalities in a dose-dependent fashion.

Breastfeeding Safety

There are no adequate reports or well-controlled studies in nursing women. **Haloperidol** enters human breast milk, and in breastfeeding infants may reach therapeutic levels. As it is unknown whether **haloperidol** poses a risk to the neonate, breastfeeding should be permitted only with caution.

Drug Interactions

An encephalopathic syndrome (characterized by weakness, lethargy, fever, tremulousness and confusion, extrapyramidal symptoms, leukocytosis, and elevated serum enzymes, BUN, and fasting glucose) followed by irreversible brain damage is reported in a few patients treated with **lithium** plus **haloperidol.** A causal relationship between these events and the concomitant administration of **lithium** and **haloperidol** has not been established; however, patients receiving such combined therapy should be monitored closely.

References

Diav-Citrin O, Shechtman S, Ornoy S, et al. J Clin Psychiatry 2005; 66:317-22.
Gill TS, Guram MS, Geber WF. Dev Pharmacol Ther 1982; 4:1-5.
Hansen LM, Megeriaqn G, Donnenfeld AE. Obstet Gynecol 1997; 90:659-61.
Karageyim AY, Kars B, Dansuk R, et al. J Matern Fetal Neonatal Med 2002; 12:353-4.
Newport DJ, Calamanas MR, DeVane CI, et al. Am J Psychiatry 2007; 164:1214-20.
Rosenheck R, Perlick D, Bingham S, et al. JAMA 2003; 290:2693-702.
Russell CS, Lang C, McCambridge M, Calhoun B. Obstet Gynecol 2001; 98:906-8.
Uematsu T, Yamada K, Matsuno H, Nakashima M. Ther Drug Monit 1991; 13:183-7.
Yoshida K, Smith B, Craggs M, Kumar R. Psychol Med 1998; 28:81-91.

Summary

Pregnancy Category: C
Lactation Category: S (likely)

- **Haloperidol** is the drug of choice for the treatment of acute or chronic psychosis during pregnancy based on clinical experience and in comparison to its alternatives.

Halothane—(Anestane; Fluothane)

International Brand Name—Fluothane (Brazil, Chile, Dominican Republic, Ecuador, El Salvador, Guatemala, India, Indonesia, Malaysia, Mexico, Peru, Taiwan); Halothan (Ecuador, Peru); Ineltano (Argentina, Paraguay); Narcotan (Bulgaria, Czech Republic, Poland); Trothane (Finland)

Drug Class

Anesthetics, general

Indications

General anesthesia

Mechanism

Unknown; disrupts the neuronal lipid membrane

Dosage with Qualifiers

Induction of anesthesia—typically 0.5-3% (usually for children)
Maintenance of anesthesia—typically 0.5-1.5%

NOTE: consult specialty text.

- **Contraindications**—hypersensitivity to drug or class; history of malignant hyperthermia, halothane-induced jaundice, or hepatitis
- **Caution**—head injury, hepatic dysfunction, arrhythmias, prolonged QT interval, increased ICP, pheochromocytoma, myasthenia gravis

Maternal Considerations

Halothane is a halogenated inhalational agent for which there is a long clinical experience during pregnancy. It and related compounds relax the myometrium both *in vitro* and *in vivo*. As a result, it should not be used for routine vaginal delivery.
Halothane is no longer used routinely by anesthesiologists, who prefer newer agents that are not significantly metabolized by the liver. **Halothane** has been used for cesarean delivery and in instances when uterine relaxation is important, such as acute uterine inversion, placental entrapment, and cervical entrapment of the after-coming head during vaginal breech delivery.
Currently preferred agents include NO donors.
Side effects include malignant hyperthermia, arrhythmia, tachycardia, cardiac arrest, prolonged QT interval, asystole, cyanosis, muscle rigidity, hypotension, hypoxia, hepatic or renal toxicity, seizures, rhabdomyolysis, and carboxyhemoglobinemia.

Fetal Considerations

Halothane rapidly crosses the human placenta, reaching an F:M ratio approaching unity within minutes. Once considered a candidate anesthetic for fetal surgery, **halothane** decreases fetal cardiac output and placental blood flow, and increases total vascular resistance in sheep. Placental vascular resistance increases out of proportion to systemic vascular resistance, shunting blood away from the site of gas exchange.

Breastfeeding Safety

There is no published experience in nursing women. It is unknown whether **halothane** enters human breast milk. Considering the indication, one-time **halothane** use is unlikely to pose a clinically significant risk to the breastfeeding neonate.

Drug Interactions

Epinephrine and NE should be employed cautiously if at all with **halothane** since their simultaneous use may induce ventricular tachycardia or VF.
Nondepolarizing relaxants and ganglionic blocking agents may be augmented by **halothane.**
Clinical experience and animal experiments suggest that **pancuronium** should be given with caution to patients receiving chronic TCA therapy who are anesthetized with **halothane** as severe ventricular arrhythmias may result.

References

Fahmy K. Int Surg 1977; 62:100-2.
Kangas I, Erkkola R, Kanto J, Mansikka M. Acta Anaesthesiol Scand 1976; 20:189-94.
Sabik JF, Assad RS, Hanley FL. J Pediatr Surg 1993; 28:542-6.
Yoo KY, Lee JC, Yoon MH, et al. Anesth Analg 2006; 103:443-7.

Summary

Pregnancy Category: C
Lactation Category: S
- **Halothane** can be used throughout pregnancy. It is important to assure maternal oxygenation and optimal positioning for maximal uterine blood flow.

Heparin—(Heparin Flush; Heparin Lok-Pak; Heparin Porcine; Hepflush; Liquaemin Sodium; Sodium Heparin)

International Brand Name—Beparine (India); Helberina (Mexico); Hepaflex (Finland, Norway); Hepalean (Canada); Heparin (Austria, Bulgaria, Czech Republic, England, Finland, Germany, Greece, Hungary, Israel, Norway, South Africa, Sweden, Switzerland); Heparina (Spain); Heparina Leo (Costa Rica, Dominican Republic, El Salvador, Guatemala, Honduras, Panama); Heparine (Belgium, Netherlands); Heparine Choay (France); Heparine Novo (Belgium, Netherlands); Heparin Injection B.P. (Australia); Heparin Leo (Canada, Denmark, Hong Kong, Indonesia, Malaysia, New Zealand, Philippines, Taiwan); Heparin Novo (South Africa, Taiwan, Thailand); Heparin Sodium B Braun (Indonesia, Malaysia); Heparin Subcutaneous (New Zealand); Inhepar (Mexico); Inviclot (Indonesia); Liquemin (Germany, Italy, Switzerland); Liquemine (Belgium, Brazil, Ecuador, Uruguay, Venezuela); Monoparin (New Zealand); Multiparin (New Zealand); Parinix (Argentina); Thromboliquine (Israel); Thrombophob (Germany); Thromboreduct (Germany); Uniparin (Australia)

Drug Class	Anticoagulants
Indications	Thromboembolic disease (treatment, prophylaxis), thrombophilias (prophylaxis), APL syndrome
Mechanism	Works synergistically with ATIII to block factor Xa activity
Dosage with Qualifiers	Thromboembolic disease (treatment)—80U/kg IV ×1, then 18U/kg/h IV to achieve an aPTT 1.5-2× baseline Thromboembolic disease (prophylaxis)—5000U SC bid 1st trimester, 7500U SC bid 2nd trimester, 10,000U SC bid 3rd trimester Thrombophilias (prophylaxis)—depends on type and history APL syndrome—81mg PO qd **aspirin** plus 5000U SC bid 1st trimester, 7500U SC bid 2nd trimester, 10,000U bid 3rd trimester *NOTE: may need to adjust the dose up for morbid obesity (>120kg).* • **Contraindications**—hypersensitivity to drug or class, active bleeding except DIC, vascular damage, conduction anesthesia • **Caution**—recent neuraxial anesthesia, severe hypertension, peptic ulcer disease, history of GI bleeding, renal dysfunction
Maternal Considerations	**Heparin** consists of sulfated, long-chain acidic mucopolysaccharides with MWs ranging from 4000 to 30,000 Da. The various LMWHs are derivatives. Each is considered an anticoagulant of choice during pregnancy, is equally effective, and has a similar risk profile. Unfractionated **heparin** has the principal advantage of low cost. Despite the long history of clinical use, there are no adequate reports or well-controlled studies in pregnant women. Perhaps the greatest clinical limitation is the dose volume that must be used considering the relatively dilute concentrations available. Therapeutic heparinization is the prophylaxis of choice for women with a mechanical heart valve. ***Side effects*** include hemorrhage, osteoporosis, thrombocytopenia, hematoma, irritation at injection site, ulceration, fever, chills, itching, urticaria, and rhinitis.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. **Heparin** does not cross the placenta, and is not associated with an adverse fetal outcome. However, a recent study suggests that both **heparin** and LMWH have the potential to reduce trophoblast invasion.
Breastfeeding Safety	There is no published experience in nursing women. It is unknown whether **heparin** enters human breast milk.

Drug Interactions

May prolong the one-stage PT. Wait at least 5h after the last IV dose or 24h after the last SC dose before blood is drawn for a PT in women also taking **dicumarol** or **warfarin.**
Aspirin, dextran, dipyridamole, hydroxychloroquine, ibuprofen, indomethacin, phenylbutazone, and other drugs that interfere with platelet aggregation (the main hemostatic defense of heparinized patients) may induce bleeding.
Anticoagulation by **heparin** is enhanced by treatment with ATIII (human) in patients with hereditary ATIII deficiency.
Digitalis, tetracyclines, **nicotine,** or antihistamines may partially counteract the anticoagulant action of **heparin.**
Heparin injection should not be mixed with **ciprofloxacin, doxorubicin, droperidol,** or **mitoxantrone** since a precipitate may form.

References

Ganapathy R, Whitley GS, Cartwright JE, et al. Hum Reprod 2007; 22:2523-7.
Kim BJ, An SJ, Shim SS, et al. J Reprod Med 2006; 51:649-54.
Rai R, Cohen H, Dave M, Regan L. BMJ 1997; 314:253-7.
Shannon MS, Edwards MB, Long F, et al. J Heart Valve Dis 2008; 17:526-32.
Ulander V, Stenqvist P, Kaaja R. Thromb Res 2002; 106:13.

Summary

Pregnancy Category: B
Lactation Category: S

- **Heparin,** both unfractionated and fractionated, is the anticoagulant of choice during pregnancy. There are pragmatic reasons to chose one versus the other reflecting indication and the gestational age.

Hepatitis A vaccine—(Havrix; Vaqta)

International Brand Name—Avaxim (Canada, Colombia, England, Hong Kong, Ireland, South Africa, Thailand); Avaxim Pediatric (Canada); Epaxal (Canada, New Zealand, Peru); HAVpur (Germany); Havrix (Austria, Canada, Chile, Costa Rica, Czech Republic, Denmark, Dominican Republic, El Salvador, England, Finland, France, Guatemala, Honduras, Hungary, Ireland, Italy, Netherlands, Nicaragua, Norway, Panama, Paraguay, Peru, Poland, Spain, Sweden, Switzerland, Uruguay, Venezuela); Havrix Junior (Australia, Hong Kong, India, Mexico); Havrix 1440 (Australia, Hong Kong, India, Mexico); Vaqta (Australia, Canada, England, Germany, Ireland, Israel, Mexico)

Drug Class

Vaccines

Indications

Maternal susceptibility

Mechanism

Immune response to inactivated virus

Dosage with Qualifiers

HAV susceptibility—1ml IM, repeat 6-8mo later

- **Contraindications**—hypersensitivity to drug or class, febrile illness
- **Caution**—immunosuppression

Maternal Considerations

HAV is a picornavirus, and the vaccine consists of inactivated virus. There are no adequate reports or well-controlled studies in pregnant women. There are no reported adverse effects on mother or fetus. Women either traveling to areas where HAV is endemic, older than 30y with chronic liver disease, waiting for or who have received liver transplants, or working with nonhuman primates should be vaccinated. HAV vaccination of chronic HCV carrier women substantially reduces morbidity and mortality rates.

The disease course is typically unaltered by pregnancy, though fulminant hepatitis is reported in the 3rd trimester. Immunoglobulin is a safe alternative for short-term protection. ***Side effects*** include anaphylaxis, local reaction, fever, rash, pharyngitis, abdominal pain, arthralgia, elevated CPK, myalgias, lymphadenopathy, hypertonic episode, photophobia, and vertigo.

Fetal Considerations

There are no adequate reports or well-controlled studies of **hepatitis A vaccine** in human fetuses. HAV is rarely transmitted to the fetus, and is not a known teratogen. The antibodies produced in response to vaccination are known to cross the placenta and may provide enhanced protection during the neonatal period. Rodent teratogenicity studies have not been conducted.

Breastfeeding Safety

There are no adequate reports or well-controlled studies in nursing women. It is unknown whether **hepatitis A vaccine** enters human breast milk. It is likely the resulting antibodies do enter breast milk, but it is unknown whether they confer any immunity for the nursing newborn. The vaccine is generally considered compatible with breastfeeding.

Drug Interactions

Preliminary results suggest that the concomitant administration of a wide variety of other vaccines is unlikely to interfere with the immune response to **hepatitis A vaccine.** However, it should be given with a different syringe and at a different injection site when given with other vaccines or IgG.
Administer with caution to individuals on anticoagulant therapy.

References

Duff B, Duff P. Obstet Gynecol 1998; 91:468-71.
Jacobs RJ, Koff RS, Meyerhoff AS. Am J Gastroenterol 2002; 97:427-34.

Summary

Pregnancy Category: C
Lactation Category: S

- **Hepatitis A vaccine** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Hepatitis B immune globulin—(BatHEP B; H-big; Hyperhep; Nabi-HB)

International Brand Name—Aunativ (Denmark); Bayhep B (Canada); Euvax-B (Thailand); Hepatect (Austria, Czech Republic, Germany, Hungary, Poland); Hepatect CP (Israel); Hepuman (Belgium); Hepuman Berna (Peru); IVheBex (France)

Drug Class

Antisera

Indications

Postexposure prophylaxis in susceptible women

Mechanism

Passive immunization

Dosage with Qualifiers

Postexposure prophylaxis—0.06ml/kg (up to 0.5ml) IM as soon after exposure as possible (within 24h)
Prevention of fetal infection—200IU IV beginning at 28w and repeated at 32 and 36w.

- **Contraindications**—hypersensitivity to drug or class
- **Caution**—history of systemic allergy to other vaccines, thrombocytopenia or another bleeding disorder

Maternal Considerations

Hepatitis B immune globulin is prepared from pooled plasma. Women who may benefit from inoculation include those exposed to household contacts, an infected sexual partner, and blood from infected individuals. **Hepatitis B immune globulin** is effective in reducing perinatal transmission of HBV to neonates born to infected women. Though there is controversy on whether the administration of immunoglobulin in the 3rd trimester reduces transmission when given antenatally to Hep Be antigen–positive women, it may be worthwhile. **Hepatitis B immune globulin** should be administered concomitantly with **hepatitis B vaccine.** Women previously vaccinated but subsequently exposed should have their immune titers checked immediately, and be covered with immunoglobulin if they are low.
Side effects include local reaction, swelling, erythema, headache, malaise, nausea, diarrhea, myalgia, and anaphylaxis.

Fetal Considerations

There are no adequate reports or well-controlled studies of **hepatitis B immune globulin** in human fetuses. While animal studies have not been conducted, though there is no reason to expect the immunoglobulin to be harmful. Further, administration to susceptible women appears to reduce the incidence of neonatal HBV. Universal vaccination is recommended postnatally.

Breastfeeding Safety

There are no adequate reports or well-controlled studies of **hepatitis B immune globulin** in nursing women. Vaccinated women have higher immunoglobulin levels in their breast milk.

Drug Interactions

Although administration of **hepatitis B immune globulin** does not interfere with measles vaccination, it is not known whether it may interfere with the immune response to other live virus vaccines. Therefore, vaccination with live virus vaccines should be deferred until approximately 3mo after administration of **hepatitis B immune globulin** (human). It may be necessary to revaccinate persons who received immunoglobulin shortly after live virus vaccination.

References

Azzari C, Resti M, Rossi ME, et al. J Pediatr Gastroenterol Nutr 1990; 10:310-5.
U.S. Public Health Service. MMWR Recomm Rep 2001; 50(RR-11):1-52.
Xiao XM, Li AZ, Chen X, et al. Int J Gynaecol Obstet 2007; 96:167-70.
Xu Q, Xiao L, Lu XB, et al. World J Gastroenterol 2006; 12:3434-7.
Yuan J, Lin J, Xu A, et al. J Viral Hepat 2006; 13:597-604.
Yue Y, Yang X, Zhang S. Chin Med J (Engl) 1999; 112:37-9.

Summary

Pregnancy Category: C
Lactation Category: S

- **Hepatitis B immune globulin** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.
- When indicated, **hepatitis B immune globulin** is effective and of minimal risk to the fetus.

Hepatitis B vaccine, recombinant—(Engerix-B; Recombivax HB)

International Brand Name—Bio-Hep-B (Israel); Engerix-B (Argentina, Brazil, Canada, Chile, Costa Rica, Dominican Republic, Ecuador, El Salvador, Guatemala, Honduras, Mexico, Nicaragua, Panama, Paraguay, Peru, South Africa); Euvax B (Korea); H-B-Vax II (England, Ireland, Mexico); HBvaxPRO (England, Ireland, New Zealand); Heberbiovac HB (Mexico); Hepavax Gene (Colombia); Recombivax HB (Canada)

Drug Class	Vaccines
Indications	Maternal susceptibility
Mechanism	Active immune response to capsular antigen
Dosage with Qualifiers	HBV susceptibility—1ml IM; repeat at both 1mo and 6mo • **Contraindications**—hypersensitivity to drug or class • **Caution**—MS
Maternal Considerations	Recombinant vaccines are biotechnologically produced, consisting of nonreplicating antigens. **Hepatitis B vaccine** appears safe and immunogenic during pregnancy, and immunization may help protect the fetus. Postpartum vaccination is also effective. The number of at-risk patients is large, and many authorities recommend routine vaccination. However, vaccination can usually be delayed until after delivery for most indications. Nonimmune women in geographic locales with high endemic rates benefit from vaccination during pregnancy. ***Side effects*** include malaise, headache, fever, N/V, abdominal pain, rhinitis, arthralgia, myalgias, Guillain-Barré syndrome, Bell's palsy, insomnia, arthritis, Stevens-Johnson syndrome, and injection site reactions such as erythema, pruritus, swelling, and nodule formation.
Fetal Considerations	There are no adequate reports or well-controlled studies of **hepatitis B vaccine** in human fetuses. Passive immunity occurs in more than half of newborns born to women vaccinated during pregnancy. Neonatal vaccination is 95% effective. There does not appear to be any substantative difference among recombinant vaccines. Rodent teratogenicity studies have not been performed, though the native virus is not a known human teratogen.
Breastfeeding Safety	There are no adequate reports or well-controlled studies in nursing women. It is unknown whether **hepatitis B vaccine** enters human breast milk, but breastfed neonates of vaccinated women have higher hepatitis B antibody levels.
Drug Interactions	No clinically relevant interactions identified.
References	Azzari C, Resti M, Rossi ME, et al. J Pediatr Gastroenterol Nutr 1990; 10:310-5. Jurema MW, Polaneczky M, Ledger WJ. Am J Obstet Gynecol 2001; 185:355-8.
Summary	**Pregnancy Category: C** **Lactation Category: S** • **Hepatitis B vaccine** is noninfectious; it appears safe and effective during pregnancy and lactation.

Hexachlorophene—(pHisoHex)

International Brand Name—Dermisan (Indonesia); pHisoHex (Canada)

Drug Class	Antiseptics; Dermatologics
Indications	Skin or wound preparation
Mechanism	Chemical inactivation
Dosage with Qualifiers	Preoperative skin preparation—wash affected area 30min prior to surgery • **Contraindications**—hypersensitivity to drug or class • **Caution**—unknown
Maternal Considerations	**Hexachlorophene** is not recommended due to narrow spectrum and the risk of percutaneous absorption. A phenol, it can be neurotoxic at high concentrations. While the wound infection rate is reduced after cleansing, and preoperative showers reduce the skin bacterial count, there are better alternatives. There are no adequate reports or well-controlled studies in pregnant women.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. **Hexachlorophene** crosses the human placenta and in rodents accumulates in neural tube structures. Occupational exposure during pregnancy is not associated with adverse outcomes, though one retrospective study suggested a relation between exposure during pregnancy and mental retardation. **Hexachlorophene** contained in vaginal lubricants is variably absorbed across the mucosa, achieving detectable levels in both the maternal and cord sera. Because of the risk for neonatal **hexachlorophene** toxicity, alternative lubricants for pelvic examinations should be used during labor.
Breastfeeding Safety	There is no published experience in nursing women. It is unknown whether **hexachlorophene** enters human breast milk.
Drug Interactions	No clinically relevant interactions identified.
References	Baltzar B, Ericson A, Kallen B, et al. J Occup Med 1979; 21:543-8. Brandt I, Dencker L, Larsson KS, Siddall RA. Acta Pharmacol Toxicol (Copenh) 1983; 52:310-3. Roeleveld N, Zielhuis GA, Gabreels F. Br J Ind Med 1993; 50:945-54. Strickland DM, Leonard RG, Stavchansky S, et al. Am J Obstet Gynecol 1983; 147:769-72. Zdeblick TA, Lederman MM, Jacobs MR, Marcus RE. Clin Orthop 1986; 213:211-5.
Summary	**Pregnancy Category: C** **Lactation Category: S** • **Hexachlorophene** should be avoided during pregnancy, but exposure requires no intervention. • There are better alternatives (e.g., **chlorhexidine, povidone-iodine**) for use during pregnancy.

Hydralazine—(Apresoline; Apresrex; Dralzine; Hyperex; Ipolina; Naselin; Nepresol; Solezorin; Sulesorin; Supres; Zinepress)

International Brand Name—Alphapress (Israel, New Zealand); Apdormin (Japan); Apresolin (Denmark, Norway, Sweden, Turkey); Apresolina (Ecuador, Mexico, Portugal, Uruguay, Venezuela); Apresoline (Canada, England, Ireland, Netherlands, Philippines, Taiwan, Thailand); Aprezin (Taiwan); Clorana (Brazil); Deselazin (Japan); Hidral (Argentina); Hydrapres (Argentina, Costa Rica, Dominican Republic, El Salvador, Guatemala, Panama, Spain); Hypatol (Japan); Hyperphen (South Africa); Nonpolin (Japan); Novo-Hylazin (Canada); Resporidin (Japan); Slow-Apresoline (Israel, Puerto Rico, South Africa); Solesorin (Japan); Tetrasoline (Japan); Travinon (Japan)

Drug Class	Antihypertensives; Vasodilators
Indications	Hypertension (moderate to severe), CHF
Mechanism	Unknown
Dosage with Qualifiers	Hypertension (moderate to severe)—begin 10-50mg PO qid ×2-4d, then 25mg PO qid ×1w; max 100mg PO qid; alternatively, 5-40mg IV/IM q4-6h; for chronic use, switch to PO ASAP CHF—begin 50-75mg PO ×1, then 50-150mg PO qid; max 3000mg/d *NOTE: may be packaged with* ***hydrochlorothiazide.*** • **Contraindications**—hypersensitivity to drug or class, CAD, mitral valve disease • **Caution**—renal dysfunction, CV disease
Maternal Considerations	**Hydralazine** is one of the most widely used drug for the treatment of acute hypertension during pregnancy. Women with severe preeclampsia whose intravascular volume is contracted are at risk for hypotension. The risk is ameliorated by the administration of appropriate intravascular volume prior to treatment. It was suggested that the incidence of hypotension is increased by the continuous infusion of **hydralazine,** but that observation may reflect a variety of other uncontrolled variables such as volume replacement and nursing protocols. Comparative study suggests other commonly used agents, such as **nifedipine** or **labetolol,** are equally effective in nulliparas for the control of hypertension with fewer hypotensive complications than **hydralazine** in multiparas. In one recent randomized trial, mini-bolus doses of **diazoxide** (15mg) did not cause maternal hypotension as previously described and, compared to **hydralazine,** produced rapid control and reduced the number of episodes of persistent severe hypertension. ***Side effects*** include agranulocytosis, neutropenia, lupus-like syndrome, palpitations, tachycardia, headache, angina, flushing, N/V, diarrhea, and peripheral edema.
Fetal Considerations	**Hydralazine** crosses the human placenta, and the F:M ratio can exceed unity. The impact of the therapeutic level on the human fetus is unknown. Vascular resistance declines in the isolated perfused placenta. Limited use during the 1st trimester reveals no evidence of teratogenicity. The impact of **hydralazine** on placental blood flow is variable and greatly influenced by the occurrence of hypotension. Rodent studies reveal that **hydralazine** is teratogenic in mice at 20-30× the MRHD and possibly in rabbits at 10-15× the MRHD, but is not teratogenic in rats.
Breastfeeding Safety	There are no adequate reports or well-controlled studies in nursing women. **Hydralazine** enters human breast milk, but the

amount ingested by the breastfeeding neonate is clinically insignificant.

Drug Interactions

MAOIs should be used with caution.
Profound hypotension may occur when **diazoxide** and **hydralazine** are injected concomitantly.
Administration with food results in higher plasma levels.

References

Aali BS, Nejad SS. Acta Obstet Gynecol Scand 2002; 81:25-30.
Hennessy A, Thornton CE, Makris A, et al. Aust N Z J Obstet Gynaecol 2007; 47:279-85.
Liedholm H, Wahlin-Boll E, Hanson A, et al. Eur J Clin Pharmacol 1982; 21:417-9.
Magee KP, Bawdon RE. Am J Obstet Gynecol 2000; 182:167-9.

Summary

Pregnancy Category: C
Lactation Category: S

- **Hydralazine** is a drug of choice for the treatment of acute hypertension during pregnancy.
- Until better evidence is available, the selection of an antihypertensive should depend on the clinician's experience and familiarity with a particular drug, and on what is known about adverse effects.
- Other alternative agents are preferable for the treatment of chronic hypertension.

Hydrochlorothiazide—(Aquazide H; Esidrix; Hydrodiuril; Hydro Par; Microzide; Oretic)

International Brand Name—Apo-Hydro (Canada, Malaysia); BPzide (India); Clothia (Japan); Dichlothiazide (Russia); Dichlotride (Belgium, Denmark, Hong Kong, Japan, Malaysia, Netherlands, Norway, Philippines, Sweden, Taiwan, Thailand); Dichlozid (Korea); Didralin (Malaysia, Thailand); Di-Ertride (Singapore); Di-Eudrin (Venezuela); Disalunil (Bulgaria); Disothiazide (Israel); Dithiazide (Australia); Diurace (Peru); Diuret-P (Thailand); Diurex (Argentina); Diursan (Paraguay); Esidrex (Austria, France, India, Israel, Italy, Japan, Netherlands, Norway, Spain, Sweden, Switzerland, Uruguay); Esidrix (Germany); H.C.T. (Indonesia); Hidrenox (Argentina); Hidroronol (Chile); Hidrosaluretil (Spain); Hychlozide (Thailand); Hydrex (Finland); Hydrex-semi (Finland); Hydrochlorzide (Malaysia); Hydrosaluric (England, Ireland); Hydrozide (Hong Kong, Thailand); Hypothiazid (Hungary); Maschitt (Japan); Newtolide (Japan); Pantemon (Japan); Ridaq (South Africa); Tandiur (Argentina)

Drug Class

Antihypertensives; Diuretics; Thiazides

Indications

Hypertension, peripheral edema

Mechanism

Inhibits sodium and chloride reabsorption from the distal convoluted tubule

Dosage with Qualifiers

Hypertension—12.5-50mg PO qd
Peripheral edema—25-200mg PO qd

NOTE: may be packaged with ***irbesartan, lisinopril, losartan, metoprolol, moexipril, propranolol, quinapril, spironolactone, telmisartan, timolol, triamterene,*** *or* ***valsartan.***

- **Contraindications**—hypersensitivity to drug or class, hypersensitivity to sulfonamides, CrCl <50ml, anuria
- **Caution**—hepatic or renal dysfunction

Maternal Considerations

There are no adequate reports or well-controlled studies in pregnant women. Low-dose diuretics are the most effective first-line treatment for the prevention of CV disease morbidity

and mortality. **Hydrochlorothiazide** leads to potassium loss and a transient reduction in intravascular volume when first initiated. Thereafter, intravascular volume recovers. Thus, thiazides should not be initiated during pregnancy but may be continued if already in chronic use. These diuretics further reduce an already constricted maternal intravascular volume in women with preeclampsia and should be avoided in such women.
Hydrochlorothiazide has been used during pregnancy for the treatment of idiopathic hypoparathyroidism.
Side effects include aplastic anemia, thrombocytopenia, agranulocytosis, renal failure, hyperglycemia, hyperuricemia, hypercalcemia, hyperlipidemia, dizziness, headache, vertigo, orthostatic hypotension, N/V, abdominal pain, paresthesias, and pancreatitis.

Fetal Considerations

Hydrochlorothiazide crosses the human placenta, achieving an F:M ratio approximating 0.5. It is concentrated in AF. While no evidence of teratogenicity has emerged during the long clinical experience, **hydrochlorothiazide** can cause neonatal electrolyte abnormalities, thrombocytopenia, and hyperglycemia when given around the time of delivery. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically.

Breastfeeding Safety

There are no adequate reports or well-controlled studies in nursing women. It is unknown whether **hydrochlorothiazide** enters human breast milk.

Drug Interactions

Alcohol, barbiturates, and narcotics may potentiate orthostatic hypotension.
May necessitate a dose adjustment in women also receiving antidiabetic drugs (oral agents and insulin).
May potentiate other antihypertensive agents.
Cholestyramine and **colestipol** resins bind **hydrochlorothiazide** and reduce its absorption from the GI tract by up to 85% and 43%, respectively.
Corticosteroids may intensify electrolyte depletion, particularly hypokalemia.
May decrease the response to pressor amines but not sufficiently to preclude their use.
May increase responsiveness to nondepolarizing skeletal muscle relaxants.
Diuretics reduce the renal clearance of **lithium** and increase the risk of toxicity.
NSAIDs may reduce the diuretic, natriuretic, and antihypertensive effects of loop, potassium-sparing, and thiazide diuretics.

References

Beermann B, Fahraeus L, Groschinsky-Grind M, Lindstrom B. Gynecol Obstet Invest 1980; 11:45-8.
George JD, Price CJ, Tyl RW, et al. Fund Appl Toxicol 1995; 26:174-80.
Kurzel RB, Hagen GA. Am J Perinatol 1990; 7:333-6.
[No authors]. IARC Monogr Eval Carcinog Risks Hum 1990; 50:293-305.
Psaty BM, Lumley T, Furberg CD, et al. JAMA 2003; 289:2534-44.

Summary

Pregnancy Category: B
Lactation Category: S

- Although diuretics are no longer first-line therapy for the treatment of hypertension during pregnancy, **hydrochlorothiazide** remains the drug of choice for the treatment of heart failure unrelated to hypertension.

- When indicated, the mother's electrolytes and hematocrit should be monitored.
- Outside of pregnancy, low-dose diuretics are the most effective first-line treatment for preventing CV disease morbidity and mortality.

Hydrocodone—(Histussin-HC; Hycodan; Hycomar; Hydrocodone Compound; Hydrocone/Mycodone; Hydromet; Hydropane; Hydrotropine; Mycodone; Tussigon)

International Brand Name—None identified.

Drug Class	Analgesics, narcotic; Antitussives; Narcotics; Sedatives
Indications	Cough, acute pain
Mechanism	Binds opioid receptors in the CNS
Dosage with Qualifiers	Cough—5-10mg PO q6h prn Acute pain—5-10mg PO q6h prn *NOTE: contains homatropine; may also be combined with* ***ibuprofen, phenylephrine, phenylpropanolamine, phenyltoloxamine,*** *or* ***pseudoephedrine,*** *depending on the indication; available in tablet or syrup form.* • **Contraindications**—hypersensitivity to drug or class, glaucoma • **Caution**—increased ICP, hepatic or renal dysfunction, history of addiction to or dependence on a drug, head injury, abdominal pain
Maternal Considerations	**Hydrocodone** is a semisynthetic opioid. Homatropine is included in the formulation at a subtherapeutic level to discourage abuse. There are no adequate reports or well-controlled studies in pregnant women. The analgesia produced by combination with **ibuprofen** is superior to that achieved with **ibuprofen** alone. Similar to **codeine,** it seems more effective for the relief of uterine cramping than episiotomy pain. ***Side effects*** include dizziness, respiratory depression, euphoria, sedation, confusion, N/V, constipation, dry mouth, urinary retention, itching, bradycardia, tachycardia, and increased intraocular pressure.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. **Hydrocodone** presumably crosses the human placenta. Rodent studies reveal IUGR at doses below those producing maternal toxicity. In an adequate dose, it can cause neonatal depression at birth.
Breastfeeding Safety	There are no adequate reports or well-controlled studies in nursing women. It is unknown whether **hydrocodone** enters human breast milk. However, **codeine** and its metabolite **morphine** are excreted in human breast milk. Breastfeeding neonates have low plasma levels during the first few days of life, in part secondary to the low concentration in milk, and in part due to the small amount of milk produced. Thus, moderate **hydrocodone** use is probably compatible with breastfeeding.

Drug Interactions ..... Has additive depressant effects if used with other narcotic analgesics, general anesthetics, phenothiazines, tranquilizers, sedative-hypnotics, or other CNS depressants (including alcohol). The dosage of one or both agents should be reduced.

References .....

Beaver WT, McMillan D. Br J Clin Pharmacol 1980; 10(Suppl 2):215S-23S.
Sunshine A, Olson NZ, O'Neill E, et al. J Clin Pharmacol 1997; 37:908-15.

Summary .....

Pregnancy Category: C
Lactation Category: S

- **Hydrocodone** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.
- This effective analgesic combination is often used postpartum.

Hydrocortisone—(Acticort; Aeroseb-Hc; Ala-Cort; Ala-Scalp; Albacort; Allercort; Alphaderm; Anusol-Hc; Balneol-Hc; Beta-Hc; Cetacort; Coracin; Coreton; Cort-Dome; Cortef; Cortenema; Cortes; Cortril; Cotacort; Dermol Hc; Eldecort; Epicort; Flexicort; Glycort; H-Cort; Hi-Cor; Hidroaltesona; Hidromar; Hidrotisona; Hycort; Hycortole; Hydrocortemel; Hydrocortone; Hydro-Tex; Hymac; Hytone; IVocort; Lacticare; Lemoderm; Lidex; Nogenic Hc; Nutracort; Otozonbase; Penecort; Proctocort; Procto-Hc; Rederm; S-T Cort; Stie-Cort; Synacort; Tega-Cort; Texacort; Topisone)

International Brand Name—Alfacort (Argentina, Paraguay); Algicortis (Italy); Alpha Derm (Belgium); Aquanil HC (Hong Kong, Mexico); Biacort (France); Calmurid (Chile); Cordicare Lotion (Korea); Coripen (Uruguay); Cortate (Canada); Cortef (Canada, Hong Kong, Hungary); Cortef Cream (New Zealand); Cortenema (Canada); Corticorenol (Bulgaria); Cortril (Belgium, Finland, Taiwan); Covocort (South Africa); Cremicort-H (Belgium); Cutaderm (South Africa); Dermacrin HC Lotion (Korea); Dermaid (Australia); Derm-Aid Cream (Hong Kong, Malaysia, Singapore); Dermaid Soft Cream (Australia); Dermocare (Korea); Dermocortal (Italy); Dioderm (England); Eczacort (Philippines); Efcortelan (Israel, South Africa); Egocort Cream (Hong Kong, Malaysia); Emo-Cort (Canada); Ficortril (Germany, Sweden); Filocot (Greece); Hidrotisona (Argentina); Hycor (Australia); Hydrocortison (Finland, Germany, Hungary); Hydrocortisone (Belgium, France); Hydrocortisone Astier (France, Switzerland); Hydrocortisonum (Netherlands); Hydrocortisyl (England, Israel); Hydrocortone (Austria, England, Finland, Ireland, Portugal, Switzerland); Hydroderm (Austria, Germany); Hydrogalen (Germany); Hydrokort (Norway); Hydrokortison (Denmark, Norway, Sweden); Hydrotopic (Philippines); Hysone (Australia); Hytisone (Hong Kong); Hytone Lotion (Korea); Kyypakkaus (Finland); Lacticare HC (Costa Rica, Dominican Republic, El Salvador, Guatemala, Honduras, Mexico, Nicaragua, Panama, Philippines, Taiwan); Lemnis Fatty Cream HC (New Zealand); Lenirit (Italy); Medrocil (Argentina); Mildison (Denmark, England, Ireland, Sweden); Mildison-Fatty (Finland); Mildison fet krem (Norway); Mildison Lipocream (England, Ireland, New Zealand); Mitocortyl Demangeaisons (France); Nutracort (Brazil, Costa Rica, Dominican Republic, El Salvador, Guatemala, Peru); Prevex HC (Thailand); Procutan (South Africa); Sanatison (Germany); Schericur (Austria, Ecuador); Schericur 0.25% (Spain); Sistral Hydrocort (Germany); Skincalm (New Zealand); Unicort (Colombia); Uniderm (Denmark, Finland, Sweden)

Drug Class ..... Corticosteroids, topical; Dermatologics

Indications ..... Inflammatory disorders, ulcerative colitis, status asthmaticus, shock, steroid-responsive dermatitis, pruritus, adrenal insufficiency

Mechanism

Unknown

Dosage with Qualifiers

Inflammatory disorders—10-320mg PO qd in 2-4 divided doses
Ulcerative colitis—100mg qd ×2-3w, then qod
Status asthmaticus—0.5-1mg/kg IM/IV q6h
Shock—0.5-2g IM/IV q2-6h
Steroid-responsive dermatitis—apply cream bid to qid
Pruritus—apply 1% or 2.5% cream thinly to affected area tid or qid
Adrenal insufficiency—5-30mg PO bid to qid; max 80mg PO qid acutely

NOTE: available in oral, parenteral, suppository, and topical preparations; may be combined with ***neomycin, oxytetracycline,*** *pramoxine, or* ***polymixin*** *and* ***neomycin.***

- **Contraindications**—hypersensitivity to drug or class, systemic fungal infection
- **Caution**—diabetes mellitus, hypertension, seizure disorder, osteoporosis, hepatic dysfunction, TB

Maternal Considerations

Hydrocortisone is a naturally occurring glucocorticoid. Adrenal corticosteroid secretion is increased during pregnancy. There are no adequate reports or well-controlled studies in pregnant women. Case reports suggest pregnancy increases requirements. ***Side effects*** include adrenal insufficiency, steroid psychosis, immunosuppression, menstrual irregularities, CHF, peptic ulcer disease, bloating, appetite change, edema, N/V, dyspepsia, headache, mood swings, insomnia, anxiety, acne, skin atrophy, hypokalemia, hyperglycemia, hypertension, and impaired wound healing.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. **Hydrocortisone** is inactivated in the placenta. Some glucocorticoids increase the risk of cleft palate in some rodents. There was no increase in registry-type studies in the general frequency of malformations in offspring of women receiving a variety of corticosteroids during pregnancy. Despite placental metabolism, 2g of **hydrocortisone** administered over 48h in divided doses improves both indices of fetal lung maturity (i.e., L:S ratio) and fetal outcomes compared to no treatment. As such, **hydrocortisone** is an alternative therapy should either **betamethasone** or **dexamethasone** be unavailable for the hastening of lung maturity. It is unknown whether repeated exposure delays myelination as has been reported in animals after either **betamethasone** or **dexamethasone.**

Breastfeeding Safety

There is no published experience in nursing women. It is unknown whether **hydrocortisone** enters human breast milk. Glucocorticoids are a normal component of breast milk. It is not known whether maternal ingestion increases the concentration. The long clinical experience is reassuring.

Drug Interactions

Drugs that induce hepatic enzymes (e.g., **phenobarbital, phenytoin, rifampin**) may increase corticosteroid clearance and require increases in corticosteroid dosage to achieve the desired response.
Drugs such as **troleandomycin** and **ketoconazole** may inhibit the metabolism of corticosteroids and thus decrease their clearance. The dose of corticosteroid should be titrated to avoid toxicity.
Corticosteroids may increase the clearance of chronic high-dose **aspirin,** potentially causing decreased salicylate levels or increased risk of salicylate toxicity should the corticosteroid be withdrawn.

Aspirin should be used cautiously in conjunction with corticosteroids in patients suffering from hypoprothrombinemia. The effect of corticosteroids on oral anticoagulation is variable. Coagulation indices should be monitored to maintain the desired anticoagulant effect.

References

Kallen B, Rydhstroem H, Aberg A. Obstet Gynecol 1999; 93:392-5.
Moore LE, Martin JN Jr. J Perinatol 2001; 21:456-8.
Park-Wyllie L, Mazzotta P, Pastuszak A, et al. Teratology 2000; 62:385-92.

Summary

Pregnancy Category: C
Lactation Category: S (likely)

- **Hydrocortisone** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.
- It is a possible substitute therapy for the enhancement of fetal lung maturity should either **betamethasone** or **dexamethasone** be unavailable.

Hydromorphone—(Dilaudid; Dilaudid-HP; Hydromorphone Hcl; Hydrostat)

International Brand Name—Diladid (Korea); Dilaudid (Australia, Austria, Canada, Germany); Dilaudid HP (Canada); Dilaudid-HP (Australia); Dolonovag (Argentina); Hydromorph Contin (Canada); Opidol (Denmark); Paliadon Retardkaps (Germany); Palladone (England, Ireland, Israel); Palladone SR (England, Ireland, Israel); Sophidone LP (France)

Drug Class

Analgesics, narcotic; Narcotics

Indications

Pain (moderate to severe), cough

Mechanism

Binds to multiple opiate receptors

Dosage with Qualifiers

Pain (moderate to severe)—begin 1-2mg IV/IM/SC q4-6h, 2-4mg PO q4-6h
Cough—1mg PO q3-4h prn
Conduction anesthesia—see specialty texts

NOTE: available in parenteral, oral, and suppository form.

- **Contraindications**—hypersensitivity to drug or class, increased ICP, respiratory depression
- **Caution**—hepatic or renal dysfunction

Maternal Considerations

Hydromorphone plus a local anesthetic (e.g., **bupivacaine**) is popular for epidural anesthesia during labor. Similar to **morphine,** it enhances the sensory blockade, thus allowing a lower concentration of local anesthetic. The result is a decrease in motor blockade. There are no well-controlled studies of women receiving **hydromorphone** chronically.
Side effects include respiratory depression, apnea, CNS depression, sedation, drowsiness, dizziness, anorexia, N/V, constipation, orthostatic hypotension, psychological and physical dependence, and ureteral spasm.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. Systemically available **hydromorphone** rapidly crosses the placenta, achieving an F:M ratio approximating unity. Rodent studies revealed teratogenicity at doses 600× the MRHD.

Recent study suggests it and other **morphine** derivatives can reduce total estrogen levels by inhibiting CYP19.

Breastfeeding Safety

There are no adequate reports or well-controlled studies in nursing women. **Hydromorphone** enters human breast milk. After intranasal administration, the breastfed newborn ingests approximately 0.67% of the maternal dose (adjusted for body weight). Considering the dose and pattern of clinical use, **hydromorphone** is compatible with breastfeeding.

Drug Interactions

Use of other CNS depressants (e.g., sedatives or hypnotics, general anesthetics, phenothiazines, tranquilizers, alcohol) may produce additive depressant effects. Respiratory depression, hypotension, and profound sedation or coma may occur.
Opioid analgesics may enhance the action of neuromuscular blocking agents and produce an excessive degree of respiratory depression.
Agonist-antagonist analgesics (e.g., **buprenorphine, butorphanol, nalbuphine, pentazocine**) should be administered with caution to a patient who has received or is receiving a pure opioid agonist analgesic. In this situation, mixed agonist-antagonist analgesics may reduce the analgesic effect of **hydromorphone** and/or may precipitate withdrawal symptoms.

References

Edwards JE, Rudy AC, Wermeling DP, et al. Pharmacotherapy 2003; 23:153-8.
Geber WF, Schramm LC. Am J Obstet Gynecol 1975; 123:705-13.
Halpern SH, Arellano R, Preston R, et al. Can J Anaesth 1996; 43:595-8.
Sinatra RS, Eige S, Chung JH, et al. Anesth Analg 2002; 94:1310-1.
Zharikova OL, Deshmukh SV, Kumar M, et al. Biochem Pharmacol 2007; 73:279-86.

Summary

Pregnancy Category: C
Lactation Category: S

- **Hydromorphone** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.
- It is a popular agent for labor epidural analgesia in combination with a local anesthetic.

Hydroquinone topical—(Aida; Banquin; Eldopaque Forte; Eldoquin Forte; Epocler; Hydroxyquinone; Melanex; Melanol; Melpaque HP; Melquin; Nuquin HP; Solaquin Forte)

International Brand Name—Aldoquin 2 (Colombia); Clariderm (Thailand); Clariderm DS (Thailand); Claripel (Argentina); Clasifel (Paraguay, Uruguay); Crema Blanca Bustillos (Mexico); Eldopaque (Costa Rica, Dominican Republic, El Salvador, Greece, Guatemala, Honduras, Hong Kong, Israel, Nicaragua, Panama, Philippines); Eldopaque Forte (Malaysia, Philippines, Taiwan); Eldoquin (Canada, Costa Rica, Dominican Republic, El Salvador, Guatemala, Honduras, Hong Kong, Israel, Mexico, Nicaragua, Panama, Philippines); Eldoquin Cream (New Zealand); Eldoquin Forte (Costa Rica, Dominican Republic, El Salvador, Guatemala, Honduras, Hong Kong, Malaysia, Nicaragua, Panama, Philippines); Esomed (Israel); Etnoderm (Chile); Gentleclean (Taiwan); Ginomi (Korea); Melanox (Indonesia); Melquine (Taiwan); Melquin HP (Korea); Neoquin (Korea); Pharquinon (Venezuela); Polyquin Forte (Singapore); Solaquin (Canada, Hong Kong, Israel); Solaquin Forte (Hong Kong, Malaysia); Ultraquin (Canada, China); Zumae (Taiwan)

Drug Class

Depigmenting; Dermatologics

Indications

Hyperpigmentation (melasma) associated with pregnancy, OCPs, HRT, or trauma

Mechanism	Suppresses melanocyte metabolism
Dosage with Qualifiers	Hyperpigmentation—apply bid; use sunscreen • **Contraindications**—hypersensitivity to drug or class, hypersensitivity to sulfites • **Caution**—unknown
Maternal Considerations	There are no adequate reports or well-controlled studies of **hydroquinone** in pregnant women. There are no indications that require use during pregnancy. Postpartum, it is often used for the treatment of melasma. ***Side effects*** include contact dermatitis, dryness, fissures, irritation, and burning.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. **Hydroquinone** crosses the human placenta and is a teratogen in chicks and some rodents. It can cause hypoploidy in human cell culture lines. Approximately 45-50% of the topically applied dose, or 3mcg/cm^2/h, is available for systemic absorption. That said, women who use **hydroxyquinone** do not experience a detectable increase in adverse pregnancy outcomes.
Breastfeeding Safety	There is no published experience in nursing women. It is unknown whether **hydroquinone** enters human breast milk. Though the systemic concentration after topical administration is likely to be low, treatment can easily be delayed until weaning.
Drug Interactions	No clinically relevant interactions identified.
References	Burgaz S, Ozcan M, Ozkul A, Karakaya AE. Drug Chem Toxicol 1994; 17:163-74. Krasavage WJ, Blacker AM, English JC, Murphy SJ. Fundam Appl Toxicol 1992; 18:370-5. Mahe A, Perret JL, Ly F, et al. Trans R Soc Trop Med Hyg 2007; 101:183-7. Prignano F, Ortonned P, Buggiani G, Lotti J. Dermatol Clin 2007; 25:337-42. Stillman WS, Varella-Garcia M, Gruntmeir JJ, Irons RD. Leukemia 1997; 11:1540-5. Wester RC, Melendres J, Hui X, et al. J Toxicol Environ Health A 1998; 54:301-17.
Summary	**Pregnancy Category: C** **Lactation Category: S** (likely) • **Hydroquinone** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk. • There are no indications that require its use during pregnancy.

Hydroxychloroquine—(Plaquenil)

International Brand Name—Dimard (Colombia); Ercoquin (Denmark, Japan, Norway); Erquin (Korea); Evoquin (Argentina, Uruguay); Geniquin (Taiwan); Oxiklorin (Finland, Korea); Plaquenil Sulfate (Argentina, Canada, China, Hong Kong, Israel, Japan, Malaysia, Mexico, Philippines, Taiwan, Thailand); Plaquinol (Brazil, Chile, Colombia, Costa Rica, Dominican Republic, Ecuador, El Salvador, Guatemala, Honduras, Nicaragua, Panama, Paraguay, Peru, Portugal, Venezuela); Quensyl (Germany); Toremonil (Japan); Yuma (Korea)

Drug Class	Antimalarials; Antiprotozoals; Antirheumatics; Immunomodulators

Indications ..... SLE, malaria treatment and prophylaxis, rheumatoid arthritis

Mechanism ..... Unknown

Dosage with Qualifiers .....

SLE—400mg PO qd or bid
Malaria treatment—begin 800mg PO bid ×1, followed 6-8h later by 400mg PO, then 400mg PO qd ×2
Malaria prophylaxis—begin 400mg PO qw ×2w prior to exposure, continue 4-6w after exposure
Rheumatoid arthritis—begin 400-600mg PO qd ×4-12w, then 200-400mg PO qid

NOTE: take with food or milk.

- **Contraindications**—hypersensitivity to drug or class, porphyria, visual field changes
- **Caution**—unknown

Maternal Considerations .....

There are no adequate reports or well-controlled studies in pregnant women. **Hydroxychloroquine** reduces serum lipids, including cholesterol, triglycerides, and LDLs. Some recommend discontinuing **hydroxychloroquine** in pregnant women with connective tissue diseases, even though it has long been used for malarial prophylaxis during pregnancy in malaria-infested areas. In one randomized trial, **hydroxychloroquine** was associated with a significant reduction in the number of flare episodes in women with SLE. Thus, it may be reasonable to continue the drug considering the terminal elimination t/2 may be up to 2mo, flares of SLE occur after discontinuation, and flares are detrimental to pregnancy outcome.
Side effects include aplastic anemia, thrombocytopenia, agranulocytosis, seizures, visual changes, ototoxicity, exfoliative dermatitis, dizziness, N/V, diarrhea, headache, ataxia, pruritus, and weight loss.

Fetal Considerations .....

There are no adequate reports or well-controlled studies in human fetuses. While there is no substantive evidence of teratogenicity in rodents, **hydroxychloroquine** crosses the placenta and is deposited in pigmented fetal tissues. However, several large clinical series in women with either malaria or SLE are reassuring.

Breastfeeding Safety .....

There are no adequate reports or well-controlled studies in nursing women. The concentration of **hydroxychloroquine** entering human breast milk is apparently very low (3.2mcg in breast milk from a woman given 800mg over 48h) and should not pose a threat to the breastfed newborn.

Drug Interactions ..... No clinically relevant interactions identified.

References .....

Borden MB, Parke AL. Drug Saf 2001; 24:1055-63.
Clowse ME, Magder L, Witter F, Petri M. Arthritis Rheum 2006; 54:3640-7.
Costedoat-Chalumeau N, Amoura Z, Aymard G, et al. Arthritis Rheum 2002; 46:1123-4.
Klinger G, Morad Y, Westall CA, et al. Lancet 2001; 358:813-4.
Levy M, Buskila D, Gladman DD, et al. Am J Perinatol 1991; 8:174-8.
Levy RA, Vilela VS, Cataldo MJ, et al. Lupus 2001; 10:401-4.
Ostensen M, Brown ND, Chiang PK, Aarbakke J. Eur J Clin Pharmacol 1985; 28:357.
Renaud C, de Montgolfier I, Vautier-Brouzes D, et al. Arch Pediatr 2006; 13:1386-90.

Summary

Pregnancy Category: C
Lactation Category: S

- **Hydroxychloroquine** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.
- The additional risk imposed by **hydroxychloroquine** on pregnancy appears modest, and the drug should not be withheld when necessary.

Hydroxyurea—(Droxea; Hydrea)

International Brand Name—Hydab (Philippines); Hydrea (Argentina, Belgium, Brazil, Canada, Chile, Ecuador, England, Greece, Hong Kong, Indonesia, Ireland, Israel, Japan, Korea, Malaysia, Mexico, Netherlands, Russia, Singapore, South Africa, Taiwan, Thailand, Uruguay); Hydrine (Korea); Litalir (Czech Republic, Germany, Hungary, Philippines, Switzerland); Neodrea (India); Onco-Carbide (Italy)

Drug Class

Antineoplastics, miscellaneous

Indications

Sickle cell disease, essential thrombocythemia, polycythemia vera, HIV infection, resistant CML, head and neck tumors, solid tumors

Mechanism

Unclear, but inhibits DNA synthesis by acting as a ribonucleotide reductase inhibitor

Dosage with Qualifiers

Sickle cell disease—15mg/kg PO qd, then increase 5mg/kd/d ×12w; max 35mg/kg/d
Essential thrombocythemia—15mg/kg PO qd; titrate to control platelet count while maintaining WBC count
Polycythemia vera—500-1500mg PO qd
HIV infection, adjunct therapy—500mg PO bid (use with an antiretroviral)
Resistant CML—20-30mg/kg PO qd
Solid tumors—80mg/kg PO q3d

- **Contraindications**—hypersensitivity to drug or class, bone marrow depression
- **Caution**—renal dysfunction, concurrent myelosuppressive agents

Maternal Considerations

There are no adequate reports or well-controlled studies of **hydroxyurea** in pregnant women. Published experience is limited to case reports and small series of sickle cell disease, thrombocythemia, and leukemia. The beneficial effects of **hydroxyurea** on sickle cell disease result from an increase in both the intracellular concentration of Hb F and the percentage of Hb F–containing RBCs, improving the hydration and prolonging the life span of the RBCs. In women with essential thrombocythemia, **hydroxyurea** reduces thrombotic events but does not increase survival. The published clinical experience suggests the risk of **hydroxyurea** during human pregnancy may be greatly overestimated.
Side effects include bone marrow suppression, anemia, thrombocytopenia, leukopenia, leukemia, pulmonary fibrosis, dermatomyositis, stomatitis, anorexia, N/V, diarrhea, constipation, erythema, dysuria, headache, dizziness, hallucinations, seizures, alopecia, and dermatitis.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **hydroxyurea** crosses the human placenta. **Hydroxyurea** is embryotoxic and a potent teratogen in a wide variety of animal models. It also causes IUGR

and impaired learning in rats. However, the human experience suggests the risk of teratogenicity is somewhat overestimated.

Breastfeeding Safety

There are no adequate reports or well-controlled studies in nursing women. **Hydroxyurea** enters human breast milk, though the kinetics require further elucidation. Considering it is a potent mutagen, **hydroxyurea** should perhaps be avoided while breastfeeding until there is additional information available.

Drug Interactions

Use with other myelosuppressive agents or radiation may increase the likelihood of bone marrow depression or other adverse events. Since **hydroxyurea** can increase the uric acid level, dosage adjustment of uricosuric medications may be necessary.

References

Byrd DC, Pitts SR, Alexander CK. Pharmacotherapy 1999; 19:1459-62.
Diav-Citrin O, Hunnisett L, Sher GD, Koren G. Am J Hematol 1999; 60:148-50.
Koh LP, Devendra K, Tien SL. Ann Acad Med Singapore 2002; 31:353-6.
Patel M, Dukes IA, Hull JC. Am J Obstet Gynecol 1991; 165:565-6.
Sylvester RK, Lobell M, Teresi ME, et al. Cancer 1987; 60:2177-8.
Thauvin-Robinet C, Maingueneau C, Robert E, et al. Leukemia 2001; 15:1309-11.
Weiner DL, Brugnara C. JAMA 2003; 289:1692-4.
Woo GH, Katayama K, Bak EJ, et al. Exp Toxicol Pathol 2004; 56:1-7.

Summary

Pregnancy Category: D
Lactation Category: NS (possibly)

- **Hydroxyurea** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.
- The risk of **hydroxyurea** during pregnancy appears overestimated.

Hydroxyzine—(Atarax; Atazina; Hyzine; Neucalm 50; Vistacot; Vistaril; Vistazine)

International Brand Name—Abacus (Thailand); AH3 N (Germany); Antizine (Thailand); Apo-Hydroxyzine (Canada); Atarax (Canada, India, Malaysia, Mexico, Peru, Thailand); Ataraxone (Argentina); Atarax P (Japan); Aterax (South Africa); Bestalin (Indonesia); Bobsule (Japan); Cedar (Colombia); Centilax (Korea); Cerax (Thailand); Darax (Thailand); Disron P (Japan); Dormirex (Colombia); Drazine (Thailand); Hiderax (Colombia); Histan (Thailand); Hizin (Thailand); Iremofar (Greece); Iterax (Indonesia, Philippines); Novohydroxyzin (Canada); Otarex (Israel); Paxistil (Belgium); Phymorax (Singapore); Postarax (Thailand); Prurid (Paraguay); Qualidrozine (Hong Kong); R-Rax (Thailand); Trandozine (Thailand); Tranquijust (Japan); Ucerax (Korea); Unamine (Thailand); Vistaril (Kenya, Sweden, Taiwan, Turkey)

Drug Class

Antiemetics; Antihistamines, H_1; Antivertigo agents; Anxiolytics; Hypnotics; Sedatives

Indications

Anxiety, pruritus, N/V, sedation, insomnia

Mechanism

Antagonizes central and peripheral H_1 receptors

Dosage with Qualifiers

Anxiety—50-100mg PO/IM q6h prn; max 600mg/d
Pruritus—25-100mg PO q6-8h prn
N/V—25-100mg IM q4-6h prn; max 600mg/d
Sedation adjunct—25-100mg IM ×1
Insomnia—50-100mg PO qhs

NOTE: do not give IV.

- **Contraindications**—hypersensitivity to drug or class
- **Caution**—asthma

Maternal Considerations

There are no adequate reports or well-controlled studies in pregnant women. **Hydroxyzine** remains a first-line agent for the treatment of pruritus and nausea during pregnancy. It is often administered with narcotic agents to reduce the frequency of nausea. **Hydroxyzine** reduces the pruritus associated with epidural or spinal **morphine** and morphine analogs. **Hydroxyzine** is superior to **droperidol** for relief of nausea associated with general anesthesia.
Side effects include seizures, wheezing, dyspnea, drowsiness, dry mouth, ataxia, headache, agitation, slurred speech, and bitter taste.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **hydroxyzine** crosses the human placenta, though its administration is associated with a significant decrease in FHR variability when administered during labor. Epidemiologic studies of women taking **hydroxyzine** for allergy symptoms are reassuring. There is a single case report of neonatal seizures associated with **hydroxyzine** withdrawal after chronic intrauterine exposue. In rodents, high doses of **hydroxyzine** are associated with an increased rate of malformations.

Breastfeeding Safety

There is no published experience in nursing women. It is unknown whether **hydroxyzine** enters human breast milk.

Drug Interactions

MAOIs may prolong and intensify the anticholinergic effects of antihistamines.
Use with **pramlintide** may delay gastric emptying.
Use with **dexmedetomidine** may increase the risk of CNS depression.

References

Einarson A, Bailey B, Jung G, et al. Ann Allergy Asthma Immunol 1997; 78:183-6.
Juneja MM, Ackerman WE 3rd, Bellinger K. J Ky Med Assoc 1991; 89:319-21.
McKenzie R, Wadhwa RK, Uy NT, et al. Anesth Analg 1981; 60:783-8.
Petrie RH, Yeh SY, Murata Y, et al. Am J Obstet Gynecol 1978; 130:294-9.
Serreau R, Komiha M, Blanc F, et al. Reprod Toxicol 2005; 20:573-4.
The Drugs and Pregnancy Study Group. Ann Pharmacother 1994; 28:17-20.

Summary

Pregnancy Category: C
Lactation Category: U

- **Hydroxyzine** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.
- The long clinical experience with **hydroxyzine** during pregnancy is reassuring.

Hyoscyamine—(A-Spas S L; Anaspaz; Cystospaz-M; Donnamar; Ed-Spaz; Gastrosed; Hyco; Hyosol SL; Hyospaz; Levbid; Levsin; Levsinex; Liqui-Sooth; Medispaz; Pasmex; Setamine; Spasdel)

International Brand Name—Levsin (Canada); Levsin SL (Hong Kong)

Drug Class	Anticholinergics; Antispasmodics; Gastrointestinals
Indications	GI or bladder spasm
Mechanism	Anticholinergic agent
Dosage with Qualifiers	GI tract spasm—0.125-0.25mg PO qac, qhs Bladder spasm—0.15-0.3mg PO qid *NOTE: may be combined with* ***pentobarbital*** *or* ***methenamine.*** • **Contraindications**—hypersensitivity to drug or class, glaucoma, ulcerative colitis, toxic megacolon, unstable CV disease, autonomic neuropathy, myasthenia gravis • **Caution**—hepatic or renal dysfunction, hot weather, hyperthyroidism, arrhythmia, CAD, CHF, GERD, pulmonary disease
Maternal Considerations	There is no published experience with **hyoscyamine** during pregnancy. ***Side effects*** include paralytic ileus, increased intraocular pressure, heatstroke, anticholinergic psychosis, confusion, blurred vision, urinary retention, dry mouth, constipation, tachycardia, palpitations, headache, loss of taste, and anhidrosis.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. **Hyoscyamine** reportedly crosses the human placenta. Rodent teratogenicity studies have not been performed.
Breastfeeding Safety	There is no published experience in nursing women. Trace amounts of **hyoscyamine** are excreted into human breast milk, though the kinetics remain to be elucidated.
Drug Interactions	Additive adverse effects resulting from cholinergic blockade may occur when used with other antimuscarinics, **amantadine, haloperidol,** phenothiazines, MAOIs, TCAs, or some antihistamines. Antacids may interfere with absorption; take **hyoscyamine** before meals and antacids after meals.
References	There are no current relevant references.
Summary	**Pregnancy Category: C** **Lactation Category: S** (likely) • **Hyoscyamine** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Ibuprofen—(Advil; Alaxan; Artril; Bloom; Brofen; Dolofen; Emflam; Fenspan; Ibren; Ibugen; Ibuprohm; Ibu-Tab; Ifen; Motrin; Nobafon; Paduden; Paxofen; Profen; Prontalgin; Tarein)

International Brand Name—Actron (Paraguay, Uruguay); Adex 200 (Israel); Adex Liqui-Gels (Israel); Advil (Brazil, Colombia, Ecuador, France, Hong Kong, Mexico, Poland, Venezuela); Advil Infantil (Mexico); Advil Liqui-Gels (Israel); Afebril (Peru); Algofen (Italy); Allipen (Korea); Am-Fam 400 (India); Ampifen (Singapore); Anadvil (France); Anbifen (Thailand); Anco (Germany); Andran (Japan); Anflagen (Japan); Antarene (France); Antiflam (South Africa); Apo-Ibuprofen (Canada); Atril 300 (Brazil); Balkaprofen (South Africa); Bestafen (Mexico); Betaprofen (South Africa); Bifen (Hong Kong, Singapore); Bluton (Japan); Brufanic (Japan); Brufen (Bangladesh, Hungary, India, Indonesia, Israel, New Zealand, Pakistan, Poland, Slovenia, South Africa, Spain); Brufen 400 (Israel); Brufen Retard (New Zealand); Brufort (Italy); Brugesic (South Africa); Brumed (Thailand); Buburone (Japan); Bufect (Indonesia); Bufect Forte (Indonesia); Bupogesic (Hong Kong); Burana (Finland); Butacortelone (Mexico); Carol (Korea); Cenbufen (Thailand); Childrens Motrin (Indonesia); Combiflam (India); Cuprofen (Thailand); Dibufen (Mexico); Diffutab SR 600 (Korea); Dolan FP (Philippines); Dolgit (Germany, Taiwan); Dolocyl (Switzerland); Dolofen-F (Indonesia); Dolomax (Peru); Dolormin (Germany); Doloxene (Costa Rica, El Salvador, Guatemala, Honduras, Nicaragua, Panama); Dolval (Mexico); Donjust B (Japan); Dorival (Spain); Drin (Greece); Druisel (Argentina); Easifon (Taiwan); Emflam-200 (India); Emodin (Argentina); Epobron (Japan); Expanfen (France); Febratic (Mexico); Febryn (Indonesia); Fenbid (England); Flamicon (Philippines); Focus (Italy); Gyno-neuralgin (Germany); H-Loniten (Colombia); IB-100 (Japan); Ibosure (Netherlands); Ibufen (Israel, Malaysia); Ibuflam (Mexico); Ibufug (Germany); Ibugesic (India); Ibuloid (Singapore); Ibumetin (Denmark, Finland, Netherlands, Norway, Sweden); Ibupen (Hong Kong); Ibupirac (Argentina); Ibuprocin (Japan); Iburon (Korea); Ibusal (Finland); Ibu-slow (Belgium); Idyl SR (Philippines); Infibu (Colombia); Ipren (Denmark, Korea, Russia, Sweden); Irfen (Switzerland); Isdol (Spain); Isodol (Spain); Lamidon (Japan); Librofem (Spain); Liptan (Japan); Lopane (Thailand); Medicol (Philippines); Mensoton (Germany); Mobilat (China); Motrin (Colombia, Ecuador, Mexico, Peru, Taiwan); Mynosedin (Japan); Nagifen-D (Japan); Napacetin (Japan); Neutropain (Hong Kong); Nobfelon (Japan); Nobgen (Japan); Norflam-T (South Africa); Norton (South Africa); Novogent (Germany); Novoprofen (Canada); Nureflex (France); Nurofen (Austria, Belgium, Czech Republic, Denmark, England, Malaysia, Netherlands, New Zealand, Philippines, Singapore, Sweden, Turkey); Nurofen for Children (Thailand); Nurofen Gel (Malaysia, New Zealand, Singapore, Thailand); Optifen (Switzerland); Opturem (Germany); Oren (Colombia); Ostarin (Indonesia); Ostofen (Thailand); Panafen (New Zealand); Pantrop (Japan); Perofen (Malaysia); Proartinal (Mexico); Profen (Hong Kong, Indonesia); Profeno (Thailand); Proris (Indonesia); Provon (Peru); Quadrax (Mexico); Ranofen (South Africa); Renidon (Philippines); Rhelafen (Indonesia); Rhelafen Forte (Indonesia); Roidenin (Japan); Rupan (Israel, Thailand); Schufen (Hong Kong); Solufen Lidose (Singapore); Spedifen (France); Spifen (France); Syntofene (France); Tabalon (Ecuador); Tabalon 400 (Mexico); Tatanal (Korea); Tofen (Thailand); Umafen (Thailand); Upfen (France); Uprofen (Taiwan); Urem (Germany); Zofen (Malaysia)

Drug Class	Analgesics, non-narcotic; Antipyretics; NSAIDs
Indications	Mild to moderate pain, fever, dysmenorrhea, osteoarthritis, rheumatoid arthritis
Mechanism	Inhibits cyclooxygenase and lipoxygenase, leading to reduced prostaglandin synthesis
Dosage with Qualifiers	Mild to moderate pain—400mg PO q4-6h; max 3200mg/d Fever—200-400mg PO q4-6h; max 1200mg/d Dysmenorrhea—400mg PO q4-6h; max 2400mg/d Osteoarthritis or rheumatoid arthritis—300-800mg PO tid or qid; take with food, max 3200mg/d • **Contraindications**—hypersensitivity to drug or class, ASA/NSAID-induced asthma, 3rd trimester pregnancy • **Caution**—hypertension, CHF, history of GI bleeding, nasal polyps
Maternal Considerations	About 5% of women report prenatal use of either **ibuprofen** or **naproxen** near conception or during pregnancy. In several different trials, the addition of **hydrocodone** significantly enhanced the analgesic efficacy of **ibuprofen.** In other trials, **ibuprofen** significantly reduced postabortal pain and was superior to **acetaminophen** for the treatment of postpartum pain and episiotomy after vaginal delivery. Prophylactic **ibuprofen** does not decrease the discomfort associated with IUD insertion. In one

prospective case-control study, prenatal **ibuprofen** or **naproxen** use increased the risk of spontaneous abortion by 80% (adjusted hazard ratio 1.8 [95% CI 1.0-3.2]). The association was stronger if the initial use was around conception or if it lasted more than a week. There is epidemiologic evidence linking it to PPH.
Side effects include renal failure, fluid retention, dyspepsia, GI bleeding, bronchospasm, thrombocytopenia, interstitial nephritis, hepatotoxicity, Stevens-Johnson syndrome, agranulocytosis, nausea, constipation, abdominal pain, headache, dizziness, rash, increased LFTs, tinnitus, and drowsiness.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. **Ibuprofen** crosses the human placenta and is found in meconium. Fetal levels are dependent on maternal, as NSAID agents are not metabolized by the fetal kidney.
Constriction of the fetal ductus arteriosus is reported, and it is similar in efficacy to **indomethacin** for closure of a neonatal PDA. There is epidemiologic evidence linking **ibuprofen** to gastroschisis. Similar adverse effects have been noted in rats where **ibuprofen** was associated with an increased prevalence of abdominal wall defects and VSD. **Ibuprofen** is as effective as **indomethacin** in closing the ductus arteriosus, but does not affect renal function to the same extent. In cows, **ibuprofen** actually enhances the rate of implantation.

Breastfeeding Safety

There are no adequate reports or well-controlled studies in nursing women. Only small amounts of **ibuprofen** are excreted into human breast milk. Less than 1mg is excreted in the breast milk of lactating women who ingest up to 400mg q6h.

Drug Interactions

Increased bleeding has been reported when using **ibuprofen** and other NSAIDs with coumarin-type anticoagulants.
Animal studies suggest that **aspirin** reduces the net anti-inflammatory activity of NSAIDs, including **ibuprofen.**
Probably reduces tubular secretion of **methotrexate** and thus may increase **methotrexate** toxicity.
May reduce the natriuretic effect of **furosemide** and thiazides in some patients. This response has been attributed to inhibition of renal prostaglandin synthesis.
Increases **lithium** levels some 15% by reducing renal **lithium** clearance 20%. This effect has been attributed to inhibition of renal prostaglandin synthesis.

References

Alano MA, Ngougmna E, Ostrea EM, Konduri GG. Pediatrics 2001; 107:519-23.
Burdan F, Szumilo J, Dudka J, et al. Braz J Med Biol Res 2006; 39:925-34.
Burdan F, Szumilo J, Dudka J, et al. Pharmacol Res 2006; 53:287-92.
Cuzzolin L, Dal Cere M, Fanos V. Drug Saf 2001; 24:9-18.
Elli M, Gaffuri B, Frigerio A, et al. Reproduction 2001; 121:151-4.
Hubacher D, Reyes V, Lillo S, et al. Am J Obstet Gynecol 2006; 195:1272-7.
Li DK, Liu L, Odouli R. BMJ 2003; 327:368-73.
Kamondetdacha R, Tanninandorn Y. J Med Assoc Thai 2008; 91:282-6.
Torfs CP, Katz EA, Bateson TF, et al. Teratology 1996; 54:84-92.
Townsend RJ, Benedetti TJ, Erickson SH, et al. Am J Obstet Gynecol 1984; 149:184-6.
Windle ML, Booker LA, Rayburn WF. J Reprod Med 1989; 34:891-5.

Summary

Pregnancy Category: B
Lactation Category: S

- Preconceptual **ibuprofen** may increase the risk of spontaneous abortion.
- 1st trimester exposure should be minimized until the completion of future studies in light of the association with gastroschisis.
- **Acetaminophen** (paracetamol) is the analgesic of choice in the 1st trimester if one must be used.
- **Ibuprofen** probably poses minimal risk when taken occasionally outside the 1st trimester.
- **Ibuprofen** is an excellent analgesic postpartum, though its efficacy is similar to that of other NSAIDs.

Ibutilide—(Corvert)

International Brand Name—None identified.

Drug Class

Antiarrhythmics, class III

Indications

Rapid conversion of recent atrial flutter/fibrillation

Mechanism

Prolongs phase 3 of the action potential

Dosage with Qualifiers

Rapid conversion of recent atrial flutter/fibrillation—0.01mg/kg IV over 10min, may repeat after 10min if no response; max 1mg/dose

- **Contraindications**—hypersensitivity to drug or class, use of a class I or III antiarrhythmic within 4h
- **Caution**—renal or hepatic dysfunction, prolonged QT interval, hypokalemia, polymorphic ventricular tachycardia

Maternal Considerations

There are no adequate reports or well-controlled studies of **ibutilide** in pregnant women. The published experience is limited to case reports and short series. Its efficacy is apparently uncompromised by pregnancy.
Side effects include bradycardia, sustained ventricular tachycardia, sustained polymorphic ventricular tachycardia, ventricular arrhythmias, tachycardia, prolonged QT interval, AV block, bradycardia, N/V, headache, and hypertension.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. Class III antiarrhythmic drugs such as **ibutilide** cause a spectrum of malformations in experimental teratology studies very similar to those reported for **phenytoin.** Class III antiarrhythmics decrease cardiac cell excitability by selectively blocking the rapid component of the I_{Kr}, an action shared with **phenytoin.** Malformations associated with selective and nonselective I_{Kr} blockers may be the dose-dependent product of embryonic bradycardia/arrhythmia resulting in (1) hypoxia, explaining embryonic death and growth restriction; (2) episodes of severe hypoxia, followed by generation of reactive oxygen species within the embryo during reoxygenation, causing orofacial clefts and distal digital reductions; and (3) alterations in embryonic blood flow and BP, inducing CV defects.

Breastfeeding Safety

There is no published experience in nursing women. It is unknown whether **ibutilide** enters human breast milk.

Drug Interactions

Supraventricular arrhythmias may mask the cardiotoxicity associated with excess **digoxin.** It is advisable to be particularly cautious in patients whose plasma **digoxin** levels are above or suspected to be above the therapeutic range.

References

Burkart TA, Kron J, Miles WM, et al. Pacing Clin Electrophysiol 2007; 30:283-6.
Danielsson BR, Skold AC, Azarbayjani F. Curr Pharm Des 2001; 7:787-802.
Kockova R, Kocka V, Kiernan T, Fahy GJ. J Cardiovasc Electrophysiol 2007; 18:545-7.
Marks TA, Terry RD. Teratology 1996; 54:157-64.

Summary

Pregnancy Category: C
Lactation Category: U

- **Ibutilide** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.
- There are other antiarrhythmic agents available for which there is more clinical experience during pregnancy and lactation.

Idarubicin—(Idamycin)

International Brand Name—Damycin (Mexico); Idamycin (Canada, Japan, Mexico); Idaralem (Mexico); Zavedos (Argentina, Austria, Brazil, Bulgaria, Chile, China, Colombia, Costa Rica, Czech Republic, Denmark, Dominican Republic, El Salvador, England, Finland, France, Germany, Greece, Guatemala, Honduras, Hong Kong, Hungary, India, Ireland, Italy, Korea, Malaysia, Netherlands, Nicaragua, Norway, Panama, Philippines, Portugal, South Africa, Spain, Sweden, Switzerland, Taiwan, Thailand, Turkey, Uruguay, Venezuela)

Drug Class

Antineoplastics, antibiotics

Indications

AML

Mechanism

Interacts with topoisomerase II and has an inhibitory effect on DNA synthesis

Dosage with Qualifiers

AML—varies with protocols

- **Contraindications**—hypersensitivity to drug or class, prior mediastinal radiation, prior use of either **daunorubicin** or **doxorubicin**
- **Caution**—unknown

Maternal Considerations

Idarubicin is an analog of **daunorubicin.** There are no adequate reports or well-controlled studies in pregnant women. The published experience is limited to case reports and short series. Its efficacy is apparently uncompromised by pregnancy.
Side effects include CHF, seizures, MI, ventricular arrhythmia, extravasation necrosis, myelosuppression, bleeding, enterocolitis, abdominal pain, infection, N/V, diarrhea, alopecia, mucositis, rash, pruritus, dyspnea, confusion, somnolence, cough, fever, and headache.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. **Idarubicin** apparently crosses the human placenta, as there are multiple case reports of fetal cardiotoxicity usually in the setting of polypharmacy. **Idarubicin** is embryotoxic and teratogenic in rodents at a fraction of the MRHD.

Breastfeeding Safety	There are no adequate reports or well-controlled studies in nursing women. It is unknown whether **idarubicin** enters human breast milk. However, considering its mechanism of action, it is perhaps best to avoid breastfeeding while **idarubicin** is administered.
Drug Interactions	No formal drug interactions studies performed.
References	Achtari C, Hohlfeld P. Am J Obstet Gynecol 2000; 183:511-2. Matsuo K, Shimoya K, Ueda S, et al. Gynecol Obstet Invest 2004; 58:186-8. Reynoso EE, Huerta F. Acta Oncol 1994; 33:709-10. Siu BL, Alonzo MR, Vargo TA, Fenrich AL. Int J Gynecol Cancer 2002; 12:399-402.
Summary	**Pregnancy Category: D** **Lactation Category: U** • **Idarubicin** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk. • **Idarubicin** poses a significant risk to the fetal heart.

Idoxuridine—(Dendrid; Imavate; Presamine)

International Brand Name—Apridin Gel (Korea); Citol Idoxuridina (Paraguay); Dendrid (Bulgaria, Czech Republic, Poland); Herpidu (Hong Kong, Malaysia, Switzerland, Taiwan, Thailand); Herplex (Ecuador, Israel); Herplex-D (Canada); Idina (Mexico); IDU (Germany); Idulea (Argentina); IDU Ophthalmic Solution (Japan); Iduridin (Denmark, Norway); Iduviran (France); Isotic Ixodine (Indonesia); Oftan IDU (Hungary); Ridinox (India); Stoxil (Malaysia, New Zealand, Thailand); Synmiol (Germany); Virusan (Israel)

Drug Class	Antivirals; Ophthalmics
Indications	HSV keratitis
Mechanism	Inhibits DNA synthesis
Dosage with Qualifiers	HSV keratitis—begin 1 gtt q1h until improvement, then q2h during the day and q4h at night • **Contraindications**—hypersensitivity to drug or class • **Caution**—unknown
Maternal Considerations	There is no published experience with **idoxuridine** during pregnancy. The quantity of drug absorbed systemically is unknown. ***Side effects*** include cloudy cornea, lacrimal punctual occlusions, blurred vision, and photophobia.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **idoxuridine** crosses the human placenta. Rodent studies reveal evidence of teratogenicity and embryotoxicity after systemic administration.
Breastfeeding Safety	There is no published experience in nursing women. It is unknown whether **idoxuridine** enters human breast milk.
Drug Interactions	Boric acid should not be co-administered since it may form a precipitate by interacting with ingredients in **idoxuridine.**
References	There is no published experience in pregnancy or during lactation.

Summary

Pregnancy Category: C
Lactation Category: U

- **Idoxuridine** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Imipenem-cilastin—(Primaxin)

International Brand Name—Pelastin IV (Indonesia); Prepenem (Korea); Primaxin (Canada, England, Greece); Tenacid (Italy); Tienam (Austria, Brazil, Chile, Colombia, Ecuador, Egypt, England, Germany, Greece, India, Indonesia, Ireland, Israel, Japan, Mexico, Peru, Poland, Slovenia, Turkey); Tienam 500 (South Africa); Zienam (Austria, Germany)

Drug Class

Antibiotics; Carbapenems

Indications

Serious bacterial infection

Mechanism

Bactericidal by inhibiting cell wall synthesis

Dosage with Qualifiers

Serious bacterial infection—250-1000mg IM/IV q12h; max 50mg/kg/d or 4000mg/d

NOTE: renal dosing.

- **Contraindications**—hypersensitivity to drug or class
- **Caution**—cephalosporin allergy, renal dysfunction, seizure disorder

Maternal Considerations

Imipenem-cilastin is broad-spectrum combination that achieves excellent pelvic tissue levels. Because of the relatively high cost, it is not considered "first-line" therapy for most obstetric and gynecologic infections. There are no adequate reports or well-controlled studies in pregnant women. The clearance of **imipenem-cilastin** is increased during pregnancy. Limited study reveals good clinical responses in women with chorioamnionitis or PPROM. While **imipenem-cilastin** provides effective prophylaxis for women undergoing nonelective cesarean delivery, it is no better than any other antibiotic agent used for this purpose. The selection of an agent for cesarean section prophylaxis typically is based on cost.
Side effects include pseudomembranous enterocolitis, seizures, thrombocytopenia, agranulocytosis, rash, diarrhea, oliguria, phlebitis, tachycardia, candidiasis, urine discoloration, gastroenteritis, elevated LFTs, elevated BUN/Cr, and N/V.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. **Imipenem-cilastin** crosses the human placenta, achieving an F:M ratio of only 0.3, while the AF:F ratio is 0.6. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically. Adverse outcomes in animal studies share an association with adverse maternal outcomes.

Breastfeeding Safety

There are no adequate reports or well-controlled studies in nursing women. Limited concentrations of **imipenem-cilastin** are excreted into human breast milk, though the kinetics remain to be elucidated. It is generally considered compatible with breastfeeding.

Drug Interactions

Probenecid produces only minimal increases in the plasma level of **imipenem** and should not be used.

Should not be mixed with or physically added to other antibiotics if given IV, though it may be if given IM.
Generalized seizures have been reported in patients who received **ganciclovir** and **imipenem-cilastin.**

References

Chimura T. Jpn J Antibiot 1994; 47:1762-8.
Heikkila A, Renkonen OV, Erkkola R. Antimicrob Agents Chemother 1992; 36:2652-5.
Matsuda S, Suzuki M, Oh K, et al. Jpn J Antibiot 1988; 41:1731-41.
Ryo E, Ikeya M, Sugimoto M. J Infect Chemother 2005; 11:32-6.

Summary

Pregnancy Category: C
Lactation Category: S

- **Imipenem-cilastin** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.
- There are alternative agents for which there is more experience during pregnancy and lactation.

Imipramine—(Imipramine Hcl; Imiprin; Janimine; Surplix; Tofnil; Tofranil; Tofranil-Pm)

International Brand Name—Antidep (India); Apo-Imipramine (Canada); Chrytemin (Japan); Daypress (Japan); Depsol (India); Depsonil (India); Ethipramine (South Africa); Fronil (Taiwan); Imidol (Japan); Imiprex (Israel); Melipramin (Czech Republic, Hungary, Poland); Melipramine (Australia); Primonil (Israel); Pryleugan (Germany); Psychoforin (Bulgaria); Sermonil (Thailand); Talpramin (Mexico); Tofranil (Argentina, Brazil, Canada, Chile, Colombia, Ecuador, Hong Kong, Indonesia, Japan, Malaysia, Mexico, Paraguay, Philippines, Taiwan, Uruguay, Venezuela); Venefon (Greece)

Drug Class

Antidepressants; Tricyclics

Indications

Depression, chronic pain, panic disorder

Mechanism

Inhibits NE and serotonin reuptake

Dosage with Qualifiers

Depression—begin 25-75mg PO qhs; max 300mg/d
Chronic pain—begin 0.2-0.3mg/kg PO qhs, increase by 50% q2-3d; max 300mg/d
Panic disorder—begin 25mg PO qhs

- **Contraindications**—hypersensitivity to drug or class, MAOI use within 14d, recovery from acute MI
- **Caution**—history of seizure, glaucoma, CAD, thyroid disease, hepatic dysfunction, suicide risk

Maternal Considerations

Depression is common during and after pregnancy but often goes unrecognized. Pregnancy is not a reason *a priori* to discontinue psychotropic drugs. **Imipramine** is the prototype TCA and is predominantly metabolized by hepatic CYP2D6. There are no adequate reports or well-controlled studies in pregnant women. It has been used extensively during pregnancy for the treatment of depression. **Imipramine** has also been used during pregnancy for the treatment of panic attack.
Side effects include MI, stroke, seizures, blood dyscrasias, thrombocytopenia, agranulocytosis, dry mouth, drowsiness, confusion, disorientation, blurred vision, and increased appetite.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. **Imipramine** binds to the placental serotonin

transporter, and presumably crosses the human placenta. It rapidly crosses the rodent placenta and is distributed throughout the fetus. While rodent teratogenicity studies are generally reassuring, several behavioral studies suggest prenatal exposure to **imipramine** alters postnatal adrenergic responses, serotonin uptake, and the response to stress.

Breastfeeding Safety

There are no adequate reports or well-controlled studies in nursing women. **Imipramine** is excreted into human breast milk, though the kinetics remain to be elucidated. It is estimated that, in women ingesting therapeutic doses of **imipramine,** the infant would ingest 0.2mg/L, or 30mcg/kg/d. Only about 3% of the maternal dose (per kg) of other tricyclics is consumed by the breastfed neonate.

Drug Interactions

CYP2D6 is reduced in a subset of Caucasians (about 7-10%) called "poor metabolizers". Reliable estimates of the prevalence of reduced CYP2D6 isozyme activity among Asian, African, and other populations are not yet available. Poor metabolizers have higher than expected plasma concentrations of TCAs when given usual doses. Depending on the fraction of drug metabolized by CYP2D6, the increase may be small or quite large.

Certain drugs inhibit CYP2D6 and make normal metabolizers resemble poor ones. An individual who is stable on a given dose of TCA may become abruptly toxic if given one of these inhibiting drugs. CYP2D6 inhibitors include some that are not metabolized by the enzyme (e.g., **cimetidine, quinidine**) and many that are substrates (many other antidepressants, phenothiazines, and the class 1C antiarrhythmics **propafenone** and **flecainide**). All SSRIs (e.g., **fluoxetine, paroxetine, sertraline**) inhibit CYP2D6 to greatly varying degrees. The extent to which SSRI-TCA interactions may pose clinical problems will depend on the degree of inhibition. Caution is indicated when using TCAs with any of the SSRIs and when switching from one class to the other. Of particular importance, sufficient time must elapse before initiating TCA treatment in a patient being withdrawn from **fluoxetine,** given the long t/2 (at least 5w may be necessary).

References

Ali SF, Buelke-Sam J, Newport GD, Slikker W Jr. Neurotoxicology 1986; 7:365-80.

Balkovetz DF, Tiruppathi C, Leibach FH, et al. J Biol Chem 1989; 264:2195-8.

DeVane CL, Simpkins JW. Drug Metab Dispos 1985; 13:438-42.

Erickson SH, Smith GH, Heidrich F. Am J Psychiatry 1979; 136:1483.

Harmon JR, Webb PJ, Kimmel GL, Delongchamp RR. Teratog Carcinog Mutagen 1986; 6:173-84.

Sovner R, Orsulak PJ. Am J Psychiatry 1979; 136(4A):451-2.

Ware MR, DeVane CL. J Clin Psychiatry 1990; 51:482-4.

Summary

Pregnancy Category: D

Lactation Category: S (likely)

- **Imipramine** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.
- As for most psychotropic drugs, using monotherapy and the lowest effective quantity given in divided doses to minimize the peaks may minimize the risks.
- Other, newer drugs may have better safety profiles.

Imiquimod—(Aldara)

International Brand Name—None identified.

Drug Class	Antivirals; Dermatologics; Immunomodulators
Indications	Genital warts
Mechanism	Unknown; induces the expression of multiple cytokines
Dosage with Qualifiers	Genital warts—apply hs 3×/w, wash off after 6-10h; max 16w • **Contraindications**—hypersensitivity to drug or class • **Caution**—unknown
Maternal Considerations	The published experience with **imiquimod** during pregnancy is limited to case reports. There are no studies of systemic absorption. ***Side effects*** include burning, hypopigmentation, pruritus, pain, fatigue, flu-like symptoms, headache, and diarrhea.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **imiquimod** crosses the human placenta. **Imiquimod** does not stimulate inflammatory cytokines when applied to cultured trophoblasts. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically.
Breastfeeding Safety	There is no experience in nursing women. However, it is unlikely, considering the dose and route, that any significant concentration of **imiquimod** enters human breast milk.
Drug Interactions	No clinically significant interactions identified.
References	Audisio T, Roca FC, Piatti C. Int J Gynaecol Obstet 2008; 100:275-6. Manlove-Simmons JM, Zaher FM, Tomai M, et al. Infect Dis Obstet Gynecol 2000; 8:105-11.
Summary	**Pregnancy Category: B** **Lactation Category: U** • **Imiquimod** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk. • Other treatment alternatives are available.

Immune globulin—(Biogam; Carimune; Gamimune N 5%; Gamimune N 10%; Gammagard S/D; Gammar-P I.V.; Immune Globulin; Iveegam En; Panglobulin; Polygam S/D; Sandoglobulin; Venoglobulin-S 5%; Venoglobulin-S 10%)

International Brand Name—Allerglobuline (South Africa); Aunativ (Israel); Baygam (Canada); Beriglobin (Austria, Germany, Israel, Sweden); Beriglobina (Brazil, Ecuador, Spain); Beriglobina P (Chile); Beriglobin P (Argentina, Taiwan); Beriglobin-P (South Africa); Citax F (Mexico); Endobulin (Czech Republic, England, Finland, South Africa); Endobuline (France); Flebogamma (Israel); Gamafine (India); Gamastan Immune Globulin (Israel); Gamimune N (Canada); Gamma 16 (Israel); Gammabulin (Hong Kong); Gammagard (Denmark, France, Hungary, Italy, Netherlands, Spain, Sweden); Gammagard S D (Canada, Hong Kong, Israel); Gammagard S/D (Malaysia); Gammonativ (Denmark, Germany, Israel, Norway, Sweden); Globuman Berna (Hong Kong, Malaysia, Peru, Philippines, South Africa, Taiwan, Thailand); IG Gamma (Israel, Philippines); Intraglobin (Germany, Italy, Switzerland, Taiwan); Intraglobin F (Israel, Thailand); IV Globulin-S (Korea); Octagam (France); Pentaglobin (Austria, Germany, Thailand); Sandoglobulin (Czech Republic, Denmark, Finland, Greece, Israel, Norway, Sweden, Switzerland); Sandoglobulina (Costa Rica, Dominican Republic, El Salvador, Guatemala, Honduras, Italy, Mexico, Nicaragua, Panama); Sandoglobuline (Belgium, France); Subcuvia (England); Venoglobulin-I (Malaysia); Venoglobulin S (Taiwan)

Drug Class ..... Immune globulins

Indications ..... ITP; alloimmune thrombocytopenia; primary immune deficiency diseases; B-cell chronic lymphocytic leukemia

Mechanism ..... Unknown; inhibits natural killer cell cytotoxicity

Dosage with Qualifiers .....

ITP—1g/kg IV; up to 3 doses on alternating days
Alloimmune thrombocytopenia (fetal therapy)—1-3g/kg IV qw from 15w until delivery
Primary immune deficiency diseases—200-400mg/kg IV ×1, then 100-300mg/kg IV qmo
B-cell chronic lymphocytic leukemia—400mg/kg IV q3-4w if hypogammaglobulinemia and/or recurrent bacterial infection

NOTE: a 5% solution initially should be infused at 0.5ml/kg/h; if well tolerated, the rate and concentration may be gradually increased to a maximum rate of 4ml/kg/h, and then the concentration increased to 10% concentration at 0.5ml/kg/h up to a maximum of 8ml/kg/h.

- **Contraindications**—hypersensitivity to drug or class, acute renal failure, chronic renal failure
- **Caution**—selective IgA deficiency, diabetes mellitus, age >65y, volume depletion, sepsis, paraproteinemia, concomitant use of known nephrotoxic drugs, CVD, prior thrombosis

Maternal Considerations .....

IV **immune globulin** (human) is a solvent/detergent treated, sterile, freeze-dried preparation of highly purified IgG derived from large pools of human plasma. The manufacturing process dramatically reduces the risk of viral transmission. The t/2 of **immune globulin** approximates 38d. **Epinephrine** should be available for treatment of any acute anaphylactic reactions. There are few well-controlled studies in pregnant women, but several on- and off-label indications deserve specific comment. In addition to the indications listed below, **immune globulin** has been used with apparent success during pregnancy for dermatomyositis, Churg-Strauss vasculitis, Guillain-Barré syndrome, and acquired hemophilia A.
ITP: ITP is a common hematologic disorder in young women. While ITP is a risk to both mother and neonate, there is no

convincing evidence it poses a risk to the fetus. Cesarean delivery is not indicated for ITP.

Alloimmune thrombocytopenia: It is now clear that maternal **immune globulin** therapy is primary treatment for fetal alloimmune thrombocytopenia. Empiric therapy (i.e., treatment of at-risk fetuses without a definitive diagnosis) is cost-effective. A high-dose weekly infusion (1-3g/kg) reduces the severity of fetal alloimmune thrombocytopenia and the risk of a fetal intracranial hemorrhage. The concurrent use of **dexamethasone** is not of added value, though nonresponders to **immune globulin** may benefit from the addition of **prednisone** 60mg PO qd. The mechanism is unknown. Maternal sera obtained after treatment with polyclonal immunoglobulin decrease constitutive and cytokine-induced ICAM-1 and VCAM-1 expression on endothelial cells. The initial fetal platelet count predicts the response to therapy, but apparently not the family history. Children with fetal alloimmune thrombocytopenia treated as fetuses have better long-term developmental-behavioral outcomes than untreated siblings, perhaps because of higher *in utero* platelet counts.

RBC alloimmunization: A number of pregnancies have been reported noting favorable outcomes with **immune globulin** (1-2g/kg qw) treatment of women with severe Rh factor disease, though that conclusion is not unanimous. Several combine immune globulin therapy with plasmapheresis. One explanation for an improved outcome would be decreased hemolysis. In support, several groups document either a decreased need for transfusion or a reduced carboxyhemoglobin level in rH factor–immunized neonates after **immune globulin** therapy. While therapy does not typically eliminate the need for fetal transfusion, it does appear to delay the gestation in which it must be started.

Recurrent abortion: The use of **immune globulin** in women with recurrent pregnancy loss remains controversial. In a recent meta-analysis, **immune globulin** was ineffective for the indication of primary recurrent abortion, but was associated with an increased the rate of live births in women with secondary recurrent miscarriage.

Side effects include anaphylaxis, urticaria, hypotension, headache, fatigue, chills, backache, leg cramps, light-headedness, fever, flushing, slight elevation of BP, N/V, thrombosis, aseptic meningitis syndrome, increased BUN/Cr, renal dysfunction, acute renal failure, osmotic nephrosis, and death.

■ Fetal Considerations

There are no adequate and well-controlled studies in human fetuses. Animal reproduction studies have not been conducted. IV **immune globulin** crosses the human placenta via the Fc′ receptors on the syncytiotrophoblast, as do endogenous immunoglobulins. However, not all commercial preparations have equal transport. Using an *in vitro* placental perfusion model, there was significant inhibition of placental anti-D IgG transfer with three commercial **immune globulin** preparations where the circulating maternal IgG concentrations were >20g/L. One product, which was not inhibitory, had lower circulating IgG levels (16.5 ± 0.9g/L) and significantly reduced placental transfer of total IgG, suggesting that the reduced functional activity of IgG from **immune globulin** preparations may correlate with poor clinical efficacy.

■ Breastfeeding Safety

There are no adequate reports or well-controlled studies in nursing women. It is unknown whether **immune globulin** enters human breast milk, though endogenous immunoglobulins are a normal component of breast milk.

Drug Interactions

Admixtures of **immune globulin** with other drugs and IV solutions have not been evaluated. They should be administered separately.

Antibodies in **immune globulin** preparations may interfere with patient responses to live vaccines, such as those for measles, mumps, and rubella.

References

Bussel JB, Berkowitz RL, Lynch L, et al. Am J Obstet Gynecol 1996; 174:1414-23.

Bussel JB, Berkowitz RL, McFarland JG, et al. N Engl J Med 1988; 319:1374-8.

Chitkara U, Bussel J, Alvarez M, et al. Obstet Gynecol 1990; 76:703-8.

Devendra K, Koh LP. Ann Acad Med Singapore 2002; 31:276-80.

Ergaz Z, Gross D, Bar-Oz B, et al. Vox Sang 1995; 69:95-9.

Gaddipati S, Berkowitz RL, Lembet AA, et al. Am J Obstet Gynecol 2001; 185:976-80.

Hot A, Perard L, Coppere B, et al. Clin Rheumatol 2007; 26:2149-51.

Hutton B, Sharma R, Fergusson D, et al. BJOG 2007; 114:134-42.

Landor M, Rubinstein A, Kim A, et al. Int Arch Allergy Immunol 1998; 115:203-9.

Practice Committee of the American Society for Reproductive Medicine. Fertil Steril 2006; 86(Suppl):S226-7.

Radder CM, Beekhuizen H, Kanhai HH, Brand A. Clin Exp Immunol 2004; 137:216-22.

Ruma MS, Moise KJ Jr, Kim E, et al. Am J Obstet Gynecol 2007; 196:138.e1-6.

Spencer JA, Burrows RF. Aust N Z J Obstet Gynaecol 2001; 41:45-55.

Thung SF, Grobman WA. Am J Obstet Gynecol 2005; 193:1094-9.

Urbaniak SJ, Duncan JI, Armstrong-Fisher SS, et al. Br J Haematol 1999; 107:815-7.

Voto LS, Sexer H, Ferreiro G, et al. J Perinat Med 1995; 23:443-51.

Ward MJ, Pauliny J, Lipper EG, Bussel JB. Am J Perinatol 2006; 23:487-92.

Williams L, Chang PY, Park E, et al. Obstet Gynecol 2007; 109:561-3.

Summary

Pregnancy Category: C
Lactation Category: S

- **Immune globulin** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.
- All infections thought transmitted by IV **immune globulin** should be reported by the health care provider to Baxter Healthcare Corporation, Hyland Immuno at 1-800-423-2862 (in the US).
- The physician should discuss the risks and benefits of this product with the patient.

Indapamide—(Depermide; Lozol; Natralix)

International Brand Name—Agelan (Hong Kong, Ireland); Damide (Italy); Dapa (Malaysia); Dapamax (South Africa, Tanzania, Uganda, Zambia, Zimbabwe); Diflerix (Hong Kong, Taiwan); Dixamid (Greece); Extur (Spain); Fludex (Austria, Belgium, Denmark, France, Greece, Netherlands, Portugal, Switzerland, Turkey); Fludex SR (Korea); Frumeron (Thailand); Hydro-Less (South Africa); Indahexal (Australia); Indalix (Hong Kong, South Africa); Indapam (Korea); Indapress (Chile); Indicontin Continus (Hong Kong); Inpamide (Thailand); Insig (Australia); Ipamix (Italy); Lorvas (India); Lozide (Canada); Magniton-R (Greece); Millibar (China, Singapore, Taiwan); Napamide (Malaysia, New Zealand, Singapore, Thailand); Naplin (New Zealand); Natrilix (Argentina, Brazil, China, Colombia, Costa Rica, Ecuador, El Salvador, England, Finland, Germany, Guatemala, Honduras, Hong Kong, India, Indonesia, Ireland, Italy, Malaysia, New Zealand, Nicaragua, Panama, Peru, South Africa, Taiwan, Uruguay, Venezuela); Natrilix SR (Australia, Costa Rica, El Salvador, Germany, Guatemala, Honduras, India, Nicaragua, Panama, Paraguay, Philippines, Singapore, Uruguay); Natrix (Japan); Natrix SR (Korea); Pamid (Israel); Rinalix (Malaysia, Singapore); Sicco (Germany); Tandix (Portugal); Tertensif (Bulgaria, Czech Republic, Finland, Poland, Spain)

Drug Class	Diuretics; Thiazides
Indications	Hypertension, CHF
Mechanism	Inhibits sodium and chloride reabsorption by the distal convoluted tubule; depresses smooth muscle contractility by reducing inward calcium and sodium and outward potassium currents
Dosage with Qualifiers	Hypertension—begin 1.25mg PO qam, increase if no response after 1w; max 5mg/d CHF—begin 2.5mg PO qam, increase if no response after 1w; max 5mg/d • **Contraindications**—hypersensitivity to drug or class, hypersensitivity to sulfonamides, hepatic or renal failure, anuria • **Caution**—unknown
Maternal Considerations	There is no published experience with **indapamide** during pregnancy. Diuretics should not be used for the treatment of physiologic edema during pregnancy. ***Side effects*** include ventricular arrhythmia, hypokalemia, hyponatremia, hyperuricemia, rash, abdominal pain, orthostatic hypotension, N/V, muscle cramps, fatigue, vertigo, and pruritus.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **indapamide** crosses the human placenta. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically. However, other thiazide diuretics have neonatal sequelae.
Breastfeeding Safety	There is no published experience in nursing women. It is unknown whether **indapamide** enters human breast milk.
Drug Interactions	**Lithium** toxicity is closely related to serum **lithium** levels and can occur at close to therapeutic levels. May add to or potentiate the hypotensive action of other antihypertensive drugs. Antihypertensive effect may be enhanced in the post-sympathectomized patient. May decrease arterial responsiveness to NE, but this diminution is not sufficient to preclude effectiveness of the pressor agent for therapeutic use.
References	There is no published experience in pregnancy or during lactation.

Summary

Pregnancy Category: B
Lactation Category: U

- **Indapamide** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.
- There are alternative agents for which there is more experience during pregnancy and lactation.

Indinavir—(Crixivan; MK-639)

International Brand Name—3TC (Argentina, Canada, Costa Rica, Dominican Republic, El Salvador, Guatemala, Honduras, Hong Kong, Indonesia, Korea, Malaysia, Mexico, New Zealand, Nicaragua, Panama, South Africa, Uruguay); Crixivan (Hong Kong, Israel, Korea, Malaysia, Philippines, Singapore, South Africa, Taiwan, Thailand); Elvenavir (Argentina); Indivan (Paraguay); Indivir (India)

Drug Class

Antivirals; Protease inhibitors

Indications

HIV infection

Mechanism

Protease inhibitor

Dosage with Qualifiers

HIV infection—800mg PO q8h; drink at least 1.5L water qd

NOTE: reduce dose for hepatic dysfunction.

- **Contraindications**—hypersensitivity to drug or class; history of nephrolithiasis; concurrent use of **astemizole, cisapride, midazolam,** or **triazolam**
- **Caution**—hepatic dysfunction, diabetes mellitus

Maternal Considerations

Indinavir is effective reducing the maternal HIV viral load to an undetectable level, especially when combined with other agents such as a nucleoside analog or a reverse transcriptase inhibitor. In one study of 4 women, clearance was increased during pregnancy as reflected in the decreased AUC. In another longitudinal study, **indinavir** AUC was 68% lower antepartum compared to postpartum, suggesting increased intestinal and/or hepatic CYP3A activity during pregnancy.
Side effects include nephrolithiasis, diabetes mellitus, N/V, diarrhea, abdominal pain, insomnia, headache, hyperbilirubinemia, hyperlipidemia, hyperglycemia, anorexia, dry mouth, malaise, taste changes, and the lipodystrophy syndrome.

Fetal Considerations

Indinavir crosses the human placenta, though the magnitude of fetal-to-maternal transfer in the isolated cotyledon is 2-3× greater than maternal-to-fetal transfer, suggesting fetal exposure is minimal. Transport is via P-glycoprotein. These *in vitro* findings are confirmed by umbilical cord blood samples. In one series, the majority of pregnancies treated had some adverse outcome, though the relationship of the retroviral therapies to the outcome was unclear. Certainly, the prevention of HIV transmission remains the ultimate priority. Though most premarketing rodent teratogenicity studies are reassuring, **indinavir** was associated in one study with delayed growth, and skeletal and ophthalmic abnormalities.

Breastfeeding Safety

There is no adequate experience in nursing women. **Indinavir** does enter human breast milk, and in a single case the M:P ratio was 5.4. It is excreted into rat breast milk. Regardless, breastfeeding is contraindicated in HIV-infected nursing women

where formula is available to reduce the risk of neonatal transmission.

Drug Interactions

Delavirdine increases the **indinavir** plasma concentration and a dosage reduction may be indicated.
Efavirenz decreases the **indinavir** plasma concentration and a dosage increase may be indicated.
Itraconazole and **ketoconazole** inhibit CYP3A4; both increase **indinavir** plasma concentrations and a dosage reduction of **indinavir** is recommended.
There is an increase in the plasma **rifabutin** concentration and a decrease in the plasma **indinavir** concentration when both are given. The dosage of both drugs will require appropriate alteration.
Should not be co-administered with **rifampin**. It is a potent CYP3A4 inducer that markedly reduces **indinavir** plasma concentrations.
Interactions between **indinavir** and less potent CYP3A4 inducers such as **phenobarbital, phenytoin, carbamazepine,** and **dexamethasone** have not been studied. These agents should be used with caution.
Calcium channel blockers are metabolized by CYP3A4, which is inhibited by **indinavir.** Use of **indinavir** with calcium channel blockers may result in increased concentrations of the calcium channel blockers that can increase or prolong their therapeutic and adverse effects.
Indinavir and **didanosine** should be administered on an empty stomach at least 1h apart as a normal gastric pH is necessary for optimal absorption. In contrast, acid rapidly degrades **didanosine,** which is formulated with buffering agents.

References

Colebunders R, Hodossy B, Burger D, et al. AIDS 2005; 19:1912-5.
Kosel BW, Beckerman KP, Hayashi S, et al. AIDS 2003; 17:1195-9.
Lorenzi P, Spicher VM, Laubereau B, et al. AIDS 1998; 12:F241-7.
Mirochnick M, Dorenbaum A, Holland D, et al. Pediatr Infect Dis J 2002; 21:835-8.
Riecke K, Schulz TG, Shakibaei M, et al. Teratology 2000; 62:291-300.
Sudhakaran S, Ghabrial H, Nation RL, et al. Antimicrob Agents Chemother 2005; 49:1023-8.
Sudhakaran S, Rayner CR, Li J, et al. Br J Clin Pharmacol 2007; 63:315-21.
Unadkat JD, Wara DW, Hughes MD, et al. Antimicrob Agents Chemother 2007; 51:783-6.

Summary

Pregnancy Category: C
Lactation Category: NS

- **Indinavir** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.
- Drug clearance is increased during pregnancy, suggesting that either the dose be increased or the plasma levels be monitored.
- Reduction of the maternal viral load to undetectable levels remains the prime goal.
- Physicians are encouraged to register pregnant women under the Antiretroviral Pregnancy Registry (1-800-258-4263) for a better follow-up of the outcome while under treatment with **indinavir.**

Indomethacin—(Indocin)

International Brand Name—Agilex (Argentina); Amuno (Germany); Amuno Retard (Germany); Antalgin Dialicels (Mexico); Apo-Indomethacin (Canada); Areumatin (Indonesia); Argilex (Argentina); Arthrexin (Australia, South Africa); Articulen (South Africa); Artrilona S (Uruguay); Artrinovo (Spain); Asimet (Malaysia); Benocid (Indonesia); Betacin (South Africa); Bonidon (Costa Rica, Dominican Republic, Ecuador, El Salvador, Guatemala, Nicaragua, Panama); Catlep (Japan); Chrono-Indocid (France); Confortid (Denmark, Finland, Israel, Norway, Sweden, Switzerland); Confortid Retard (Denmark); Confortid Retardkapseln (Switzerland); Docin (Thailand); Dolazal (Netherlands); Dometin (Netherlands); Durametacin (Germany); Elmego Spray (Thailand); Elmetacin (Germany, New Zealand); Flamaret (South Africa); Grindocin (Mexico); IDC (Thailand); Idicin (India); IM-75 (Argentina); Imbrilon (England, Ireland); Imet (Italy, South Africa); Inacid (Spain); Indacin (Japan); Indalgin (Taiwan); Indo (Malaysia, Singapore); Indocap (India); Indocap S.R. (India); Indocid (Argentina, Austria, Belgium, Brazil, Canada, Denmark, England, France, Greece, Hong Kong, Israel, Malaysia, Mexico, Netherlands, Norway, Peru, Philippines, Portugal, Switzerland, Taiwan, Thailand, Venezuela); Indocid R (Hong Kong); Indocid-R (New Zealand); Indocolir (Germany); Indocollyre (France, Hong Kong, Israel, Korea); Indogesic (Hong Kong, Israel); Indolag (Israel, Puerto Rico, South Africa); Indolar SR (England); Indomecin (Colombia); Indomed (Israel); Indomed F (Thailand); Indomee (Sweden); Indomelan (Austria); Indometicina McKesson (Costa Rica, Dominican Republic, El Salvador, Guatemala, Honduras, Nicaragua, Panama); Indometin (Finland); Indomin (Israel); Indono (Thailand); Indo-Phlogont (Germany); Indorem (Puerto Rico); Indosima (Paraguay); Indo-Tablinen (Germany); Indotard (Israel); Indovis (Israel); Indoy (Taiwan); Indrenin (Czech Republic); Indylon (South Africa); Inflazon (Japan); Lauzit (Japan); Malival (Mexico); Malival AP (Mexico); Metacen (Italy); Methacin (Malaysia); Methocaps (South Africa); Metindol (Bulgaria, Czech Republic, Poland, Thailand); Novomethacin (Canada); Reumacid (Israel); Reusin (Spain); Rheumacid (South Africa); Rheumacin (New Zealand); Rheumacin SR (New Zealand); Salinac (Japan); Sidocin (Taiwan); Vi-Gel (Philippines); Vonum (Germany)

Drug Class	Analgesics, non-narcotic; Antiarthritics; NSAIDs; Anti-inflammatories
Indications	Dysmenorrhea, mild to moderate pain, osteoarthritis or rheumatoid arthritis, tocolysis
Mechanism	Inhibits cyclooxygenase and lipoxygenase, leading to reduced prostaglandin synthesis
Dosage with Qualifiers	Dysmenorrhea—25mg PO tid or qid Mild to moderate pain—25-50mg PO tid prn Osteoarthritis or rheumatoid arthritis—begin 25mg PO bid or tid, or 50mg prn qid, increase by 25-50mg q7d; max 200mg/d Tocolysis—50mg PR or PO load, then 25mg PO/PR q6h ×2d *NOTE: available in liquid, tablet, and suppository.* • **Contraindications**—hypersensitivity to drug or class, ASA/NSAID-induced asthma, 3rd trimester pregnancy • **Caution**—hypertension, CHF, history of GI bleeding, nasal polyps
Maternal Considerations	**Indomethacin** is used off-label for the treatment of presumed preterm labor. In that scenario, it significantly prolongs gestation (48-72h), a degree similar to β-mimetic agents and, in small trials, **magnesium sulfate.** The latter is relevant since in meta-analyses **magnesium sulfate** is no better than placebo for tocolysis. The interval is adequate for the administration of corticosteroids to enhance fetal lung maturity. **Indomethacin** is no better and likely inferior to calcium channel blockers such as **nifedipine,** which has a stronger safety profile. Continuing **indomethacin** after the successful treatment of presumed preterm labor does not further delay delivery or enhance outcome and should not be condoned. Similarly, **indomethacin** is advocated for the treatment of the sonographically detected short cervix. Here, too, there is little quality evidence to support the practice. It does not appear to delay preterm delivery of women with a dilated cervix independent of cerclage. **Indomethacin** has multiple non–prostaglandin-related actions, including the inhibition of MMPs 2 and 9 in amnion, chorion, and decidua. Such actions may contribute to its

anti-inflammatory effect. **Indomethacin** reduces renal free water clearance and can cause abrupt maternal weight gain and edema when first initiated. **Indomethacin** should probably be avoided in women at risk for delivery within 24h, as a 50mg dose reproducibly prolongs the maternal bleeding time, in half of which cases will reach abnormal levels.
Side effects include renal failure, fluid retention, dyspepsia, GI bleeding, bronchospasm, thrombocytopenia, interstitial nephritis, hepatotoxicity, Stevens-Johnson syndrome, agranulocytosis, nausea, constipation, abdominal pain, headache, dizziness, rash, increased LFTs, tinnitus, and drowsiness.

Fetal Considerations

Indomethacin crosses the placenta, and fetal sequelae are common. Fetal levels are dependent on maternal, as NSAIDs are not metabolized by the fetal kidney. A third of fetuses exposed to **indomethacin** for 1w or more develop oligohydramnios or evidence of ductal constriction. These adverse effects are completely avoidable as there are no demonstrable benefits over the long term for the indication of preterm labor or incompetent cervix. Other prostaglandin synthase inhibitors reputedly have a lower incidence of fetal sequelae when used as a tocolytic agent, though the quantity of clinical experience is much smaller than that for **indomethacin.** These differences are clear in the neonate when comparing **ibuprofen** to **indomethacin** for the closure of a PDA. Because of its effect on fetal urine output, **indomethacin** is used to treat idiopathic polyhydramnios. It should not, however, be used in twin gestations complicated by the so-called stuck twin, or the ''oligo-polyhydramnios sequence.'' In this scenario, there is no evidence that **indomethacin** prolongs gestation, and it can lead to fetal renal shutdown. The effects of **indomethacin** on the fetal kidneys are dose- and duration-dependent. Stopping it typically results in reversal of the abnormal sonographic findings. **Indomethacin** is used postnatally for the pharmacologic closure of a PDA. Constriction of the fetal ductus is common when **indomethacin** is used for the treatment of preterm labor. It, too, reverses with cessation, and the long-term impact of *in utero* ductal constriction on the otherwise healthy fetus is currently unknown. A short course (<48h) of **indomethacin** for the treatment of preterm labor does not alter the newborn's responsiveness to **indomethacin** postnatally. In uncontrolled trials, **indomethacin** tocolysis was associated with an increased risk of IVH and NEC in the neonate. These reports remain to be confirmed. In other uncontrolled studies, neurodevelopment was unaffected by antenatal exposure.

Breastfeeding Safety

There are no adequate reports or well-controlled studies in nursing women. The quantity of **indomethacin** excreted into human breast milk is low, such that the breastfed neonate would ingest <1% of the maternal dose per day. Neonatal plasma levels are typically below detection.

Drug Interactions

Diflunisal should not be used. It decreases the renal clearance and significantly increases the plasma concentration of **indomethacin.** Combined use has been associated with fatal GI hemorrhage. Should not be used with other NSAIDs. Chronic concurrent administration of **aspirin** decreases **indomethacin** concentration some 20%.
Patients receiving oral anticoagulants should be observed for a change in their PT if **indomethacin** is added.
Probenecid increases the **indomethacin** plasma level. Therefore, a lower total daily dosage of **indomethacin** may produce a satisfactory therapeutic effect.

Decreases the tubular secretion of **methotrexate** and may potentiate its toxicity.
NSAIDs increase **cyclosporine**-induced toxicity, possibly due to decreased synthesis of renal prostacyclin. NSAIDs should be used with caution in patients taking **cyclosporine,** and renal function should be carefully monitored.
A clinically relevant increase in the plasma **lithium** level results from a decrease in renal **lithium** clearance. This effect is attributed to inhibition of prostaglandin synthesis.
May increase the serum concentration and prolong the t/2 of **digoxin.** Serum **digoxin** levels should be closely monitored when **indomethacin** and **digoxin** are used together.
In some patients, **indomethacin** reduces the diuretic, natriuretic, and antihypertensive effects of loop, potassium-sparing, and thiazide diuretics. The patient should be observed closely to determine if the desired diuretic effect is obtained.
Reduces basal plasma renin activity (PRA), as well as those elevations of PRA induced by **furosemide** or by salt or volume depletion.
Should not be administered with **triamterene** as it may cause reversible acute renal failure.
May cause hyperkalemia in patients on potassium-sparing diuretics.
NSAIDs may blunt the antihypertensive effect of β-adrenoceptor blockers. Patients should be observed carefully to confirm the desired therapeutic effect.
May reduce the antihypertensive effect of **captopril.**
May cause a false-negative **dexamethasone** suppression test.

References

Amin SB, Kamaluddeen M, Sangem M. Am J Obstet Gynecol 2008; 199:41.e1-8.
Berghella N, Prasentcharo-Ensuk W, Cotter A, et al. Am J Perinatal 2008 Nov 19(Epub ahead of print).
Besinger RE, Niebyl JR, Keyes WG, Johnson TR. Am J Obstet Gynecol 1991; 164:981-6.
Bivins HA Jr, Newman RB, Fyfe DA, et al. Am J Obstet Gynecol 1993; 169:1065-70.
Carlan SJ, O'Brien WF, O'Leary TD, Mastrogiannis D. Obstet Gynecol 1992; 79:223-8.
Cordero L, Nankervis CA, Gardner D, Giannone PJ. J Perinatol 2007; 27:22-7.
Gyetvai K, Hannah ME, Hodnett ED, Ohlsson A. Obstet Gynecol 1999; 94:869-77.
Iannucci TA, Besinger RE, Fisher SG, et al. Am J Obstet Gynecol 1996; 175:1043-6.
King JF, Flenady VJ, Papatsonis DN, et al. Cochrane Database Syst Rev 2002; (2):CD002255.
Lebedevs TH, Wojnar-Horton RE, Yapp P, et al. Br J Clin Pharmacol 1991; 32:751-4.
Lunt CC, Satin AJ, Barth WH Jr, Hankins GD. Obstet Gynecol 1994; 84:820-2.
Newton ER, Shields L, Ridgway LE 3rd, et al. Am J Obstet Gynecol 1991; 165:1753-9.
Restaino I, Kaplan BS, Kaplan P, et al. Am J Med Genet 1991; 39:252-7.
Robin YM, Reynaud P, Orliaguet T, et al. Pathol Res Pract 2000; 196:791-4.
Suarez RD, Grobman WA, Parilla BV. Obstet Gynecol 2001; 97:921-5.
Ulug U, Goldman S, Ben-Shlomo I, Shalev E. Mol Hum Reprod 2001; 7:1187-93.

Weintraub Z, Solovechick M, Reichman B, et al. Arch Dis Child Fetal Neonatal Ed 2001; 85:F13-7.

Summary

Pregnancy Category: B
Lactation Category: S

- **Indomethacin** is popular as a tocolytic agent allowing for the administration of corticosteroids.
- **Indomethacin** has a significant impact on the fetal and at times maternal renal and CV systems.
- Chronic therapy with **indomethacin** for short/dilated cervix or prior preterm labor does not delay delivery and is discouraged outside of a research setting.
- **Indomethacin** should be used during pregnancy only if the benefit justifies the potential perinatal risk.

Infliximab—(Remicade)

International Brand Name—Remicade (Argentina, Brazil, Canada, Chile, Colombia, Hong Kong, Israel, Korea, Malaysia, Mexico, Peru, Philippines, Singapore, Thailand, Venezuela); Revellex (South Africa)

Drug Class

Anti-inflammatories; Antirheumatics; Inflammatory bowel disease agents; Monoclonal antibodies; Tumor necrosis factor modulators

Indications

Crohn's disease, rheumatoid arthritis

Mechanism

A chimeric monoclonal antibody that binds and inhibits TNF-α

Dosage with Qualifiers

Crohn's disease, moderate to severe—5mg/kg IV ×1
Crohn's disease, fistulizing—5mg/kg IV ×1 for weeks 0, 2, 6
Rheumatoid arthritis—begin 3mg/kg IV ×1 for weeks 0, 2, 6; may increase dose up to 10mg/kg

- **Contraindications**—hypersensitivity to drug or class, hypersensitivity to mouse proteins, active infection
- **Caution**—pregnancy, MS, chronic or recurrent infections, latent TB, demyelinating disease

Maternal Considerations

There are no adequate reports or well-controlled studies of **infliximab** use during pregnancy. The current experience is limited to case reports and small series.
Side effects include sepsis, opportunistic infections, worsening of CHF, chest pain, serum sickness–like reaction, lupus-like syndrome, fever, chills, myalgias, backache, arthralgias, dizziness, N/V, dyspepsia, pruritus, rash, URI, UTI, hypertension, hypotension, facial or hand edema, and elevated LFTs.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. It appears that **infliximab** crosses the human placenta. Limited case reports are reassuring. Rodent teratogenicity studies have not been performed.

Breastfeeding Safety

There are no adequate reports or well-controlled studies in nursing women. **Infliximab** is a high-MW antibody. No drug was detected in 2 women studied over multiple time points.

Drug Interactions

Use with **etanercept** (another TNF-α–blocking agent) and **anakinra** (an IL-1 antagonist) increases the risks of serious

infection and neutropenia without providing any additional benefit compared to these drugs alone.

References

Hale TW. Medications and Mother's Milk, 10th ed. Amarillo, TX: Pharmasoft Publishing, 2002:374.
Mahadevan U, Kane S, Sandborn WJ, et al. Aliment Pharmacol Ther 2005; 21:733-8.
Roux CH, Brocq O, Breuil V, et al. Rheumatology (Oxford) 2007; 46:695-8.
Srinivasan R. Am J Gastroenterol 2001; 96:2274-5.
Vasiliauskas EA, Church JA, Silverman N, et al. Clin Gastroenterol Hepatol 2006; 4:1255-8.

Summary

Pregnancy Category: C
Lactation Category: S (likely)

- **Infliximab** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.
- Early experience in women with medically significant diseases is reassuring.

Influenza vaccine—(Fluimmune; Fluogen; Flu Shield; Flushield; Fluvirin; Fluzone)

International Brand Name—Agrippal (England, Ireland, Italy, Philippines, South Africa); Agrippal S1 (Hong Kong); Alorbat (Germany); Begrivac (Austria, Germany); Begrivac F (Israel); Fluad (Hong Kong); Fluarix (Argentina, Australia, Brazil, Chile, Hong Kong, Mexico, New Zealand); Fluviral S/F (Canada); Fluvirin (England, Ireland); Fluvirine (France); Fluzone (Canada, England, Ireland); Hiberix (Australia, Costa Rica, El Salvador, Guatemala, Honduras, India, Nicaragua, Panama, Peru, Taiwan, Thailand); Inflexal (Austria, Italy, Spain); Inflexal Berna (Philippines, South Africa); Inflexal Berna Polyvalent Vaccine (Malaysia); Inflexal V (England, Ireland); Influvac (Australia, South Africa); Mastaflu (England, Ireland); Mutagrip (Belgium, France, Germany, Netherlands, Spain); Sandovac (Austria); Vaxigrip (Austria, Belgium, Bulgaria, Denmark, France, Greece, Hong Kong, India, Israel, Korea, Netherlands, New Zealand, Norway, Philippines, South Africa); X-Flu (South Africa)

Drug Class

Vaccines

Indications

Nonimmune status

Mechanism

Active immunity

Dosage with Qualifiers

Nonimmune status—0.5ml IM ×1

- **Contraindications**—hypersensitivity to drug or class, hypersensitivity to eggs, past history of Guillain-Barré syndrome, active febrile illness
- **Caution**—unknown

Maternal Considerations

All pregnant women >12w gestation should be vaccinated in preparation for influenza season. Pregnant women have increased susceptibility to viral respiratory diseases, and the most common one is influenza. Influenza-associated excess mortality during pregnancy was documented during the pandemics of 1918-1919 and 1957-1958. The increased risk might result from (1) increased HR, stroke volume, and oxygen consumption; (2) decreased lung capacity; and (3) changes in immunologic function. A study during 17 interpandemic influenza seasons revealed that the relative risk for hospitalization for cardiorespiratory conditions during pregnancy increased from 1.4 between 14 and 20w gestation to 4.7 between 37 and 42w

gestation, compared to women 1-6mo postpartum. Researchers estimate that an average of 1-2 hospitalizations can be prevented for every 1000 pregnant women vaccinated. Thus, all women who intend to become pregnant or are pregnant should receive the **influenza vaccine.** Vaccination can occur in any trimester. One study of influenza vaccination of >2000 pregnant women demonstrated no adverse fetal effects associated with **influenza vaccine.** If a pregnant woman develops influenza, she should be treated with supportive care. Antiviral medications should be reserved for cases where the benefits outweigh the risks.
Side effects include sepsis, opportunistic infections, worsening of CHF, chest pain, serum sickness–like reaction, lupus-like syndrome, fever, chills, myalgias, backache, arthralgias, dizziness, N/V, dyspepsia, pruritus, rash, URI, UTI, hypertension, hypotension, facial or hand edema, and elevated LFTs.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **influenza vaccine** crosses the human placenta. Vaccine-stimulated IgG crosses the placenta, perhaps conveying some degree of passive immunity, and it was recently reported that B- and T-cell immune responses occur in the fetus after influenza vaccination. Maternal influenza vaccination reduces respiratory illness rates in their infants by almost ⅔ up to 6m of age. There is no evidence heat-killed vaccine is teratogenic if given in the 1st trimester. Rodent teratogenicity studies have not been performed.

Breastfeeding Safety

There is no published experience in nursing women. It is unknown whether **influenza vaccine** enters human breast milk. It is likely the stimulated maternal IgG is excreted into the breast milk.

Drug Interactions

There are conflicting reports on the effects of **influenza vaccine** on the elimination of some drugs metabolized by the hepatic CYP system.
Hypoprothrombinemia in patients receiving **warfarin** and elevated serum **theophylline** concentrations have occurred.
Patients with impaired immune responsiveness, whether due to immunosuppressive therapy (including irradiation, large amounts of corticosteroids, antimetabolites, alkylating agents, and cytotoxic agents), a genetic defect, HIV infection, leukemia, lymphoma, generalized malignancy, or other causes, may have a reduced antibody response to active immunization procedures. If feasible, specific serum antibody titers or other immunologic responses may be determined after immunization to assess immunity. Chemoprophylaxis may be indicated for high-risk persons who are expected to have a poor antibody response to **influenza vaccine.** Short-term (<2w) corticosteroid therapy or intra-articular, bursal, or tendon injections with corticosteroids should not be immunosuppressive. Inactivated vaccines are not a risk to immunocompromised individuals, although their efficacy may be substantially reduced.

References

Goldman RD, Koren G. Can Fam Physician 2002; 48:1768-9.
Heinonen OP, Shapiro S, Monson RR, et al. Int J Epidemiol 1973; 2:229-35.
Irving WL, James DK, Stephenson T, et al. BJOG 2000; 107:1282-9.
Neuzil KM, Reed GW, Mitchel EF, et al. Am J Epidemiol 1998; 148:1094-102.
Rastogi D, Wang C, Mao X, et al. J Clin Invest 2007; 117:1637-46.
Ressel GW. Am Fam Physician 2002; 66:894-9.

Sumaya CV, Gibbs RS. J Infect Dis 1979; 140:141-6.
Zaman K, Roy E, Arifeen SE, et al. N Engl J Med 2008; 359:1555-64.

Summary

Pregnancy Category: C
Lactation Category: S (likely)
- Pregnant women >12w gestation should be vaccinated in preparation for influenza seasons.

Insulin aspart—(NovoLog)

International Brand Name—NovoMix 30 (Australia, Israel); Novorapid (Israel)

Drug Class

Antidiabetic agents; Hypoglycemics

Indications

Diabetes mellitus

Mechanism

Stimulates peripheral glucose uptake, inhibits hepatic glucose production, inhibits adipocyte lipolysis, inhibits proteolysis, and enhances protein synthesis

Dosage with Qualifiers

Diabetes mellitus—individualized; should include an intermediate- or long-acting insulin

NOTE: give SC <15min qac, onset <0.5h, peak 0.1-3h, max duration 3-5h.
DKA—begin 0.1U/kg IV bolus, then 0.1U/kg/h infusion; decrease infusion rate when glucose <275mg/dl

- **Contraindications**—hypersensitivity to drug or class, hypoglycemia
- **Caution**—hypokalemia, renal or hepatic dysfunction

Maternal Considerations

Insulin aspart is a rapid-acting human insulin analog whose onset is roughly twice as fast as regular human insulin. It is similar to **insulin lispro,** which is similar to regular human insulin in controlling postprandial hyperglycemia without increasing the risk of hypoglycemia. **Insulin aspart** has an added advantage over regular human insulin in that it can be taken immediately before the meal, rather than 30-60min before.
One recent and well-powered RCT concluded that **insulin aspart** is at least as safe and effective as regular human insulin when used in basal-bolus therapy with neutral protamine Hagedorn (NPH) insulin in pregnant women with type 1 diabetes, and may potentially offer some benefits in terms of postprandial glucose control and preventing severe hypoglycemia. Careful monitoring of glucose levels coupled with active regulation of the insulin dose is crucial for an optimal outcome.
Side effects are similar to regular human insulin and include hypoglycemia, hypokalemia, lipodystrophy, pruritus, rash, and injection site reaction.

Fetal Considerations

Insulin does not cross the placenta. Hyperglycemia is associated with both an embryopathy and fetopathy. Women with insulin-requiring diabetes prepregnancy are at increased risk of bearing a child with a structural malformation. The magnitude of the risk correlates directly with the overall degree of hyperglycemia. Normalization of glucose prior to conception lowers the risk below that of control populations. Euglycemia after the embryonic stage prevents the diabetic fetopathy. While rodent

teratogenicity studies revealed increased early pregnancy losses, these were likely the product of severe hypoglycemia.

Breastfeeding Safety

There is no published experience in nursing women. It is unknown whether **insulin aspart** enters human breast milk. Human insulin is a normal component of breast milk. A wide body of clinical experience with similar insulin preparations suggests it will be compatible with breastfeeding. Lactating women may require dose or meal adjustments or both.

Drug Interactions

Many drugs affect glucose metabolism and may necessitate an insulin dose adjustment. Drugs that can increase the hypoglycemic effect include ACEIs, **disopyramide,** fibrates, **fluoxetine,** MAOIs, oral hypoglycemic agents, **propoxyphene,** salicylates, somatostatin analogs (e.g., **octreotide**), and sulfonamide antibiotics.
Drugs that can decrease the hypoglycemic effect include corticosteroids, **danazol,** diuretics, estrogens and progestogens (e.g., in oral contraceptives), **isoniazid, niacin,** phenothiazine derivatives, **somatropin,** sympathomimetic agents (e.g., **epinephrine, salbutamol, terbutaline**), and thyroid hormones. β-Blockers, **clonidine, lithium,** and alcohol may either potentiate or weaken the hypoglycemic effect of insulin. **Pentamidine** may sometimes cause hypoglycemia which is sometimes followed by hyperglycemia.
Signs and symptoms of hypoglycemia may be reduced or absent under the influence of sympatholytic medicinal products such as β-blockers, **clonidine, guanethidine,** and **reserpine.**

References

Mathiesen ER, Kinsley B, Amiel SA, et al; Insulin Aspart Pregnancy Study Group. Diabetes Care 2007; 30:771-6.
Simmons D. Curr Diab Rep 2002; 2:331-6.

Summary

Pregnancy Category: C
Lactation Category: S

- Euglycemia for the duration of pregnancy is the goal of diabetes mellitus therapy during pregnancy.
- **Insulin aspart** is a clinically attractive insulin for the control of postprandial glucose levels at least as effectively as regular human insulin.
- **Insulin aspart** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Insulin glargine—(Lantus)

International Brand Name—Lantus (Argentina, India, Israel, Paraguay)

Drug Class

Antidiabetic agents; Hypoglycemics

Indications

Diabetes mellitus

Mechanism

Stimulates peripheral glucose uptake, inhibits hepatic glucose production, inhibits adipocyte lipolysis, inhibits proteolysis, and enhances protein synthesis

Dosage with Qualifiers

Diabetes mellitus—individualized qhs (± rapid- or short-acting insulin) for women who require basal insulin to control hyperglycemia

NOTE: onset 1h, no true peak, max duration 24h; must not be mixed or diluted with any other insulin or solution.

- **Contraindications**—hypersensitivity to drug or class, hypoglycemia, IV administration
- **Caution**—hypokalemia, renal or hepatic dysfunction

Maternal Considerations

Insulin glargine is a long-acting recombinant insulin analog. There are no adequate reports or well-controlled studies in pregnant women. The published expereince is confined to case reports and small series. Though the fact that insulin requirements can change dramatically between 16 and 30w gestation, one might intuit the long-acting profile of **insulin glargine** renders it a poor choice for acute management. However, the case reports suggest it may work well for the basal release of insulin between meals. Careful monitoring of glucose levels coupled with active regulation of the insulin dose is crucial for an optimal outcome.
Side effects include hypoglycemia, hypokalemia, lipodystrophy, pruritus, rash, and injection site reaction.

Fetal Considerations

There are no adequate reports or well-controlled studies of **insulin glargine** in human fetuses. Insulin does not cross the placenta. Hyperglycemia is associated with both an embryopathy and fetopathy. Women with insulin-requiring diabetes prepregnancy are at increased risk of bearing a child with a structural malformation. The magnitude of the risk correlates directly with the overall degree of hyperglycemia. Normalization of glucose prior to conception lowers the risk below control populations. Euglycemia after the embryonic stage prevents the diabetic fetopathy. While rodent teratogenicity studies revealed increased early pregnancy losses, these were likely the product of severe hypoglycemia.

Breastfeeding Safety

There is no published experience in nursing women. It is unknown whether **insulin glargine** enters human breast milk. Human insulin is a normal component of breast milk. A wide body of clinical experience with similar insulin preparations suggests it will be compatible with breastfeeding. Lactating women may require dose or meal adjustments or both.

Drug Interactions

Many drugs affect glucose metabolism and may necessitate an insulin dose adjustment. Drugs that can increase the hypoglycemic effect include ACEIs, **disopyramide,** fibrates, **fluoxetine,** MAOIs, oral hypoglycemic agents, **propoxyphene,** salicylates, somatostatin analogs (e.g., **octreotide**), and sulfonamide antibiotics.
Drugs that can decrease the hypoglycemic effect include corticosteroids, **danazol,** diuretics, estrogens and progestogens (e.g., in oral contraceptives), **isoniazid, niacin,** phenothiazine derivatives, **somatropin,** sympathomimetic agents (e.g., **epinephrine, salbutamol, terbutaline**), and thyroid hormones. β-Blockers, **clonidine, lithium,** and alcohol may either potentiate or weaken the hypoglycemic effect of insulin. **Pentamidine** may sometimes cause hypoglycemia which is sometimes followed by hyperglycemia.
Signs and symptoms of hypoglycemia may be reduced or absent under the influence of sympatholytic medicinal products such as β-blockers, **clonidine, guanethidine,** and **reserpine.**

References

Devlin JT, Hothersall L, Wilkis JL. Diabetes Care 2002; 25:1095-6.
Hofmann T, Horstmann G, Stammberger I. Int J Toxicol 2002; 21:181-9.

Price N, Bartlett C, Gillmer M. BJOG 2007; 114:453-7.
Torlone E, Gennarini A, Ricci NB, Bolli GB. Eur J Obstet Gynecol Reprod Biol 2007; 132:238-9.

Summary

Pregnancy Category: C
Lactation Category: S

- Euglycemia for the duration of pregnancy is the goal of diabetes mellitus therapy during pregnancy.
- **Insulin glargine** is an attractive agent to provide basal insulin release for the regulation of hyperglycemia during pregnancy. Otherwise, it probably should not be used during pregnancy.

Insulin lispro—(Humalog)

International Brand Name—Humalog Lispro (Costa Rica, El Salvador, France, Guatemala, Honduras, Israel, Korea, Mexico, Nicaragua, Panama, Peru); Insuline Lispro Humalog (France)

Drug Class

Antidiabetic agents; Hypoglycemics

Indications

Diabetes mellitus

Mechanism

Stimulates peripheral glucose uptake, inhibits hepatic glucose production, inhibits adipocyte lipolysis, inhibits proteolysis, and enhances protein synthesis

Dosage with Qualifiers

Diabetes mellitus—individualized SC administration

NOTE: give <15min qac, onset <0.5h, peak 0.5-1.5h, max duration 4-6h.
NOTE: also available as a protamine suspension that prolongs the duration of activity, or in a mix, either 50:50 or 75:25 (75% lispro protamine).

- **Contraindications**—hypersensitivity to drug or class, hypoglycemia, IV administration
- **Caution**—hypokalemia, renal or hepatic dysfunction

Maternal Considerations

Insulin lispro is a rapid-acting human insulin analog with the same potency as regular human insulin. In nonpregnant patients, **insulin lispro** is superior to regular human insulin for the control of postprandial hyperglycemia without increasing the risk of hypoglycemia. **Insulin lispro** has an added advantage over regular human insulin that it can be taken immediately before the meal, rather than 30-60min before. The published experience suggests that similar pregnancy outcomes are obtained with fewer hypoglycemic episodes compared to regular human insulin. Though there are no adequate reports or well-controlled studies in pregnant women, many state that either this agent or **insulin aspart** should replace regular human insulin in combination with a long-acting insulin because of a more physiologic release profile. Careful monitoring of glucose levels coupled with active regulation of the insulin dose is crucial for an optimal outcome. ***Side effects*** include hypoglycemia, hypokalemia, lipodystrophy, pruritus, rash, and injection site reaction.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. Native insulin and **insulin lispro,** specifcally, do not cross the human placenta. Hyperglycemia is associated with both an embryopathy and fetopathy. Women with insulin-requiring diabetes prepregnancy are at increased risk of bearing a

child with a structural malformation. The magnitude of the risk correlates directly with the overall degree of hyperglycemia. Normalization of glucose prior to conception lowers the risk below control populations. Euglycemia after the embryonic stage prevents the diabetic fetopathy. While rodent teratogenicity studies revealed increased early pregnancy losses, these were likely the product of severe hypoglycemia.

Breastfeeding Safety

There is no published experience in nursing women. It is unknown whether **insulin lispro** enters human breast milk. Human insulin is a normal component of breast milk. A wide body of clinical experience with similar insulin preparations suggests it will be compatible with breastfeeding. Lactating women may require dose or meal adjustments or both.

Drug Interactions

Many drugs affect glucose metabolism and may necessitate an insulin dose adjustment. Drugs that can increase the hypoglycemic effect include ACEIs, **disopyramide,** fibrates, **fluoxetine,** MAOIs, oral hypoglycemic agents, **propoxyphene,** salicylates, somatostatin analogs (e.g., **octreotide**), and sulfonamide antibiotics.

Drugs that can decrease the hypoglycemic effect include corticosteroids, **danazol,** diuretics, estrogens and progestogens (e.g., in oral contraceptives), **isoniazid, niacin,** phenothiazine derivatives, **somatropin,** sympathomimetic agents (e.g., **epinephrine, salbutamol, terbutaline**), and thyroid hormones. β-Blockers, **clonidine, lithium,** and alcohol may either potentiate or weaken the hypoglycemic effect of insulin. **Pentamidine** may sometimes cause hypoglycemia which is sometimes followed by hyperglycemia.

Signs and symptoms of hypoglycemia may be reduced or absent under the influence of sympatholytic medicinal products such as β-blockers, **clonidine, guanethidine,** and **reserpine.**

References

Bhattacharyya A, Brown S, Hughes S, Vice PA. QJM 2001; 94:255-60.

Buchbinder A, Miodovnik M, McElvy S, et al. Am J Obstet Gynecol 2000; 183:1162-5.

Di Cianni G, Volpe L, Ghio A, et al. Diabetes Care 2007; 30:e11.

Holcberg G, Tsadkin-Tamir M, Sapir O, et al. Eur J Obstet Gynecol Reprod Biol 2004; 115:117-8.

Jovanovic L. Endocr Pract 2000; 6:98-100.

Jovanovic L, Ilic S, Pettitt DJ, et al. Diabetes Care 1999; 22:1422-7.

Loukovaara S, Immonen I, Teramo KA, Kaaja R. Diabetes Care 2003; 26:1193-8.

[No authors]. Prescrire Int 1998; 7:67-8.

Scherbaum WA, Lankisch MR, Pawlowski B, Somville T. Exp Clin Endocrinol Diabetes 2002; 110:6-9.

Wyatt JW, Frias JL, Hoyme HE, et al; IONS study group. Diabet Med 2005; 22:803-7.

Summary

Pregnancy Category: B
Lactation Category: S

- Euglycemia for the duration of pregnancy is the goal of diabetes mellitus therapy during pregnancy.
- Growing clinical experience suggests **insulin lispro** is a good choice for a rapid-acting insulin during pregnancy and lactation.
- However, there is more experience to support **insulin aspart** as the first choice.

Insulin, pork—(Iletin I; Iletin II; Iletin II Lente Pork; Iletin II Lente (Pork); Iletin II Nph Pork; Iletin II Nph (Pork); Iletin II Protamine, Zinc (Pork); Iletin II Pzi Pork; Iletin II Reg. Pork; Iletin II Regular (Pork); Iletin II Regular (Pork) Conc; Insulatard Nph; Insulin Lente Purified Pork; Insulin L Purified Pork; Insulin Nph Purified Pork; Insulin N Purified Pork; Insulin Purified; Insulin Regular Pork; Insulin Regular Purified Pork; Insulin R Purified Pork; Mixtard; Regular Iletin II; Velosulin)

International Brand Name—None identified.

Drug Class	Antidiabetic agents; Hypoglycemics
Indications	Diabetes mellitus
Mechanism	Stimulates peripheral glucose uptake, inhibits hepatic glucose production, inhibits adipocyte lipolysis, inhibits proteolysis, and enhances protein synthesis
Dosage with Qualifiers	Diabetes mellitus—individualized; available in the following forms and characteristics when given SC: *R(egular)*—0.5-1U/kg SC qd in 3-4 divided doses: give 30-60min qac, onset 0.5h, peak 2-4h, duration 6-8h *L(ente)*—give 30min before meal or qhs, onset 1-3h, peak 8-12h, duration 18-24h *N(PH)*—give 30-60min before breakfast, onset 1-2h, peak 18-24h, duration 18-24h *U(ltralente)*—0.5-1U/kg/d SC in 1 or 2 divided doses: give 30-60min before meal; onset 4-8h, peak 16-18h, duration >36h DKA—begin 0.1U/kg IV bolus of R, then 0.1U/kg/h infusion; decrease infusion rate when glucose <275mg/dl • **Contraindications**—hypersensitivity to drug or class, hypoglycemia, IV administration (N, L) • **Caution**—hypokalemia, renal or hepatic dysfunction, thyroid disorder
Maternal Considerations	Native insulin is isolated from the porcine pancreas and modified to produce three additional compounds with differing absorption patterns. Although it was the mainstay of diabetes therapy for decades, most diabetic patients begin therapy or switch to therapy with a human insulin analog. Careful monitoring of glucose levels coupled with active regulation of the insulin dose is crucial for an optimal outcome. An insulin infusion may be desirable at times during hospitalization. A basal rate can be provided with regular insulin (100U/100ml) infused at a rate 0.55-1.5U/h. ***Side effects*** include hypoglycemia, hypokalemia, lipodystrophy, pruritus, rash, and injection site reaction.
Fetal Considerations	There are no adequate reports or well-controlled studies of **porcine insulin** in human fetuses. Insulin does not cross the placenta. Hyperglycemia is associated with both an embryopathy and fetopathy. Women with insulin-requiring diabetes prepregnancy are at increased risk of bearing a child with a

structural malformation. The magnitude of the risk correlates directly with the overall degree of hyperglycemia. Normalization of glucose prior to conception lowers the risk below control populations. Euglycemia after the embryonic stage prevents the diabetic fetopathy. While rodent teratogenicity studies revealed increased early pregnancy losses, these were likely the product of severe hypoglycemia.

Breastfeeding Safety

There are no adequate reports or well-controlled studies in nursing women. It is unknown whether **porcine insulin** enters human breast milk. Human insulin is a normal component of breast milk. A wide body of clinical experience with similar insulin preparations suggests it will be compatible with breastfeeding. Lactating women may require dose or meal adjustments or both.

Drug Interactions

Many drugs affect glucose metabolism and may necessitate an insulin dose adjustment. Drugs that can increase the hypoglycemic effect include ACEIs, **disopyramide,** fibrates, **fluoxetine,** MAOIs, oral hypoglycemic agents, **propoxyphene,** salicylates, somatostatin analogs (e.g., **octreotide**), and sulfonamide antibiotics.

Drugs that can decrease the hypoglycemic effect include corticosteroids, **danazol,** diuretics, estrogens and progestogens (e.g., in oral contraceptives), **isoniazid, niacin,** phenothiazine derivatives, **somatropin,** sympathomimetic agents (e.g., **epinephrine, salbutamol, terbutaline**), and thyroid hormones. β-Blockers, **clonidine, lithium,** and alcohol may either potentiate or weaken the hypoglycemic effect of insulin. **Pentamidine** may sometimes cause hypoglycemia which is sometimes followed by hyperglycemia.

Signs and symptoms of hypoglycemia may be reduced or absent under the influence of sympatholytic medicinal products such as β-blockers, **clonidine, guanethidine,** and **reserpine.**

References

No current relevant references were identified.

Summary

Pregnancy Category: C
Lactation Category: U

- Euglycemia for the duration of pregnancy is the goal of diabetes mellitus therapy during pregnancy.
- Most patients now begin therapy with a human insulin analog.

Insulin, recombinant human—(Humulin R, L, N, and U)

International Brand Name—Actrapid (Finland, France, Indonesia, New Zealand); Actrapid HM (France, Germany, Hong Kong, Israel, Italy, Malaysia, Philippines, South Africa, Taiwan, Thailand); Actrapid Human (Indonesia, Japan, Korea); Berlinsulin Actrapid Normal U-40 (Germany); Berlinsulin H Basal U-40 (Germany); Biohulin (Korea); Human Actrapid (India, Ireland); Human Nordisulin (India); Huminsulin ''Lilly'' Normal (Austria); Huminsulin Normal (Germany, Switzerland); Humulin (Regular) (Greece); Humulina Regular (Spain); Humulin C (Ecuador, Peru); Humuline Regular (Sweden); Humulin R (Bulgaria, China, Colombia, Costa Rica, Czech Republic, Dominican Republic, El Salvador, Guatemala, Honduras, Hong Kong, Hungary, Indonesia, Italy, Korea, Malaysia, Mexico, Nicaragua, Panama, Paraguay, Philippines, Thailand, Venezuela); Humulin-R (Canada, Colombia, Dominican Republic, El Salvador, Guatemala, Honduras, Nicaragua, Panama); Humulin Regular (Denmark, Finland, Norway, Portugal, Sweden, Taiwan); Insulina (Spain); Insulina Actrapid HM (Spain); Insulin Actrapid HM (Bulgaria); Insulina Humulin R (Argentina); Insulina Velosulin HM (Spain); Insuline (Netherlands); Insuline Actrapid (Belgium, Netherlands); Insuline Humuline Regular (Netherlands); Insuline Velosulin Humaan (Netherlands); Insulin Hoechst-Rapid U-100 (Switzerland); Insulin Human Actrapid (England); Insulin ''Novo Nordisk'' Actrapid HM (Austria); Insulin ''Novo Nordisk'' Velosulin HM (Austria); Insulin Velosulin HM (Israel); Insuman (Brazil, Chile); Insuman Basal (France, Germany); Insuman Infusat (Germany); Insuman Rapid (France, Germany); Novolin R (China, Ecuador, Korea, Mexico, Peru); Orgasulin Rapid (France); Umuline Profil 10 (France); Umuline Profil 20 (France); Umuline Profil 30 (France); Umuline Profil 40 (France); Umuline Profil 50 (France); Velosulin (Denmark, Finland); Velosuline Humaine (France); Velosulin HM (Austria)

Drug Class	Antidiabetic agents; Hypoglycemics
Indications	Diabetes mellitus
Mechanism	Stimulates peripheral glucose uptake, inhibits hepatic glucose production, inhibits adipocyte lipolysis, inhibits proteolysis, and enhances protein synthesis
Dosage with Qualifiers	Diabetes mellitus—individualized; available in the following forms and characteristics when given SC: *R(egular)*—0.5-1U/kg SC qd in 3-4 divided doses: give 30-60min qac, onset 0.5h, peak 2-4h, duration 6-8h *L(ente)*—give 30min before meal or qhs, onset 1-3h, peak 8-12h, duration 18-24h *N(PH)*—give 30-60min before breakfast, onset 1-2h, peak 6-12h, duration 18-24h *U(ltralente)*—0.5-1U/kg/d SC in 1-2 divided doses: give 30-60min before meal; onset 4-8h, peak 16-18h, duration >36h DKA—begin 0.1U/kg IV bolus of R, then 0.1U/kg/h infusion; decrease infusion rate when glucose <275mg/dl • **Contraindications**—hypersensitivity to drug or class, hypoglycemia, IV administration (N, L, U) • **Caution**—hypokalemia, renal or hepatic dysfunction, thyroid disorder
Maternal Considerations	**Human recombinant insulin** is synthesized from bacteria containing the human insulin gene. It is then modified to produce three additional compounds with differing absorption patterns. There is a large body of clinical experience using **human recombinant insulin** during pregnancy. Careful monitoring of glucose levels coupled with active regulation of the insulin dose is crucial for an optimal outcome. An insulin infusion may be desirable at times during hospitalization. A basal rate can be provided with regular insulin (100U/100ml) infused at a rate 0.55-1.5U/h. ***Side effects*** include hypoglycemia, hypokalemia, lipodystrophy, pruritus, rash, and injection site reaction.
Fetal Considerations	Insulin does not cross the placenta. Hyperglycemia is associated with both an embryopathy and fetopathy. Women with

insulin-requiring diabetes prepregnancy are at increased risk of bearing a child with a structural malformation. The magnitude of the risk correlates directly with the overall degree of hyperglycemia. Normalization of glucose prior to conception lowers the risk below control populations. Euglycemia after the embryonic stage prevents the diabetic fetopathy. While rodent teratogenicity studies revealed increased early pregnancy losses, these were likely the product of severe hypoglycemia.

Breastfeeding Safety

There are no adequate reports or well-controlled studies in nursing women. It is unknown whether **human recombinant insulin** enters human breast milk. Human insulin is a normal component of breast milk. A wide body of clinical experience with similar insulin preparations suggests it will be compatible with breastfeeding. Lactating women may require dose or meal adjustments or both.

Drug Interactions

Many drugs affect glucose metabolism and may necessitate an insulin dose adjustment. Drugs that can increase the hypoglycemic effect include ACEIs, **disopyramide,** fibrates, **fluoxetine,** MAOIs, oral hypoglycemic agents, **propoxyphene,** salicylates, somatostatin analogs (e.g., **octreotide**), and sulfonamide antibiotics.
Drugs that can decrease the hypoglycemic effect include corticosteroids, **danazol,** diuretics, estrogens and progestogens (e.g., in oral contraceptives), **isoniazid, niacin,** phenothiazine derivatives, **somatropin,** sympathomimetic agents (e.g., **epinephrine, salbutamol, terbutaline**), and thyroid hormones. β-Blockers, **clonidine, lithium,** and alcohol may either potentiate or weaken the hypoglycemic effect of insulin. **Pentamidine** may sometimes cause hypoglycemia which is sometimes followed by hyperglycemia.
Signs and symptoms of hypoglycemia may be reduced or absent under the influence of sympatholytic medicinal products such as β-blockers, **clonidine, guanethidine,** and **reserpine.**

References

No current relevant references were identified.

Summary

Pregnancy Category: B
Lactation Category: S

- Euglycemia for the duration of pregnancy is the goal of diabetes mellitus therapy during pregnancy.
- **Human recombinant insulin** is a mainstay for the treatment of hyperglycemia in pregnant and lactating women.

Insulin, semisynthetic human—(Velosulin BR)

International Brand Name—None identified.

Drug Class

Antidiabetic agents; Hypoglycemics

Indications

Diabetes mellitus

Mechanism

Stimulates peripheral glucose uptake, inhibits hepatic glucose production, inhibits adipocyte lipolysis, inhibits proteolysis, and enhances protein synthesis

Dosage with Qualifiers

Diabetes mellitus—individualized as noted; 0.5-1U/kg SC qd in 3-4 divided doses: give 30-60min qac, onset 0.5h, peak 1-3h, duration 6-8h

- **Contraindications**—hypersensitivity to drug or class, hypoglycemia, IV administration
- **Caution**—hypokalemia, renal or hepatic dysfunction, thyroid disorder

Maternal Considerations

Human semisynthetic insulin is synthesized from purified pork insulin, and then enzymatically modified to the human structure. It is functionally the same as regular human insulin. There are no published reports of its use during pregnancy or lactation. Careful monitoring of glucose levels coupled with active regulation of the insulin dose is crucial for an optimal outcome.
Side effects include hypoglycemia, hypokalemia, lipodystrophy, pruritus, rash, and injection site reaction.

Fetal Considerations

There are no adequate reports or well-controlled studies of **human semisynthetic insulin** in human fetuses. Insulin does not cross the placenta. Hyperglycemia is associated with both an embryopathy and fetopathy. Women with insulin-requiring diabetes prepregnancy are at increased risk of bearing a child with a structural malformation. The magnitude of the risk correlates directly with the overall degree of hyperglycemia. Normalization of glucose prior to conception lowers the risk below control populations. Euglycemia after the embryonic stage prevents the diabetic fetopathy. While rodent teratogenicity studies revealed increased early pregnancy losses, these were likely the product of severe hypoglycemia.

Breastfeeding Safety

There is no published experience in nursing women. It is unknown whether **human semisynthetic insulin** enters human breast milk. Human insulin is a normal component of breast milk. A wide body of clinical experience with similar insulin preparations suggests it will be compatible with breastfeeding. Lactating women may require dose or meal adjustments or both.

Drug Interactions

Many drugs affect glucose metabolism and can necessitate an insulin dose adjustment. Drugs that can increase the hypoglycemic effect include ACEIs, **disopyramide,** fibrates, **fluoxetine,** MAOIs, oral hypoglycemic agents, **propoxyphene,** salicylates, somatostatin analogs (e.g., **octreotide**), and sulfonamide antibiotics.
Drugs that can decrease the hypoglycemic effect include corticosteroids, **danazol,** diuretics, estrogens and progestogens (e.g., in oral contraceptives), **isoniazid, niacin,** phenothiazine derivatives, **somatropin,** sympathomimetic agents (e.g., **epinephrine, salbutamol, terbutaline**), and thyroid hormones. β-Blockers, **clonidine, lithium,** and alcohol may either potentiate or weaken the hypoglycemic effect of insulin. **Pentamidine** may sometimes cause hypoglycemia which is sometimes followed by hyperglycemia.
Signs and symptoms of hypoglycemia may be reduced or absent under the influence of sympatholytic medicinal products such as β-blockers, **clonidine, guanethidine,** and **reserpine.**

References

There is no published experience in pregnancy or during lactation.

Summary

Pregnancy Category: B
Lactation Category: S

- Euglycemia for the duration of pregnancy is the goal of diabetes mellitus therapy during pregnancy.
- A reasonable alternative to regular human insulin.

Interferon alfa-2a, recombinant—(Roferon A)

International Brand Name—Green-Alpha (Korea); Roceron (Norway); Roceron-A (Denmark, Finland, Poland, Sweden); Roferon A (Austria, Belgium, Bulgaria, Canada, Hungary, Portugal, Puerto Rico); Roferon-A (Argentina, Brazil, Chile, Czech Republic, Ecuador, England, France, Germany, Greece, Hong Kong, India, Indonesia, Italy, Japan, Korea, Malaysia, Mexico, Netherlands, New Zealand, Paraguay, Peru, Philippines, Russia, Spain, Switzerland, Taiwan, Thailand, Turkey, Uruguay, Venezuela); Roferon-A HSA Free (Singapore)

Drug Class

Antineoplastics, interferon; Antivirals, interferon; Immunomodulators

Indications

Chronic HCV infection with compensated liver disease, AIDS-associated Kaposi's sarcoma, hairy cell leukemia

Mechanism

Unknown

Dosage with Qualifiers

Chronic HCV infection with compensated liver disease—3 million U/d SC/IM 3×/w for 52w
AIDS-associated Kaposi's sarcoma—begin 36 million U/d SC/IM ×10-12w, then 3×/w
Hairy cell leukemia—begin 3 million U/d ×16-24w, then 3×/w

- **Contraindications**—hypersensitivity to drug or class, autoimmune hepatitis
- **Caution**—myelosuppression or myelosuppressive agents, seizure disorder, cardiac disease, severe hepatic or renal dysfunction, depression, CNS disorder, diabetes, thyroid disorders, nephrotoxic or hepatotoxic agents, autoimmune disorder

Maternal Considerations

There are no adequate reports or well-controlled studies in pregnant women. Case reports document the use of **interferon alfa-2a** during pregnancy to treat essential thrombocythemia, CML, and chronic HCV infection. A decrease in serum estradiol and progesterone levels is reported in women receiving human leukocyte interferon.
Side effects include leukopenia, anemia, seizures, pulmonary or hepatic toxicity, delirium, arrhythmias, cardiomyopathy, MI, GI bleeding, hypertension, flu-like symptoms, rash, anorexia, abdominal pain, diarrhea, arthralgias, dry mouth, dizziness, headache, paresthesias, emotional lability, anxiety, and injection site reaction.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. The risk of HCV vertical transmission is estimated to approximate 5%. **Interferon alfa-2a** does not cross the isolated perfused human placenta. There is a single case report of a preterm birth associated with IUGR and neonatal lupus-like syndrome. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically. However, it increases the risk of abortion when given at multiples of the MRHD to rhesus monkeys early in gestation. There is no detectable effect in late gestation.

Breastfeeding Safety

There is no published experience in nursing women. It is unknown whether **interferon alfa-2a** enters human breast milk. Breastfeeding is contraindicated in HIV-infected nursing women where formula is available to reduce the risk of neonatal transmission.

Drug Interactions

May reduce the clearance of **theophylline.**
May reduce hepatic CYP activity.
Use with IL-2 may potentiate the risk of renal failure.
The neurotoxic, hematotoxic, or cardiotoxic effects of previously or concurrently administered drugs may be increased by interferons.
Interactions could occur following concurrent administration of centrally acting drugs.

References

Dumas JC, Giroux M, Teixeira MG, et al. Therapie 1993; 48:73-5.
Fritz M, Vats K, Goyal RK. J Perinatol 2005; 25:552-4.
Milano V, Gabrielli S, Rizzo N, et al. J Matern Fetal Med 1996; 5:74-8.
Vantroyen B, Vanstraelen D. Acta Haematol 2002; 107:158-69.
Waysbort A, Giroux M, Mansat V, et al. Antimicrob Agents Chemother 1993; 37:1232-7.

Summary

Pregnancy Category: C
Lactation Category: U

- **Interferon alfa-2a** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Interferon alfa-2b, recombinant—(Intron A)

International Brand Name—Bioferon (Paraguay, Thailand, Uruguay); Intron A (Argentina, Brazil, Chile, Costa Rica, Dominican Republic, Ecuador, El Salvador, Guatemala, Honduras, Hong Kong, Israel, Japan, Kenya, Nicaragua, Panama, Peru, Philippines, South Africa, Taiwan, Venezuela); Intron-A (Canada, Ecuador, Greece, Indonesia, Malaysia, Mexico, Peru, Singapore, Thailand); Introna (Austria, Denmark, Finland, France, Norway, Sweden); Peg-Intron (Hong Kong, Israel); Reaferon (Korea)

Drug Class

Antineoplastics, interferon; Antivirals, interferon; Immunomodulators

Indications

Condyloma acuminatum, chronic HCV and HBV infection, AIDS-associated Kaposi's sarcoma, hairy cell leukemia

Mechanism

Unknown

Dosage with Qualifiers

Condyloma acuminatum—reconstitute 10 million U/1ml diluent; inject 0.1ml SC into the base of the wart 3×/w ×3w, may inject up to 5 warts per session; a 2nd course may be given 12w later
Chronic HCV infection—3 million U SC/IM 3×/w ×16w; if a response, continue total 18-24mo
Chronic HBV infection—10 million U SC/IM 3×/w ×16w
AIDS-associated Kaposi's sarcoma—30 million U/m^2 SC/IM 3×/w
Hairy cell leukemia—2 million U/m^2 SC/IM 3×/w

NOTE: may be combined with ***ribavirin.***

- **Contraindications**—hypersensitivity to drug or class, autoimmune hepatitis
- **Caution**—myelosuppression or myelosuppressive agents, seizure disorder, cardiac disease, severe hepatic or renal dysfunction, depression, CNS disorder, diabetes mellitus, thyroid disorders, nephrotoxic or hepatotoxic agents, autoimmune disorder

Maternal Considerations

There are no adequate reports or well-controlled studies in pregnant women. Case reports document the use of **interferon alfa-2b** during pregnancy for the treatment of chronic HCV

infection and essential thrombocythemia. HIV infection is not a contraindication to HCV infection therapy. Liver disease caused by chronic HCV infection is the second leading cause of death in some HIV-infected populations.
Side effects include leukopenia, thrombocytopenia, anemia, seizures, pulmonary or hepatic toxicity, delirium, suicidal ideation, arrhythmias, cardiomyopathy, MI, GI bleeding, hypertension, peripheral neuropathy, flu-like symptoms, rash, anorexia, abdominal pain, diarrhea, arthralgias, dry mouth, cough, dizziness, headache, paresthesias, emotional lability, anxiety, and injection site reaction.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **interferon alfa-2b** crosses the placenta, though other interferons do not. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically. However, it increases the risk of abortion when given at multiples of the MRHD to rhesus monkeys early in gestation.

Breastfeeding Safety

There are no adequate reports or well-controlled studies in nursing women. Only a scant quantity of **interferon alfa-2b** enters human breast milk. Breastfeeding is contraindicated in HIV-infected nursing women where formula is available to reduce the risk of neonatal transmission.

Drug Interactions

Use decreases **theophylline** clearance, nearly doubling serum levels.
The neurotoxic, hematotoxic, or cardiotoxic effects of previously or concurrently administered drugs may be increased by interferons.
Interactions could occur following concurrent administration of centrally acting drugs.

References

Kumar AR, Hale TW, Mock RE. J Hum Lact 2000; 16:226-8.
Ozaslan E, Yilmaz R, Simsek H, Tatar G. Ann Pharmacother 2002; 36:1715-8.
Pardini S, Dore F, Murineddu M, et al. Am J Hematol 1993; 43:78-9.

Summary

Pregnancy Category: C
Lactation Category: U
- **Interferon alfa-2b** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Interferon alfa-N3—(Alferon N)

International Brand Name—None identified.

Drug Class

Antivirals, interferon; Immunomodulators

Indications

Condyloma acuminatum

Mechanism

Unknown

Dosage with Qualifiers

Condyloma acuminatum—0.05ml (250,000U) SC at the base of each wart (max 0.5ml per session) 2×/w ×8w

NOTE: wait at least 3mo before considering a repeat course.

- **Contraindications**—hypersensitivity to drug or class, hypersensitivity to egg proteins or **neomycin**
- **Caution**—unstable angina, CHF, COPD, diabetes mellitus, thrombophlebitis, thrombophilia, myelosuppression, seizure disorder

Maternal Considerations

Interferon alfa-N3 is derived from human leukocytes. There is no published experience with **interferon alfa-N3** during pregnancy. It had no effect on the menstrual cycle of treated, nonpregnant women. ***Side effects*** include flu-like syndrome, fever, sweating, itching, dizziness, insomnia, arthralgia, myalgia, back pain, and headache.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **interferon alfa-N3** crosses the placenta, though other interferons do not. Rodent teratogenicity studies have not been performed.

Breastfeeding Safety

There is no published experience in nursing women. It is unknown whether **interferon alfa-N3** enters human breast milk.

Drug Interactions

The neurotoxic, hematotoxic, or cardiotoxic effects of previously or concurrently administered drugs may be increased by interferons. Interactions could occur following concurrent administration of centrally acting drugs.

References

There is no published experience in pregnancy or during lactation.

Summary

Pregnancy Category: C
Lactation Category: U

- **Interferon alfa-N3** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Interferon alfacon-1—(Infergen)

International Brand Name—Infergen (Canada)

Drug Class

Antivirals, interferon; Immunomodulators

Indications

Chronic HCV infection with compensated liver disease

Mechanism

Unknown

Dosage with Qualifiers

Chronic HCV infection with compensated liver disease—9mcg SC 2-3×w ×24w

NOTE: a pretreatment eye exam is recommended in patients with hypertension or diabetes mellitus.

- **Contraindications**—hypersensitivity to drug or class, hypersensitivity to *E. coli*–derived products, decompensated hepatic disease, autoimmune hepatitis
- **Caution**—preexisting cardiac disease, leukopenia, myelosuppression, autoimmune disorders

Maternal Considerations

Interferon alfacon-1 is a non–naturally occurring recombinant type-I interferon. There is no published experience during pregnancy.

Side effects include depression, suicidal ideation, suicide, hypertension, supraventricular arrhythmias, chest pain, MI, leukopenia, granulocytopenia, thrombocytopenia, ophthalmologic disorders, and hypothyroidism.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **interferon alfacon-1** crosses the human placenta, though other interferons do not. While rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically, there is an increase in embryonic loss in both rodents and some monkeys.

Breastfeeding Safety

There is no published experience in nursing women. It is unknown whether **interferon alfacon-1** enters human breast milk.

Drug Interactions

No formal drug interaction studies have been conducted with **interferon alfacon-1.** It should be used cautiously in patients receiving agents that cause myelosuppression or are metabolized by hepatic CYPs.
The neurotoxic, hematotoxic, or cardiotoxic effects of previously or concurrently administered drugs may be increased by interferons. Interactions could occur following concurrent administration of centrally acting drugs.

References

There is no published experience in pregnancy or during lactation.

Summary

Pregnancy Category: C
Lactation Category: U
- **Interferon alfacon-1** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Interferon beta-1a—(Avonex; Rebif)

International Brand Name—Rebif (Australia, Canada, France, Hong Kong, Israel, Mexico, Peru, Taiwan)

Drug Class

Immunomodulators; Neurologics

Indications

Relapsing MS

Mechanism

Unknown

Dosage with Qualifiers

Relapsing MS—30mcg IM qw

- **Contraindications**—hypersensitivity to drug or class
- **Caution**—seizure disorder, depression

Maternal Considerations

There are no adequate reports or well-controlled studies of **interferon beta-1a** in pregnant women. The relapse rate of MS decreases during pregnancy and increases postpartum. Menstrual irregularities occurred in monkeys treated with 100× the MRHD. Anovulation and decreased serum progesterone levels were also noted transiently in some animals. These effects are reversible by discontinuing the drug. Treatment with twice the recommended weekly dose had no effect on cycle duration or ovulation.
Side effects include seizures, cardiac arrest, hemorrhage, anemia, asthenia, diarrhea, fever, chills, flu-like symptoms, increase LFTs, depression, suicidal ideation, and injection site reaction.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **interferon beta-1a** crosses the placenta; other interferons do not. Limited study suggests an increase in the rates of pregnancy wastage and IUGR. There was no evidence of teratogenicity in either rodent or monkey studies. However, it was embryolethal or an abortifacient in cynomolgus monkeys administered doses approximately twice the cumulative weekly human dose either during organogenesis or later in pregnancy.

Breastfeeding Safety

There is no published experience in nursing women. It is unknown whether **interferon beta-1a** enters human breast milk.

Drug Interactions

Other interferons reduce hepatic CYP drug metabolism. Formal hepatic drug metabolism studies have not been conducted with **interferon beta-1a** in humans. Hepatic microsomes isolated from treated rhesus monkeys showed no impact on hepatic CYP activity.
Due to its potential to cause neutropenia and lymphopenia, proper monitoring of patients is required if **interferon beta-1a** is given in combination with myelosuppressive agents.
The neurotoxic, hematotoxic, or cardiotoxic effects of previously or concurrently administered drugs may be increased by interferons.
Interactions could occur following concurrent administration of centrally acting drugs.

References

Boskovic R, Wide R, Wolpin J, et al. Neurology 2005; 65:807-11.
Hellwig K, Brune N, Haghikia A, et al. Acta Neurol Scand 2008; 118:24-8.

Summary

Pregnancy Category: C
Lactation Category: U

- **Interferon beta-1a** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Interferon beta-1b, recombinant—(Betaferon; Betaseron)

International Brand Name—Beneseron (Korea); Betaferon (Argentina, Brazil, Canada, Chile, Costa Rica, Dominican Republic, El Salvador, Honduras, Hong Kong, Israel, Korea, Malaysia, Mexico, Nicaragua, Panama, Peru, Philippines, Singapore, South Africa, Thailand, Uruguay)

Drug Class

Immunomodulators; Neurologics

Indications

Relapsing MS

Mechanism

Unknown

Dosage with Qualifiers

Relapsing MS—0.25mg (8 million U) SC qod

- **Contraindications**—hypersensitivity to drug or class
- **Caution**—seizure disorder, depression

Maternal Considerations

There are not adequate reports or well controlled studies of **interferon beta-1b** during pregnancy. The relapse rate of MS decreases during pregnancy and increases postpartum. Menstrual irregularities occur in monkeys treated with 100× the MRHD. Anovulation and decreased serum progesterone levels were also

noted transiently in some animals. These effects reversed after stopping the drug. Treatment with twice the recommended dose had no effect on cycle duration or ovulation.
Side effects include shock, seizures, cardiac arrest, arrhythmias, anemia, muscle aches, asthenia, fever, chills, flu-like symptoms, nausea, diarrhea, dyspepsia, and injection site reaction.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **interferon beta-1b** crosses the human placenta; other interferons do not. Limited study suggests an increase in the rates of pregnancy wastage and IUGR. There is no evidence of teratogenicity in either rodent or monkey studies. However, there was a significant increase in embryolethal and abortifacient effects in cynomolgus monkeys treated with twice the weekly human dose.

Breastfeeding Safety

There is no published experience in nursing women. It is unknown whether **interferon beta-1b** enters human breast milk.

Drug Interactions

Caution should be exercised when administering **interferon beta-1b** in combination with other potentially myelosuppressive agents. The neurotoxic, hematotoxic, or cardiotoxic effects of previously or concurrently administered drugs may be increased by interferons. Interactions could occur following concurrent administration of centrally acting drugs.

References

Boskovic R, Wide R, Wolpin J, et al. Neurology 2005; 65:807-11.
Hellwig K, Brune N, Haghikia A, et al. Acta Neurol Scand 2008; 118:24-8.

Summary

Pregnancy Category: C
Lactation Category: U

- **Interferon beta-1b** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.
- It may be wise if a woman becomes pregnant or plans to become pregnant while taking **interferon beta-1b** that she consider discontinuing therapy.

Interferon gamma-1b, recombinant—(Actimmune)

International Brand Name—Immukin (Hong Kong); Imufor (Austria, Germany); Imukin (Australia, Austria, Czech Republic, Denmark, Finland, France, Germany, Greece, Italy, Norway, Spain, Sweden, Switzerland); Imukin Inj. (New Zealand)

Drug Class

Immunomodulators

Indications

Chronic granulomatous disease; severe, malignant osteopetrosis

Mechanism

Unknown

Dosage with Qualifiers

Chronic granulomatous disease—50mcg/m^2 (1 million IU/m^2) if body surface area >0.5 m^2 and 1.5mcg/kg if body surface area <0.5 m^2
Severe, malignant osteopetrosis—50mcg/m^2 (1 million IU/m^2) if body surface area >0.5 m^2 and 1.5mcg/kg if body surface area <0.5 m^2

NOTE: expressed as 1 million IU/50mcg. This is equivalent to what was previously expressed as units (1.5 million U/50mcg).

- **Contraindications**—hypersensitivity to drug or class, hypersensitivity to *E. coli* products
- **Caution**—preexisting cardiac disease, myelosuppression, seizure disorder

Maternal Considerations

There is no published experience with **interferon gamma-1b** during pregnancy.
Side effects include fever, headache, rash, chills, fatigue, diarrhea, N/V, myalgias, arthralgias, and local injection site reactions.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **interferon gamma-1b** crosses the human placenta; other interferons do not. Studies in pregnant primates treated with intravenous doses 2-100× the MRHD revealed no teratogenic activity. However, **interferon gamma-1b** increased the incidence of abortion in primates given 100× the MRHD.

Breastfeeding Safety

There is no published experience in nursing women. It is unknown whether **interferon gamma-1b** enters human breast milk.

Drug Interactions

Caution should be exercised when administering **interferon gamma-1b** in combination with other potentially myelosuppressive agents.
The neurotoxic, hematotoxic, or cardiotoxic effects of previously or concurrently administered drugs may be increased by interferons. Interactions could occur following concurrent administration of centrally acting drugs.

References

No current relevant references.

Summary

Pregnancy Category: C
Lactation Category: U

- **Interferon gamma-1b** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.
- It may be wise if a woman becomes pregnant or plans to become pregnant while taking **interferon gamma-1b** that she consider discontinuing therapy if medically feasible.

Iodoquinol—(Diiodohydroxyquin; Drioquilen; Yodoxin)

International Brand Name—Depofin (Mexico); Diodoquin (Canada, El Salvador, Guatemala, Honduras, Mexico, Nicaragua); Entero-diyod serral (Mexico); Floraquin (Taiwan)

Drug Class

Antimicrobials; Antiprotozoals

Indications

Intestinal amebiasis

Mechanism

Amebicidal against the trophozoites and cysts of *Entamoeba histolytica*

Dosage with Qualifiers

Intestinal amebiasis—650mg PO tid pc ×20d

- **Contraindications**—hypersensitivity to drug or class, hepatic dysfunction
- **Caution**—thyroid disease

Maternal Considerations	There is no recent published experience with **iodoquinol** during pregnancy. ***Side effects*** include optic neuritis, optic atrophy, peripheral neuropathy, acne, urticaria, pruritus, N/V, diarrhea, abdominal pain, headache, thyromegaly, and fever.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **iodoquinol** crosses the human placenta. Rodent teratogenicity studies have not been performed.
Breastfeeding Safety	There are no adequate reports or well-controlled studies in nursing women. It is unknown whether **iodoquinol** enters human breast milk.
Drug Interactions	**Iodoquinol** may interfere with the immune response to typhoid vaccine.
References	There is no published experience in pregnancy or during lactation.
Summary	**Pregnancy Category: C** **Lactation Category: U** • **Iodoquinol** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Iohexol—(Omnipaque)

International Brand Name—None identified.

Drug Class	Diagnostics, radiopharmaceutical
Indications	Radiography, CT scanning
Mechanism	Iodine-containing contrast medium
Dosage with Qualifiers	Radiography, CT scanning—2-4ml IV as needed; volume varies based on the patient volume of distribution *NOTE: available in concentrations of 140 and 350mg/ml.* • **Contraindications—**hypersensitivity to drug or class • **Caution**—unknown
Maternal Considerations	**Iohexol** is a nonionic ragiographic contrast medium of low osmolality used extensively in clinical radiology. Side effects are scant even in patients with a history of iodine hypersensitivity or adverse reactions to other radiographic contrast agents. There are no adequate reports or well-controlled studies of **iohexol** in pregnant women. **Iohexol** was previously used to evaluate the GFR of pregnant women at term. ***Side effects*** include transient malaise and vomiting.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. **Iohexol** crosses the human placenta in significant concentration, and it was used to identify an omphalomesenteric duct cyst in a twin pregnancy and a congenital diaphragmatic hernia in another.
Breastfeeding Safety	There are no adequate reports or well-controlled studies in nursing women. **Iohexol** enters human breast milk, but <0.2% of the drug would be ingested by the unsupplemented neonate over

	24h. These agents as a group are poorly absorbed orally (<1%), and the half-life of injected **iohexol** approximates 2h. As a result, **iohexol** seems to be of little risk to the breastfeeding neonate.
Drug Interactions	Drugs that lower the seizure threshold should be avoided, especially phenothiazine derivatives including those used for antihistaminic or antinauseant properties. Other agents to be avoided include MAOIs, TCAs, CNS stimulants, psychoactive drugs described as analeptics, major tranquilizers, or antipsychotic drugs. Such medications should be discontinued at least 48h before myelography, should not be used for the control of N/V during or after myelography, and should not be resumed for at least 24h postprocedure. Consider prophylactic use of anticonvulsants in nonelective procedures in patients on these drugs.
References	Frennby B, Sterner G. Eur Radiol 2002; 12:475-84. Moon AJ, Katzberg RW, Sherman MP. J Pediatr 2000; 136:548-9. Nielsen ST, Matheson I, Rasmussen JN, et al. Acta Radiol 1987; 28:523-6. Strevens H, Wide-Swensson D, Torffvit O, Grubb A. Scand J Clin Lab Invest 2002; 62:141-7. Urban BA, Duhl AJ, Ural SH, et al. AJR Am J Roentgenol 1999;172:809-12.
Summary	**Pregnancy Category: C** **Lactation Category: S** • **Iohexol** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Ipecac syrup

International Brand Name—None identified.

Drug Class	Antidotes; Emetics; Toxicology agents
Indications	Emesis induction
Mechanism	Induces vomiting both locally and centrally
Dosage with Qualifiers	Emesis induction—15-30ml PO followed by 200-300ml water; repeat in 30min if no response • **Contraindications**—hypersensitivity to drug or class, unconscious patient • **Caution**—ingestion of either gasoline, kerosene, or volatile oil alkali or acid; more than 1h since ingestion; <6mo of age
Maternal Considerations	There is no published experience with **ipecac** during pregnancy. There is, however, a long clinical experience with its use to treat patients who have ingested toxic substances. **Ipecac** is cardiotoxic if not vomited. ***Side effects*** include cardiotoxicity (chronic use), diarrhea, choking, drowsiness, cough, dyspepsia, CNS depression, lethargy, and myopathy.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. It is unknown if **ipecac** crosses the human placenta. Rodent teratogenicity studies have not been performed.

Breastfeeding Safety	There are no adequate reports or well-controlled studies in nursing women. It is unknown whether **ipecac** enters human breast milk.
Drug Interactions	**Ipecac** may decrease adsorbtion of activated charcoal.
References	No current relevant references were identified.
Summary	**Pregnancy Category: C** **Lactation Category: S** • **Ipecac** is a workhorse for the treatment of acute intoxication. • **Ipecac** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Ipratropium bromide—(Atrovent; Disne-Asmol)

International Brand Name—Aerovent (Israel); Apo-Ipravent (Canada); Apovent (Israel); Aproven (Australia); Atem (Israel, Italy); Atronase (Belgium); Atrovent (Argentina, Canada, Colombia, Costa Rica, Dominican Republic, Ecuador, El Salvador, Guatemala, Honduras, Mexico, Nicaragua, Panama, Paraguay, Peru, Uruguay, Venezuela); Atrovent Aerosol (New Zealand); Atrovent N (Malaysia, Singapore); Atrovent Nasal (Hong Kong, New Zealand); Ipra Uni-dose (New Zealand); Ipravent (Hong Kong, India); Ipvent (South Africa); Narilet (Spain); Tropium (Costa Rica, Dominican Republic, El Salvador, Guatemala, Honduras, Nicaragua, Panama)

Drug Class	Anticholinergics; Bronchodilators
Indications	Bronchospasm, rhinitis, rhinorrhea
Mechanism	Antagonizes cholinergic receptors.
Dosage with Qualifiers	Bronchospasm—2-3 puffs INH tid or qid; alternatively 500mcg NEB q6-8h Rhinitis—2 sprays/nostril bid or tid (0.03%) Rhinorrhea associated with cold—2 sprays/nostril tid or qid (0.06%) *NOTE: available in bronchial and nasal (0.03% and 0.06%) inhalers.* • **Contraindications**—hypersensitivity to drug or class, hypersensitivity to soybean or peanuts • **Caution**—narrow-angle glaucoma
Maternal Considerations	The published experience with **ipratropium** during pregnancy is limited to case reports. Mild asthma during pregnancy is managed with inhaled β_2-agonists; therapy for moderate asthma includes inhaled **cromolyn,** inhaled **beclomethasone,** and oral **theophylline.** Severe gestational asthma should be treated with oral corticosteroids at the lowest effective dosage. The pharmacologic management of acute asthma during pregnancy includes nebulized β_2-agonists, **ipratropium,** and IV **methylprednisolone.** ***Side effects*** include cough, bronchospasm (nasal inhaler), headache, palpitations, nervousness, dizziness, nausea, dry mouth, pharyngitis, rash, blurred vision, and URI.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **ipratropium** crosses the human placenta. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically. The highest doses (1000× the MRHD) were associated with embryotoxicity.

Breastfeeding Safety

There is no published experience in nursing women. It is unknown whether **ipratropium** enters human breast milk. While lipid-insoluble quaternary bases enter breast milk, it is unlikely **ipratropium** reaches the neonate to a significant degree since it is not well absorbed systemically after inhalation or oral administration.

Drug Interactions

Although minimally absorbed systemically, there is some potential for an additive interaction if used with other anticholinergic medications.

References

[No authors]. Ann Allergy Asthma Immunol 2000; 84:475-80.
Schatz M. Drug Saf 1997; 16:342-50.

Summary

Pregnancy Category: B
Lactation Category: S

- **Ipratropium** is an effective agent for the management of acute asthma.
- There are alternative agents for which there is more experience during pregnancy and lactation.

Irbesartan—(Aprovel; Avapro; Irban; Irovel)

International Brand Name—Approvel (Germany); Aprovel (Colombia, Hong Kong, Indonesia, Malaysia, Mexico, Peru, Philippines, Singapore, South Africa, Taiwan, Thailand); Arbez LR (Philippines); Avapro (Argentina, Australia, Brazil, Canada, Mexico); Irban (Israel); Iretensa (Indonesia); Irovel (India); Irvell (Indonesia); Karvea (Australia)

Drug Class

ACEI/A2R-antagonists; Antihypertensives

Indications

Hypertension

Mechanism

Selectively antagonizes the AT-1 receptor

Dosage with Qualifiers

Hypertension—begin 150mg PO qd (if alone); max 300mg/d

- **Contraindications**—hypersensitivity to drug or class, pregnancy
- **Caution**—renal artery stenosis, history of ACE angioedema, hepatic or renal dysfunction, volume depletion, hyponatremia, CHF

Maternal Considerations

The published experience with **irbesartan** during pregnancy is limited to case reports and small series. Women taking inhibitors of renin-angiotensin should be placed on effective contraception and switched to another class of agents if they plan to or as soon as they become pregnant.
Side effects include angioedema, hypotension, hyperkalemia, dizziness, URI symptoms, back pain, diarrhea, fatigue, dyspepsia, thrombocytopenia, and neutropenia.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **irbesartan** crosses the human placenta. Drugs that act directly on the renin-angiotensin system can cause perinatal morbidity and death. Adverse effects are noted in almost half of exposed pregnancies. Morbidity includes hypotension, neonatal skull hypoplasia, anuria, and reversible or irreversible renal failure. Oligohydramnios may be associated with limb contractures, craniofacial deformation, and hypoplastic lung development. Oligohydramnios may not appear

until after the fetus has sustained irreversible injury. Rarely, there is no alternative antihypertensive agent available. In these rare cases, women should be counseled on the hazards, and serial ultrasound examinations performed to assess the intra-amniotic environment. If oligohydramnios is observed, **irbesartan** should be discontinued unless lifesaving for the mother. Antenatal surveillance may be appropriate depending upon gestation.

Breastfeeding Safety — There is no published experience in nursing women. While it is unknown whether **irbesartan** enters human breast milk, it is excreted at low concentration in rodent milk.

Drug Interactions — No clinically significant interactions identified.

References — Velazquez-Armenta EY, Han JY, Choi JS, et al. Hypertens Pregnancy 2007; 26:51-66.

Summary

Pregnancy Category: C (1st trimester), **D** (2nd and 3rd trimesters)
Lactation Category: U

- **Irbesartan** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.
- Women should be counseled on the risks and switched to a different class of antihypertensives prior to conception or during the 1st trimester.

Irinotecan—(Camptosar)

International Brand Name—Campto (France, Germany, Hong Kong, Indonesia, Israel, Japan, Korea, Philippines, Thailand); Irinotel (India); Topotecin (Japan)

Drug Class — Antineoplastics, topoisomerase inhibitor

Indications — Metastatic colon cancer

Mechanism — Topoisomerase I inhibitor

Dosage with Qualifiers — Colon cancer, metastatic—dosing protocols vary; consult specialty resources

- **Contraindications**—hypersensitivity to drug or class
- **Caution**—hyperbilirubinemia, concurrent or history of abdominal or pelvic radiation

Maternal Considerations — There is no published experience with **irinotecan** during pregnancy. Women of childbearing potential should be advised to avoid becoming pregnant while receiving **irinotecan.**
Side effects include diarrhea, N/V, myelosuppression, anemia, thrombocytopenia, neutropenia, leukopenia, sepsis, thromboembolism, acute renal failure, ileus, asthenia, abdominal weakness, alopecia, anorexia, fever, dyspepsia, insomnia, constipation, headache, chills, and dizziness.

Fetal Considerations — There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **irinotecan** crosses the human placenta, but it does cross the rat placenta. Rodent teratogen studies reveal **irinotecan** is embryotoxic and teratogenic, causing a variety of external, visceral, and skeletal abnormalities, along with decreased learning.

Breastfeeding Safety

There is no published experience in nursing women. It is unknown whether **irinotecan** enters human breast milk. **Irinotecan** is concentrated in rodent breast milk, and should probably be considered incompatible with breastfeeding until further study.

Drug Interactions

Adverse effects such as myelosuppression and diarrhea could be exacerbated by other antineoplastic agents having similar adverse effects.
Patients who previously received pelvic/abdominal irradiation are at increased risk of severe myelosuppression. Concurrent use is not recommended.
Hyperglycemia has been reported in patients with a history of diabetes mellitus or evidence of glucose intolerance.
The incidence of akathisia in clinical trials of **irinotecan** using weekly dosage was greater (8.5%, 4/47 patients) when **prochlorperazine** was administered on the same day as **irinotecan** rather than when given on separate days (1.3%, 1/80 patients). The 8.5% incidence of akathisia, however, is within the range reported for use of **prochlorperazine** when given as a premedication for other chemotherapies.
In view of the potential risk of dehydration secondary to vomiting and/or diarrhea, it would be reasonable to withhold diuretics both during **irinotecan** use and during periods of active vomiting or diarrhea.

References

There is no published experience in pregnancy or during lactation.

Summary

Pregnancy Category: D
Lactation Category: NS (possibly)
- **Irinotecan** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Iron dextran—(Dexferrum; Feostat; Heparan; Imexon; Infed; Iodex; Norefmi; Orferon; Pri-Dextra; Proferdex)

International Brand Name—Cosmofer (England, Germany, Ireland, Korea); Dexiron (Canada); Driken (Mexico); Hibiron (Indonesia); Imferon (India); Infufer (Canada)

Drug Class

Hematinics; Minerals

Indications

Iron deficiency and supplementation

Mechanism

Essential component in many proteins, including Hb

Dosage with Qualifiers

Iron deficiency—DOSE (ml) = 0.0442 × (desired Hb−observed Hb) × lean body weight (LBW) + (0.26 × LBW). IV/IM test dose required prior to the first therapeutic dose (0.5ml over at least 30sec for IV); wait 1h between test and dose administration; if total replacement dose given as a single dose diluted in 250-1000ml normal saline or D_5W, infuse over 4-6h.
LBW (female) = 45.5kg + 2.3kg for each inch above 5 feet.

NOTE: Provided as 50mg/ml elemental iron injection. IM dose *should not exceed 100mg/d;* IV dose *should rate should not exceed 50mg (1ml)/min.*

- **Contraindications**—hypersensitivity to drug or class, anemia not associated with iron deficiency
- **Caution**—CV disease, renal infection, increased LFTs, rheumatoid arthritis

Maternal Considerations

There is no evidence that iron supplementation improves pregnancy outcome in the industrialized world. That is not true, however, in developing countries where the treatment of iron deficiency anemia reduces both the antenatal and postnatal maternal morbidity and mortality. Under these circumstances, **iron dextran** is more effective than oral treatment in correcting anemia and reducing the need for transfusion. The IM administration of 3 doses (250mg Fe) at monthly intervals appears effective and well tolerated; it may be used in women who cannot tolerate oral iron. However, IM administration of iron is appropriate only in hospital settings well equipped to treat an anaphylactic crises. Folic acid supplementation is recommended.

Side effects include chest pain, abdominal pain, convulsions, N/V, seizures, headache, hematuria, hypotension, urticaria, respiratory arrest, dyspnea, arthralgia, and arthritis.

Fetal Considerations

There are no adequate reports or well-controlled studies of **iron dextran** in human fetuses. Iron crosses the placenta, but the effect of supplementation on that transport is unclear. There is some evidence that maternal **iron dextran** IV supplementation increases the fetal iron stores, but it is unclear which form of iron crosses.

Breastfeeding Safety

Maternal iron supplementation does not alter the concentration of iron in breast milk, though traces of unmetabolized **iron dextran** are found in human milk.

Drug Interactions

May form nephrotoxic chelates when used with **dimercaprol**. α-Tocopherol may decrease the hematologic response.

References

Bauminger BB, Walters G, Whither JT, Duke AB. J Clin Pathol 1982; 35:502-6.

Bingham D, Khalaf MM, Walters G, Whicher JT. J Clin Pathol 1983; 36:907-9.

Cuervo LG, Mahomed K. Cochrane Database Syst Rev 2007; (2):CD003094.

Jenkinson D. J Trop Med Hyg 1984; 87:71-4.

Komolafe JO, Kati O, Ijadunola KT, Ogunniyi SO. J Obstet Gynaecol 2003; 23:628-31.

Kumpf VJ. Nutr Clin Pract 1996; 11:139-46.

Mahale AR, Shah SH. Asia Oceania J Obstet Gynaecol 1993; 19:141-4.

Sharma JB, Jain S, Mallika V, et al. Am J Clin Nutr 2004; 79:116-22.

Solomons NW, Schumann K. Am J Clin Nutr 2004; 79:1-3.

Takahashi S, Kubota Y, Matsuoka O. J Radiat Res (Tokyo) 1983; 24:137-47.

Summary

Pregnancy Category: C
Lactation Category: S

- Though the risk of routine iron supplementation during pregnancy and lactation is probably minimal, there is no improvement in perinatal outcome or reduction in maternal morbidity in the industrialized world.
- IM/IV regimen may be appropriate in underdeveloped countries where the general health is poor; iron deficiency anemia is common and associated with antepartum and postpartum morbidity; and antenatal care is hindered by distance, acceptance, or compliance with tablet taking.

Isocarboxazid—(Marplan)

International Brand Name—Enerzer (Japan); Marplan (Denmark)

Drug Class ..... Antidepressants; MAO inhibitors

Indications ..... Depression

Mechanism ..... Nonselective hydrazine MAOI

Dosage with Qualifiers .....

Depression—begin 10mg PO bid; increase by 10mg q2-3d reaching 40mg/d after 1w; thereafter, may increase by another 20mg/d for a max of 60mg/d

NOTE: reserved for patients who have not responded satisfactorily to other antidepressants.

- **Contraindications**—hypersensitivity to drug or class; cerebrovascular or CV disease; pheochromocytoma; hepatic or renal disease; concurrent or recent use of MAOIs, TCAs, SSRIs, **buspirone,** sympathomimetics, **meperidine, dextromethorphan,** foods rich in tyramine, anesthetics, antihypertensives, **caffeine,** and CNS depressants.
- **Caution**—alcohol ingestion, renal dysfunction, frequent headaches

Maternal Considerations .....

Depression is common during and after pregnancy, but typically goes unrecognized. Pregnancy is not a reason *a priori* to discontinue psychotropic drugs. A major depressive episode (DSM-IV) implies a prominent and relatively persistent (almost every day for at least 2w) depressed or dysphoric mood that interferes with daily functioning. It includes at least 5 of the following 9 symptoms: depressed mood, loss of interest in usual activities, significant change in weight and/or appetite, insomnia or hypersomnia, psychomotor agitation or retardation, increased fatigue, feelings of guilt or worthlessness, slowed thinking or impaired concentration, and a suicide attempt or suicidal ideation. There are no adequate reports or well-controlled studies of **isocarboxazid** in pregnant women.
Side effects include hypotension, hepatotoxicity, lower seizure threshold, dry mouth, nausea, diarrhea, dizziness, and syncope.

Fetal Considerations .....

There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **isocarboxazid** crosses the human placenta; it does cross the rat placenta. Rodent teratogenicity studies have not been performed. Prolonged treatment during rodent pregnancy is associated with behavioral changes.

Breastfeeding Safety .....

There is no published experience in nursing women. It is unknown whether **isocarboxazid** enters human breast milk.

Drug Interactions .....

Administer with caution to patients receiving **disulfiram.** In a single study, rats given high intraperitoneal doses of an MAOI plus **disulfiram** experienced severe toxicity, including convulsions and death.
Concomitant use of other psychotropic agents is generally not recommended because of possible potentiating effects.
The MAO inhibitory effects of **isocarboxazid** may persist for a substantial period after discontinuation. To avoid potentiation, terminate **isocarboxazid** 10d before beginning the new agent.

■ **References** ····· Sato T, Yamamoto S, Moroi K. Jpn J Pharmacol 1972; 22:629-33.

■ **Summary** ·····

Pregnancy Category: C
Lactation Category: U

- **Isocarboxazid** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.
- There are alternative agents for which there is more experience during pregnancy and lactation.

Isoflurane—(Forane)

International Brand Name—Aerane (Korea); Aerrane (China, India, Indonesia, Israel, Netherlands, New Zealand, Philippines, Spain, Thailand); Floran (Israel); Forane (Argentina, Austria, Brazil, Bulgaria, China, Czech Republic, Germany, Hong Kong, Hungary, Indonesia, Ireland, Israel, Italy, Japan, Malaysia, New Zealand, Paraguay, Philippines, Poland, Russia, South Africa, Spain, Taiwan, Thailand, Turkey, Uruguay); Forene (Denmark, Venezuela); Forthane (Australia); Isoflurano (Chile, Ecuador); Isorane (Mexico); Sofloran (Mexico)

■ **Drug Class** ····· Anesthetics, general

■ **Indications** ····· Anesthesia, induction and maintenance

■ **Mechanism** ····· Unknown

■ **Dosage with Qualifiers** ·····

Anesthesia, induction—dosing varies, typically 1.5-3% ×7-10min for surgical anesthesia. (There are few if any indications to induce anesthesia with gas in adults.)
Anesthesia, maintenance—dosing varies, typically 1-2.5% with nitrous oxide, 1.5-3% with oxygen only

*NOTE: all commonly used muscle relaxants are markedly potentiated by **isoflurane,** the effect being most profound with nondepolarizing agents; see specialty texts.*

- **Contraindications**—hypersensitivity to drug or class, history of malignant hyperthermia
- **Caution**—head injury, increased ICP, myasthenia gravis, cardiac risk factors

■ **Maternal Considerations** ·····

There are no adequate reports or well-controlled studies in pregnant women. **Isoflurane** has been used clinically without pregnancy-related sequelae for many years. Like other halogenated anesthetic agents, **isoflurane** produces uterine relaxation. The inhibitory potency of **sevoflurane** and **desflurane** are comparable to, whereas that of **isoflurane** is smaller than, **halothane.** Minimum alveolar concentrations causing a 50% inhibition of the contractile amplitude were 1.7, 1.4, 2.35, and 1.7 ($p < .05$), respectively.
Side effects include malignant hyperthermia, muscle rigidity, tachycardia, cyanosis, arrhythmias, increased ICP, hepatotoxicity, laryngospasm, shivering, N/V, delirium, and uterine relaxation.

■ **Fetal Considerations** ·····

There are no adequate reports or well-controlled studies in human fetuses. **Isoflurane** rapidly crosses the human placenta, achieving an F:M ratio approximating unity. It has been used for fetal surgery and to facilitate uterine maneuvers. **Isoflurane** produces moderate fetal hypotension and bradycardia in sheep. However, fetal cerbral oxygenation remains constant despite a decrease in the fetal MAP by 20%. More recently, evidence has emerged that at least in rodents, exposure to such agents leads to neuroapoptosis with permanent brain damage.

Breastfeeding Safety

There is no published experience in nursing women. It is unknown whether **isoflurane** enters human breast milk. However, considering the indications and dosing, one-time **isoflurane** use is unlikely to pose a clinically significant risk to the breastfeeding neonate.

Drug Interactions

Isoflurane potentiates the relaxant effect of all muscle relaxants. Minimum alveolar concentration is reduced by use with nitrous oxide.

References

McClaine RJ, Uemura K, McClaine DJ, et al. Anesth Analg 2007; 104:397-406.
Omae T, Uchida O, Kuro M, Chiba Y. Masui 2002; 51:49-52.
Rizzi S, Canter LB, Ori C, Jevtovic-Jodorovic V. Brain Pathol 2008; 18:198-210.
Yoo KY, Lee JC, Yoon MH, et al. Anesth Analg 2006; 103:443-7.

Summary

Pregnancy Category: C
Lactation Category: U

- There is large clinical experience with **isoflurane** for general anesthesia during pregnancy. It is a reasonable selection when general anesthesia is required.
- **Isoflurane** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Isoniazid—(Abdizide; Dipicin; Eutizon; Fetefu; INH; Isonicid; Laniazid; Niazid; Nydrazid; Nydrazyd; Rimifon)

International Brand Name—Antimic (Thailand); Curazid Forte (Philippines); Dianicotyl (Greece); Diazid (Japan); Europlex (Philippines); Hidrazida (Portugal); Hydra (Japan); Hydrazide (Japan); Hydrazin (Taiwan); Iscotin (Japan, Taiwan); Isokin (India); Isonex (India, Indonesia); Isoniac (Argentina); Isoniazida N.T. (Ecuador); Isoniazid Atlantic (Hong Kong); Isonicid (Hungary); Isotamine (Canada); Isozid (Germany); Medic Aid Isoniazid (Philippines); Nicetal (Ecuador); Nicotibine (Belgium); Nicozid (Italy); Nidrazid (Czech Republic); PMS Isoniazid (Canada); Rimicid (Bulgaria); Rimifon (France, Spain, Switzerland); Tibinide (Sweden); Tubilysin (Finland); Valifol (Mexico); Yuhan-Zid (Korea)

Drug Class

Antimycobacterials

Indications

Tuberculosis, prophylaxis and infection

Mechanism

Inhibits lipid and nucleic acid synthesis

Dosage with Qualifiers

TB prophylaxis—300mg PO qd ×6-12mo; consider the addition of 25-50mg **pyridoxine** PO qd
TB infection—5mg/kg PO/IM qd ×9-24mo; max 300mg/d

*NOTE: may be combined with **rifampin** with or without **pyrazinamide.***

- **Contraindications**—hypersensitivity to drug or class, acute hepatic disease
- **Caution**—hepatic or renal dysfunction, alcohol ingestion

Maternal Considerations

Isoniazid is metabolized primarily by acetylation and dehydrazination. Approximately half of blacks and Caucasians are "slow acetylators" and the rest "rapid acetylators"; the majority of Eskimos and Orientals are rapid acetylators. The rate of acetylation does not significantly alter effectiveness, but slow acetylation may lead to higher blood levels and increase toxicity. The risk of **isoniazid**-induced hepatitis is age-related and

increased by alcohol ingestion. TB is experiencing a "rebirth" in many countries, and untreated TB in pregnancy is a significant threat to mother, fetus, and family. Women with untreated HIV and TB are at particular risk of death. Pregnant women in the US but born in another country should be screened for TB at the first prenatal visit. There are no adequate reports or well-controlled studies of **isoniazid** in pregnant women. Adherence to treatment is especially difficult because of a general fear of any medication and pregnancy-related nausea. All 4 first-line drugs (**isoniazid, rifampin, ethambutol,** and **pyrazinamide**) have an excellent safety record in pregnancy. Prophylactic **pyridoxine** is indicated. Antepartum treatment of latent TB has the greatest likelihood of success secondary to a higher degree of compliance. ***Side effects*** include aplastic anemia, agranulocytosis, thrombocytopenia, leukopenia, optic neuritis, peripheral neuropathy, hepatotoxicity, seizures, N/V, epigastric pain, diarrhea, dizziness, rash, acne, euphoria, agitation, tinnitus, and elevated LFTs.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. **Isoniazid** crosses the human placenta, but has not been associated with an increased risk of malformations. Congenital TB is rare but does occur. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically. Embryotoxicity may occur in some rodents.

Breastfeeding Safety

There are no adequate reports or well-controlled studies in nursing women. Only scant amounts of **isoniazid** are excreted into human breast milk. It is generally considered compatible with breastfeeding, and is not adequate treatment for neonatal TB. In addition to **isoniazid, rifampin, ethambutol,** and **streptomycin** (first-line agents), as well as **kanamycin** and **cycloserine** (second-line agents), are considered by the American Academy of Pediatrics to be compatible with breastfeeding.

Drug Interactions

May inhibit the hepatic metabolism of **ranolazine,** increasing the risks of QT prolongation and arrythmia.
May trigger a hypertensive crisis when used with **carbidopa** or **levodopa.**
May delay recover from **fentanyl** anesthesia.
May increase insulin or other hypoglycemic agent requirements.

References

Boggess KA, Myers ER, Hamilton CD. Obstet Gynecol 2000; 96:757-62.
Bothamley G. Drug Saf 2001; 24:553-65.
Brost BC, Newman RB. Obstet Gynecol Clin North Am 1997; 24:659-73.
Gupta A, Nayak U, Ram M, et al; Byramjee Jeejeebhoy Medical College–Johns Hopkins University Study Group. Clin Infect Dis 2007; 45:241-9.
Sackoff JE, Pfeiffer MR, Driver CR, et al. Am J Obstet Gynecol 2006; 194:451-6.
Smith KC. Curr Opin Infect Dis 2002; 15:269-74.
Tran JH, Montakantikul P. J Hum Lact 1998; 14:337-40.

Summary

Pregnancy Category: C
Lactation Category: S

- There is a long clinical experience with **isoniazid** during pregnancy. It should not be withheld when otherwise indicated.
- Women born outside of the US should be skin tested and treated during pregnancy if discovered to have latent TB.

Isoproterenol—(Aerolone; Isopro Aerometer; Isuprel; Medihaler-Iso; Norisodrine; Vapo-Iso)

International Brand Name—Isolin (India); Isoprenalin (Sweden); Isuprel HCl (Belgium, France, Hong Kong, Thailand); Isuprel Mistometer (Israel); Isuprel Nebulimetro (Peru); Proternol L (Taiwan); Saventrine (Finland, Greece, Singapore)

Drug Class	Adrenergic agonists; Antiarrhythmics; β-Agonists; Bronchodilators
Indications	Emergent arrhythmia, atropine-resistant bradycardia, CHB after VSD closure, bronchospasm
Mechanism	Nonspecific β-adrenergic agonist
Dosage with Qualifiers	Emergent arrhythmia—0.02-0.06mg IV ×1, then 2-20mcg/min IV infusion Atropine-resistant bradycardia—2-10mcg/min IV infusion CHB after VSD closure—0.02-0.06mg IV ×1 Bronchospasm during anesthesia—0.01-0.02mg IV ×1; may be repeated if necessary Bronchodilator—1 deep inhalation; may repeat after 5min if necessary; max 5 inhalations/d *NOTE: available in IV and inhaler forms.* • **Contraindications**—hypersensitivity to drug or class, hypersensitivity to sulfites, digitalis intoxication, angina • **Caution**—renal dysfunction, CV disease, diabetes mellitus, hyperthyroidism, hypokalemia
Maternal Considerations	There are no adequate reports or well-controlled studies of **isoproterenol** in pregnant women. It has been suggested its addition to epidural **bupivacaine** and **sufentanil** speeds the onset of analgesia. ***Side effects*** include hypotension, arrhythmias, cardiac arrest, bronchospasm, Stokes-Adams seizures, nervousness, insomnia, headache, tremor, angina, tachycardia, dyspepsia, N/V, and flushing.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. **Isoproterenol** crosses the human placenta, though the kinetics remain to be elucidated. It has been used (unsuccessfully) to treat fetal complete CHB. There are no reports of fetal compromise associated with **isoproterenol** despite numerous case reports and series. Rodent teratogenicity studies have not been performed.
Breastfeeding Safety	There is no published experience in nursing women. It is unknown whether **isoproterenol** enters human breast milk. Other β-agonists are considered compatible with breastfeeding.
Drug Interactions	Should not be injected with **epinephrine** simultaneously because both are direct cardiac stimulants and may trigger a serious arrhythmia. If desired they may be alternated, provided an interval of at least 4h has elapse. Use cautiously if at all with inhalational anesthetics such as **halothane** that could sensitize the myocardium to sympathomimetic amines.

Use cautiously with other sympathomimetic aerosol bronchodilators.
β-Adrenergic agonists should be used cautiously with MAOIs or TCAs since the action of the β-adrenergic agonists on the vascular system may be potentiated.
β-Receptor blocking agents and **isoproterenol** inhibit each other.

References

Groves AM, Allan LD, Rosenthal E. Circulation 1995; 92:3394-6.
Marcus MA, Vertommen JD, Van Aken H, et al. Anesth Analg 1998; 86:749-52.

Summary

Pregnancy Category: C
Lactation Category: S (likely)
- **Isoproterenol** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Isosorbide dinitrate—(Cardio; Cedocarb; Dilatrate-Sr; Dinisor; Insucar; Isd; Iso-Bid; Isobid; Isocard; Isonate; Iso-Par; Isorbid; Isordil; Isorem; Isotrate; Rigedal; Sorbitrate)

International Brand Name—Acordin (Switzerland); Angibid SR (Korea); Angiolong (China); Angitrit (Thailand); APO-ISDN (Canada, Malaysia); Bideren (Philippines); Caranil (Japan); Cardopax (Denmark); Cardopax Retard (Denmark); Carsodil (Korea); Carvasin (Italy); Cedocard (Austria, Belgium, England, Netherlands, Philippines, Switzerland); Cedocard Retard (Austria, England, Indonesia, Netherlands, Russia); Cedocard SR (Canada); Conducil (Argentina); Cordil (Israel); Cordil 40 SR (Israel); Cornilat (Slovenia); Coronex (New Zealand); Corosorbide (Argentina); Corovliss (Germany); Corovliss Retard (Germany); Diconpin (Germany); Difutrat (Slovenia); Dilanid (South Africa); Duranitrat (Germany); Hartsorb (Thailand); ISDN (Germany); Ismo 20 (Ecuador); Isobar (Philippines); Isobide (Taiwan); Isobinate (Thailand); Isocardide (Israel); Isocard Retard (Israel); Isocord (Brazil, Colombia); Isoday 40 (Israel); Isogen (Australia); Isoket (Bulgaria, China, Czech Republic, Germany, Hong Kong, Indonesia, Israel, Philippines, Poland, Portugal, Russia, Switzerland, Uruguay, Venezuela); Isoket Retard (Bulgaria, Czech Republic, England, Germany, Hong Kong, India, Korea, Malaysia, Portugal, Switzerland); Isoket Spray (Korea); Iso Mack (Germany, Switzerland); Iso-Mack (Denmark); Isomack (Austria, Korea); Iso Mack Retard (Ecuador, Indonesia, Israel, Thailand); Iso-Mack Retard (Malaysia); Isomack Retard (China, Hong Kong); Isomack Spray (Korea); Isonit (Finland); Iso-Puren (Germany); Isorbid (Mexico); Isorbide (Peru); Isordil (Argentina, Australia, Belgium, Brazil, Canada, Colombia, Costa Rica, Dominican Republic, Ecuador, El Salvador, Guatemala, Honduras, Hong Kong, Hungary, India, Indonesia, Ireland, Israel, Malaysia, Netherlands, Nicaragua, Panama, Paraguay, Philippines, Portugal, South Africa, Taiwan, Thailand, Turkey); Isorem (Thailand); Isostenase (Germany); Isotard 20 (Israel); Isotard 40 (Israel); Izo (Thailand); Langoran (France); Langoran LP (France); Lomilan (Slovenia); Maycor (Argentina, Czech Republic, Germany); Maycor Retard (Bulgaria, Czech Republic, Spain); Mono Mack (Costa Rica, Dominican Republic, El Salvador, Guatemala, Honduras, Panama); Nitorol (Malaysia, Philippines, Taiwan); Nitrol (Japan); Nitrol R (Japan); Nitrosid (Finland); Nitrosid Retard (Finland); Nitrosorbide (Italy, South Africa); Nitrosorbon (Germany, Philippines); Nosim (Argentina); Pensodril (Greece); Pensordil (Greece); Risordan (France, Greece); Risordan LP (France); Sigillum (Argentina); Soni-Slo (England, Israel, South Africa); Sorbangil (Norway, Sweden); Sorbichew (England); Sorbid (Turkey); Sorbidilat (Austria, Switzerland); Sorbidilat Retard (Austria); Sorbidilat SR (Switzerland); Sorbidin (Australia); Sorbitrate (Belgium, England, France, India, Malaysia); Sorbonit (Hungary, Poland); Storo (Japan); Surantol (Argentina); Tinidil (Slovenia); U-Sorbide (Taiwan); Vascardin (Indonesia, Israel, South Africa); Vasodilat (Argentina)

Drug Class

Nitrates; Vasodilators

Indications

Angina prophylaxis

Mechanism

An NO donor that stimulates cGMP production, causing smooth muscle relaxation

Dosage with Qualifiers

Angina prophylaxis—begin 5mg PO qd; space doses at least 5h apart, max 80mg/d; alternatively for SR, begin 20mg PO bid

NOTE: check package insert of preparation for recommended dose, as there are variations.

- **Contraindications**—hypersensitivity to drug or class, hypotension, cardiogenic shock, **sildenafil** use
- **Caution**—volume depletion

Maternal Considerations

There are no adequate reports or well-controlled studies in pregnant women. **Isosorbide dinitrate** may be a useful alternative treatment for acute hypertension in women with severe preeclampsia (5mg SL). In one small study of preeclamptic women, sustained use was associated with a decline in the uterine artery Doppler-measured flow resistance. It was used in one instance to facilitate the manual removal of a retained placenta. ***Side effects*** include methemoglobinemia, headache, lightheadedness, hypotension, syncope, tachycardia, flushing, peripheral edema, vomiting, fainting, and rebound hypertension.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **isosorbide dinitrate** crosses the placenta. SL administration has no effect on the FHR pattern. In one small study of preeclamptic women, sustained use was associated with a decline in the umbilical artery Doppler-measured flow resistance and the maximum AF pocket increased. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically. Embryotoxicity occurs in rodents with doses 50-100× the MRHD.

Breastfeeding Safety

There are no adequate reports or well-controlled studies in nursing women. It is unknown whether **isosorbide dinitrate** enters human breast milk.

Drug Interactions

Vasodilating effects may be additive with those of other vasodilators, especially alcohol.

References

Martinez-Abundis E, Gonzalez-Ortiz M, Hernandez-Salazar F, Huerta-y-Lucas MT. Gynecol Obstet Invest 2000; 50:39-42.
Nakatsuka M, Takata M, Tada K, et al. J Ultrasound Med 2002; 21:831-6.
Thaler I, Amit A, Kamil D, Itskovitz-Eldor J. Am J Hypertens 1999; 12:341-7.
Thaler I, Kahana H. Obstet Gynecol 2002; 100:987-91.

Summary

Pregnancy Category: C
Lactation Category: U

- **Isosorbide dinitrate** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Isosorbide mononitrate—(Imdur; Imtrate; Ismo; Isopen-20; Monoket)

International Brand Name—Angistad (Philippines); Arsorb (Australia); Cardismo (Indonesia); Cincordil (Brazil, Colombia); Conpin (Germany); Conpin Retardkaps (Germany); Corangin (China, New Zealand); Corangin SR (Taiwan); Coxime (Taiwan); Coxine SR (Taiwan); Duride (Malaysia); Effox (Poland); Elan (Italy); Elantan (Austria, Costa Rica, Czech Republic, Dominican Republic, El Salvador, England, Germany, Guatemala, Honduras, Hong Kong, Indonesia, Ireland, Korea, Malaysia, Mexico, Nicaragua, Panama, Peru, Philippines, Switzerland, Taiwan, Thailand, Venezuela); Elantan LA (Malaysia); Elantan Long (China, Czech Republic, Germany, Hong Kong, Malaysia, Peru, Philippines); Elantan Retard (Switzerland); Elonton SR (Korea); Etimonis (China); Imdex (Hong Kong); Imdex CR (Singapore); Imdur (Canada, Denmark, England, Hong Kong, Ireland, Korea, Philippines, Portugal, Sweden); Imdur 60 (Mexico, Taiwan); Imdur Durules (Australia); Ismexin (Finland); ISMN (Austria, Germany); ISMO (Chile, China, Denmark, England, Ireland, Italy, Netherlands, Spain, Sweden, Switzerland); Ismo 20 (Hong Kong, India, Indonesia, Malaysia, New Zealand, Philippines, Puerto Rico, South Africa, Taiwan, Thailand); Ismox (Finland); Isobid (Korea); Isolan (Argentina); Isomon (Greece); Isomonat (Austria, Czech Republic); Isomonit (Germany, Poland); Isonite (Korea); Isopen-20 (Thailand); Isotril ER (Korea); Iturol (Japan); Medocor (Ecuador); Monicor (France); Monis (Colombia); Monit 20 (India); Monoclair (Germany); Mono Corax (Germany); Mono Corax Retard (Germany); Monocord 20 (Israel); Monocord 40 (Israel); Monocord 50 SR (Israel); Monodur Durules (Australia); Monoket (Italy, Norway, Paraguay, Sweden); Monoket OD (Norway, Sweden); Monoket Retard (Austria, Italy); Monolong (Germany); Monolong 40 (Israel); Monolong 60 (Israel); Mono Mack (China, Ecuador, Mexico, Peru, South Africa); Mono-Mack (Czech Republic); Monomax (Korea); Mononit (Bulgaria, Poland); Mononit 20 (Israel); Mononit 40 (Israel); Mononit Retard 50 (Israel); Monopront (Finland); Mono-Sanorania (Germany); Monosorbitrate (India); Monosordil (Greece); Monotrate (India); Nitramin (Greece); Pentacard (Belgium, China, Indonesia); Vasotrate (India)

Drug Class	Nitrates; Vasodilators
Indications	Angina prophylaxis
Mechanism	NO donor that stimulates cGMP production, causing smooth muscle relaxation
Dosage with Qualifiers	Angina prophylaxis—30-60mg PO qd in 1 or divided doses depending on the preparation; max 240mg/d *NOTE: check package insert of preparation for recommended dose, as there are variations.* • **Contraindications**—hypersensitivity to drug or class, **sildenafil** use, hypotension • **Caution**—acute MI, hypotension, shock
Maternal Considerations	There are several case reports of its use in pregnant women with an acute MI. **Isosorbide mononitrate** is absorbed across the vaginal mucosa. It was investigated as a cervical ripening agent prior to 1st trimester abortion. It has also been studied as a cervical ripening agent where it (20 or 40mg) increases the maternal pulse rate and the maternal systolic and pulse pressures. In another RCT comparing it to **misoprostol, misoprostol** was superior for cervical ripening though both drugs were associated with a high frequency of side effects. In two other RCTs testing its ability to promote labor, it was inferior to prostaglandins but better than placebo. ***Side effects*** include orthostatic hypotension, palpitations, arrhythmia, chest pain, thrombocytopenia, N/V, headache, blurred vision, asthenia, dry mouth, constipation, abdominal pain, flatulence, bronchitis, sinusitis, and rash.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. In the studies of its use either as a cervical ripening agent or treatment for preeclampsia, **isosorbide mononitrate** produced Doppler changes consistent with a maternal systemic effect. In another study where cervical ripening

was the indication, **isosorbide mononitrate** (40mg) increased the FHR some 15 bpm. There was no significant effect on umbilical artery resistance. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically. Embryotoxicity occurs in rodents with doses 50-100× the MRHD.

Breastfeeding Safety ..... There are no adequate reports or well-controlled studies in nursing women. It is unknown whether **isosorbide mononitrate** enters human breast milk.

Drug Interactions ..... Vasodilating effects may be additive with those of other vasodilators, especially alcohol.

References .....

Bates CD, Nicoll AE, Mullen AB, et al. BJOG 2003; 110:64-7.
Chanrachakul B, Herabutya Y, Punyavachira P. Int J Gynaecol Obstet 2002; 78:139-45.
Ledingham MA, Thomson AJ, Lunan CB, et al. BJOG 2001; 108:276-80.
Nicoll AE, Mackenzie F, Greer IA, Norman JE. Am J Obstet Gynecol 2001; 184:958-64.
Osman I, MacKenzie F, Norrie J, et al. Am J Obstet Gynecol 2006; 194:1012-21.
Radulovic N, Norstrom A, Ekerhovd E. Acta Obstet Gynecol Scand 2007; 86:344-8.
Rameez MF, Goonewandene IM. J Obstet Gynaecol Res 2007; 33:452-6.
Thaler I, Amit A, Jakobi P, Itskovitz-Eldor J. Obstet Gynecol 1996; 88:838-43.
Wolfler MM, Facchinetti F, Venturini P, et al. Am J Obstet Gynecol 2006; 195:1617-22.

Summary .....

Pregnancy Category: C
Lactation Category: U

- **Isosorbide mononitrate** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.
- There are superior agents for either cervical ripening or the induction of labor.

Isotretinoin—(Accutane)

International Brand Name—Accure (Australia); Accutane Roche (Canada); Acnal SC (Korea); Acnetrex (Philippines); Acnotin (Hong Kong, Thailand); Akinol (Korea); Aknenormin (Germany); Curacne Ge (France); Curatane (Israel); Isotane (Thailand); Isotren (Korea); Isotret-Hexal (Germany); Isotrex (Argentina, Australia, Brazil, Costa Rica, Denmark, Dominican Republic, El Salvador, England, Guatemala, Honduras, Indonesia, Ireland, Korea, Nicaragua, Panama, Taiwan); Isotrex Gel (Colombia, France, Germany, Hong Kong, Israel, Malaysia, Mexico, New Zealand, Philippines, Spain, Thailand); Newtinon SC (Korea); Nimegen (Singapore); Oratane (Hong Kong, Malaysia, Singapore); Pinple (Korea); Procuta Ge (France); Roaccutan (Argentina, Austria, Colombia, Denmark, Ecuador, Finland, Germany, Italy, Mexico, Paraguay, Peru, Portugal, Uruguay, Venezuela); Roaccutane (Belgium, Bulgaria, China, Costa Rica, Czech Republic, Dominican Republic, El Salvador, England, France, Ghana, Greece, Guatemala, Honduras, Hong Kong, Ireland, Kenya, Korea, Malaysia, Netherlands, Nicaragua, Panama, Philippines, Poland, Puerto Rico, South Africa, Switzerland, Taiwan, Tanzania, Thailand, Uganda, Zambia); Roaccuttan (Colombia); Roacnetan (Chile); Roacutan (Brazil, Spain); Roacuttan (Hungary); Sotret (Thailand); Tretin (Korea)

Drug Class ..... Acne agents; Dermatologics; Retinoids

Indications ..... Acne, severe cystic; keratinization disorders

Mechanism ..... Unknown

Dosage with Qualifiers

Acne, severe cystic—begin 0.5-2mg/kg/d ×15-20w
Keratinization disorders—0.5-2mg/kg/d PO in divided doses bid; max 4mg/kg/d

NOTE: informed consent required.

- **Contraindications**—hypersensitivity to drug or class, hypersensitivity to parabens, pregnancy
- **Caution**—psychiatric disorder, lactation, exposure to bright sunlight, seizure disorder, hyperlipidemia, history of pancreatitis, diabetes mellitus

Maternal Considerations

Isotretinoin is contraindicated during pregnancy. Only manufacturer-approved physicians may prescribe it. Though many fail to comply patients must be capable of complying with mandatory contraceptive measures. Patients should be cautioned not to self-medicate with **St. John's wort** because of a possible interaction with oral contraceptives, increasing the risk of an unplanned pregnancy. It is critical women of childbearing potential select and commit to use 2 forms of effective contraception simultaneously, at least 1 of which must be a primary form, unless absolute abstinence is the chosen method, or the patient has undergone a hysterectomy. In one study, a cohort of 8609 women between 13 and 45 years of age with a first prescription for **isotretinoin** was identified. Pregnancies, spontaneous and elective abortions, and birth defects were identified using procedure codes and medical diagnoses. Ninety (90) became pregnant for an annual pregnancy rate of 32.7/1000 person-years of treatment. Of these, 76 terminated, 3 had a spontaneous abortion, and 2 had trauma during delivery resulting in neonatal death. There were only 9 live births. Among the live births, only one had a congenital anomaly of the face and neck (11%). Adjusting for potential confounders, predictors of becoming pregnant while on **isotretinoin** were lower socioeconomic level, one or more visits to the doctor or to the emergency department, or one or more hospitalization while on **isotretinoin;** concomitant **isotretinoin** and oral contraceptive use had a preventive effect.
Side effects include major birth defects, depression, psychosis, suicidal ideation, hepatotoxicity, pseudotumor cerebri, allergic vasculitis, cataracts, hearing impairment, neutropenia, thrombocytopenia, agranulocytosis, hypertriglyceridemia, elevated LFTs, inflammatory bowel disease, pancreatitis, vascular thrombosis, seizures, dry skin, skin fragility, pruritus, epistaxis, conjunctivitis, photosensitivity, arthralgia, peeling of the palms, decreased night vision, tinnitus, and nail bed changes.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. **Isotretinoin** and its active metabolites crosses the human (and subhuman primate) placenta, and it is a known human teratogen. Multiple organ systems are affected, including CNS, CV, and endocrine organs. Mental retardation without external malformation has also been reported. Similar malformations occur in rodents.

Breastfeeding Safety

There is no published experience in nursing women. It is unknown whether **isotretinoin** enters human breast milk. Considering its effect on the fetus, breastfeeding is considered contraindicated.

Drug Interactions

Patients should be advised against taking vitamin supplements containing vitamin A to avoid additive toxic effects.
Combined use with tetracyclines may increase the risk of pseudotumor cerebri (benign intracranial hypertension).

Systemic corticosteroids are known to cause osteoporosis. No formal clinical studies have been conducted to assess if there is an interactive effect on bone loss between systemic corticosteroids and **isotretinoin.**
Associated with depression in some patients. Women should be cautioned not to self-medicate with **St. John's wort** as there are reports of breakthrough bleeding in women on oral contraceptives shortly after starting **St. John's wort**. Pregnancies have also been reported by users of combined hormonal contraceptives and **St. John's wort**.

References

Berard A, Azoulay L, Koren G, et al. Br J Clin Pharmacol 2007; 63:196-205.
Brinker A, Trontell A, Beitz J. J Am Acad Dermatol 2002; 47:798-9.
Gorgos D. Dermatol Nurs 2002; 14:284.
Tzimas G, Nau H, Hendrickx AG, et al. Teratology 1996; 54:255-65.

Summary

Pregnancy Category: X
Lactation Category: NS

- **Isotretinoin** is a well-documented teratogen in humans and contraindicated during pregnancy and lactation.

Isradipine—(DynaCirc)

International Brand Name—Dynacirc (Colombia, Costa Rica, Dominican Republic, Ecuador, El Salvador, Guatemala, Honduras, Hong Kong, Malaysia, Mexico, Nicaragua, Panama, Philippines, South Africa, Taiwan, Thailand, Venezuela); Dynacirc SRO (Chile, Colombia, Costa Rica, Dominican Republic, Ecuador, El Salvador, Guatemala, Honduras, Hong Kong, Korea, Malaysia, Mexico, New Zealand, Nicaragua, Panama, Peru, Philippines, Thailand); Icaz LP (France); Icaz SRO (Philippines); Lomir (Austria, Belgium, Bulgaria, Czech Republic, Denmark, Finland, Germany, Greece, Hungary, Ireland, Israel, Netherlands, Norway, Poland, Portugal, South Africa, Spain, Sweden, Switzerland); Lomir Retard (Denmark); Lomir SRO (Austria, Czech Republic, Finland, Hungary, Italy, Netherlands, Norway, Poland, Portugal, Spain, Sweden, Switzerland); Prescal (England, Ireland); Vascal (Netherlands)

Drug Class

Antihypertensives; Calcium channel blockers; Dihydropyridines

Indications

Hypertension

Mechanism

Inhibits calcium influx into smooth muscle

Dosage with Qualifiers

Hypertension—begin 2.5mg PO bid, increasing by 2.5mg PO bid q2-4w prn; max 10mg/d

NOTE: available in sustained-release format.

- **Contraindications**—hypersensitivity to drug or class
- **Caution**—CHF

Maternal Considerations

There are no adequate reports or well-controlled studies in pregnant women. Calcium channel antagonists may be the tocolytic of choice based on their performance in meta-analyses. *In vitro*, **isradipine** is a superior tocolytic compared to **ritodrine** and **magnesium sulfate.** It has been used with success to treat preeclamptic hypertension with efficacy similar to **methyldopa** prior to delivery.
Side effects include palpitations, tachycardia, headache, hypotension, dizziness, fatigue, edema, flushing, rash, urinary frequency, and N/V.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. While **isradipine** crosses the human placenta, achieving an F:M ratio of about 0.25, Doppler-measured resistances in the umbilical artery are unaltered. Rodent studies are reassuring, revealing no evidence of teratogenicity despite the use of doses higher than those used clinically. There is, however, an increased frequency of IUGR at the highest doses studied.

Breastfeeding Safety

There is no published experience in nursing women. It is unknown whether **isradipine** enters human breast milk.

Drug Interactions

Severe hypotension has been reported during **fentanyl** anesthesia and concomitant use of a β-blocker and a calcium channel blocker.
Cimetidine may increase the **isradipine** mean peak plasma concentrations (36%) and significantly increase the AUC (50%). Careful monitoring for adverse reactions is advised.
Rifampicin significantly increases **isradipine** metabolism, causing a clinically significant reduction in its levels.

References

Kantas E, Cetin A, Kaya T, Cetin M. Acta Obstet Gynecol Scand 2002; 81:825-30.
King JF, Flenady VJ, Papatsonis DN, et al. Cochrane Database Syst Rev 2002; (2):CD002255.
Lunell NO, Bondesson U, Grunewald C, et al. Am J Hypertens 1993; 6:110S-1S.
Montan S, Anandakumar C, Arulkumaran S, et al. J Perinat Med 1996; 24:177-84.
Wide-Swensson DH, Ingemarsson I, Lunell NO, et al. Am J Obstet Gynecol 1995; 173:872-8.

Summary

Pregnancy Category: C
Lactation Category: U

- Calcium channel antagonists are effective for the control of BP, and may be the tocolytic of choice.
- **Isradipine** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.
- There are alternative calcium channel antagonists for which there is more experience in pregnancy and lactation.

Itraconazole—(Sporanox)

International Brand Name—Candistat (India); Canditral (Singapore, Thailand); Carexa (Mexico); Forcanox (Indonesia); Fungitrazol (Indonesia); Furolnok (Indonesia); Hitrazole (Korea); Icona (Thailand); Irta (Korea); Isox (Mexico); Itodal (Peru); Itra (Thailand); Itracon (Thailand); Itranax (Mexico); Itrizole (Japan); Itzol (Indonesia); Konitra (Korea); Micoral (Peru); Norspor (Thailand); Nufatrac (Indonesia); Onikonazole (Korea); Orungal (Bulgaria, Hungary, Poland); Quali-Itrazole (Hong Kong); Sempera (Germany); Sinozol (Mexico); Spazol (Thailand); Sporacid (Indonesia); Sporal (Thailand); Sporanox (Argentina, Brazil, Canada, Chile, China, Colombia, Ecuador, Hong Kong, Indonesia, Korea, Malaysia, Paraguay, Philippines, Taiwan, Uruguay, Venezuela); Sporanox 15 D (Costa Rica, Dominican Republic, El Salvador, Guatemala, Honduras, Mexico, Nicaragua, Panama, Peru); Sporanox IV (Hong Kong); Sporlab (Thailand); Spornar (Thailand); Spyrocon (Indonesia); Trachon (Indonesia); Trisporal (Netherlands)

Drug Class

Antifungals

Indications

Fungal infection

Mechanism

Inhibits CYP-dependent synthesis of ergosterol

Dosage with Qualifiers

Fungal infection—begin 200mg PO bid ×3d, or 200mg IV bid ×4 doses for life-threatening disease
Onychomycosis of the fingernails—200mg PO bid ×7d, off ×21d; repeat ×1
Onychomycosis of the toenails—200mg PO qd ×12w
Candidiasis, oropharyngeal—swish first 20ml PO qd ×1-2w
Candidiasis, esophageal—swish first 10ml PO qd ×2w after symptoms resolve, total 3w

NOTE: always confirm diagnosis prior to initiating therapy; available in tablet, parenteral, and oral liquid forms; give tablets with food and solution without.

- **Contraindications**—hypersensitivity to drug or class; use of either **astemizole, terfenadine, pimozide, quinidine, dofetilide,** or **cisapride;** lactation; CHF or history of CHF; LV dysfunction
- **Caution**—hepatic or renal dysfunction

Maternal Considerations

There are no adequate reports or well-controlled studies of **itraconazole** in pregnant women. There are several case reports of its use during pregnancy without note of diminished efficacy. There are also reports suggesting that the efficacy of oral contraceptives to block ovulation may be reduced by simultaneous use of **itraconazole.**
Side effects include hepatic toxicity or failure, CHF, pulmonary edema, angioedema, Stevens-Johnson syndrome, N/V, diarrhea, headache, hypertension, fatigue, fever, pruritus, hypokalemia, dizziness, anorexia, malaise, somnolence, and albuminuria.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. **Itraconazole** interacts with a major placental transporter, P-glycoprotein. In one prospective cohort study, there was no evidence of teratogenicity or fetal sequelae. In rodents, doses of **itraconazole** 5-20× the MRHD were associated with maternal and embryotoxicity, and teratogenicity in the survivors, consisting predominantly of skeletal defects. In another rodent study, skeletal defects occurred after early exposure (day 8), while cleft lip and palate were seen following later exposure (day 13).

Breastfeeding Safety

There is no published experience in nursing women. **Itraconazole** enters human breast milk, but the pharmacokinetics are presently unclear. According to the manufacturer, the maximum M:P ratio is 1.77, the milk concentration is 70mcg/L, and a theoretic infant dose is 10mcg/kg/d.

Drug Interactions

Numerous drug interactions are described, and the following is meant only as an illustrative summary.
Itraconazole and its major metabolite, hydroxyitraconazole, are inhibitors of CYP3A4. As such, it can decrease the elimination of drugs metabolized by CYP3A4, and as a result increase plasma concentrations of these drugs. Such drugs include **alfentanil, alprazolam, atorvastatin, budesonide, buspirone, busulfan, carbamazepine, cerivastatin, cilostazol, cisapride, cyclosporine, dexamethasone, digoxin, disopyramide, docetaxel, dofetilide, diazepam,** dihydropyridines, **eletriptan,** ergot alkaloids, **halofantrine, indinavir, lovastatin, methylprednisolone, midazolam,** oral hypoglycemics, **pimozide, quinidine, rifabutin, ritonavir, saquinavir, simvastatin, sirolimus, tacrolimus, triazolam, trimetrexate, verapamil,** vinca alkaloids, and **warfarin.** Other inhibitors of CYP3A4 may increase the plasma concentrations of **itraconazole.** These drugs include

clarithromycin, erythromycin, indinavir, and **ritonavir.** Patients who must take **itraconazole** with one of these drugs should be monitored closely for signs or symptoms of increased or prolonged pharmacologic effects of **itraconazole.** Whenever possible, plasma concentrations should be monitored, and dosage adjustments made after **itraconazole** therapy is initiated.
Inducers of CYP3A4 may decrease the plasma concentrations of **itraconazole** and thus block efficacy. These drugs include antacids, **carbamazepine,** H_2-receptor antagonists, **isoniazid, nevirapine, phenobarbital, phenytoin,** proton pump inhibitors, **rifabutin,** and **rifampin.**

References

Aoki F, Sando Y, Tajima S, et al. Intern Med 2001; 40:1128-31.
Bar-Oz B, Moretti ME, Bishai R, et al. Am J Obstet Gynecol 2000; 183:617-20.
Tiboni GM, Marotta F, Del Corso A, Giampietro F. Toxicol Lett 2006; 167:8-18.
van Puijenbroek EP, Feenstra J, Meyboom RH. Ned Tijdschr Geneeskd 1998; 142:146-9.

Summary

Pregnancy Category: C
Lactation Category: U

- **Itraconazole** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Ivermectin—(Mectizan; Stromectol)

International Brand Name—Ivermectina (Costa Rica, Dominican Republic, El Salvador, Guatemala, Honduras, Nicaragua, Panama); Ivermectol (India); Ivexterm (Mexico); Mectizan (France); Quanox Gotas (Colombia); Revectina (Brazil); Sanifer (Uruguay); Securo (Argentina); Stromectol (France)

Drug Class

Antiparasitics

Indications

Strongyloidiasis, onchocerciasis, scabies

Mechanism

Increases cell membrane permeability in nerves and muscle

Dosage with Qualifiers

Strongyloidiasis—200mcg/kg PO ×1 taken with water
Onchocerciasis—150mcg/kg PO ×1 taken with water; re-treatment often necessary
Scabies—200mcg/kg PO ×1

- **Contraindications**—hypersensitivity to drug or class
- **Caution**—hyperreactivity to onchderm

Maternal Considerations

There are no adequate reports or well-controlled studies of **ivermectin** in pregnant women. The few published cases report no sequelae. Further, there have been several mass exposures of pregnant women during community-based treatment of onchocerciasis. No increase in adverse pregnancy outcomes was noted.
Side effects include pruritus, fever, edema, rash, lymphadenopathy, dizziness, chest pain, abdominal distention, tachycardia, abnormal eye sensation, hypotension, and elevated LFTs.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. It is not known whether **ivermectin** crosses the

human placenta; it does appear to block P-glycoprotein–mediated efflux. There have been several mass exposures of pregnant women during community-based treatment of onchocerciasis. No increase in pregnancy wastage or malformations was observed.

Breastfeeding Safety

There are no adequate reports or well-controlled studies in nursing women. Only ⅓ of the maternal plasma **ivermectin** level is achieved in human breast milk. It is unlikely to pose a clinically significant risk to the breastfeeding infant.

Drug Interactions

No clinically significant interactions identified.

References

Ballent M, Lifschitz A, Virkel G, et al. J Vet Pharmacol Ther 2007; 30:242-8.
Doumbo O, Soula G, Kodio B, Perrenoud M. Bull Soc Pathol Exot 1992; 85:247-51.
Ogbuokiri JE, Ozumba BC, Okonkwo PO. Eur J Clin Pharmacol 1993; 45:389-90.
Pacque M, Munoz B, Poetschke G, et al. Lancet 1990; 336:1486-9.

Summary

Pregnancy Category: C
Lactation Category: S (likely)

- **Ivermectin** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Kanamycin—(Kantrex; Klebcil)

International Brand Name—Kamycine (France); Kanacin (Korea); Kanamed (Thailand); Kanamicina Gen-Far (Peru); Kanamycin Capsules Meiji (Thailand); Kanamycin Meiji (Hong Kong, Philippines); Kanamycin Novo (South Africa); Kanamycin Sanbe (Indonesia); Kancin (India, Malaysia, Philippines, Taiwan, Thailand); Kanoxin (Indonesia, Thailand); Randikan (Mexico)

Drug Class	Aminoglycosides; Antibiotics
Indications	Bacterial infection
Mechanism	Inhibits protein synthesis by binding the 30S ribosomal subunit, leading to cell destruction
Dosage with Qualifiers	Bacterial infection—15mg/kg/d IM/IV in 2-3 divided doses *NOTE: renal dosing; peak 25-35mcg/ml, trough <10mcg/ml.* • **Contraindications**—hypersensitivity to drug or class • **Caution**—myasthenia gravis, other nephrotoxic agents, renal dysfunction, vestibular or cochlear implant
Maternal Considerations	There are no adequate reports or well-controlled studies in pregnant women. **Kanamycin** is a second-line agent for the treatment of TB, but is otherwise not used widely during pregnancy and offers no advantages over other aminoglycosides. Routine monitoring of peak and trough levels is not required in otherwise healthy women with normal renal function. ***Side effects*** include nephrotoxicity, ototoxicity, tinnitus, enterocolitis, pseudotumor cerebri, pruritus, N/V, diarrhea, weakness, tremor, muscle cramps, anorexia, edema, vertigo, agranulocytosis, thrombocytopenia, and elevated BUN/Cr.
Fetal Considerations	There are no well-controlled studies in human fetuses. Case reports suggest the degree of human placental transfer is incomplete. **Kanamycin** crosses the placenta in rodents, and most likely in humans, as other aminoglycosides do. There is no evidence of teratogenicity for any of the aminoglycosides. In guinea pigs, doses of **kanamycin** 20× the MRHD had no obvious side effects. However, otic nerve damage has been reported after an *in utero*–exposed neonate was challenged postnatally.
Breastfeeding Safety	There are no adequate reports or well-controlled studies in nursing women. **Kanamycin** enters human breast milk, but is generally considered compatible with breastfeeding.
Drug Interactions	*In vitro* mixing of an aminoglycoside with β-lactam–type antibiotics (penicillins or cephalosporins) may result in significant mutual inactivation. A reduction in aminoglycoside serum t/2 or serum levels has been reported in patients with impaired renal function and in some patients with normal renal function even when administered separately by different routes. Such inactivation is usually clinically significant only in the setting of severely impaired renal function. Concurrent and/or sequential use of diuretics or other neurotoxic and/or nephrotoxic antibiotics may increase the prevalence and severity of adverse responses.
References	Czeizel AE, Rockenbauer M, Olsen J, Sorensen HT. Scand J Infect Dis 2000; 32:309-13. Good RG, Johnson GH. Obstet Gynecol 1971; 38:60-2.

Pacifici GM. Int J Clin Pharmacol Ther 2006; 44:57-63.
Wang Z, Liou L. Ann Otol Rhinol Laryngol 1994; 103:983-5.

Summary

Pregnancy Category: D
Lactation Category: S (likely)
- For most indications, there are alternative agents for which there is more experience during pregnancy and lactation.

Ketamine—(Ketalar)

International Brand Name—Anesject (Indonesia); Calypsol (Israel, Puerto Rico, Thailand); Keta-Hameln (Thailand); Ketalin (Mexico); Ketamax (Philippines); Ketanest (Bulgaria, Czech Republic, Germany); Ketmin (India); Ketolar (Spain); Soon-Soon (Taiwan); Tekam (Israel)

Drug Class

Anesthesia, general

Indications

Induction of anesthesia

Mechanism

Unknown; a dissociative anesthetic that is a known noncompetitive antagonist of NMDA receptors

Dosage with Qualifiers

Induction of anesthesia—1-1.5mg IV over 1min or 5-10mg/kg IM

*NOTE: **atropine** may be used to decrease salivation.*

- **Contraindications**—hypersensitivity to drug or class, hypertension, elevated ICP, glaucoma, thyrotoxicosis, CHF, psychosis
- **Caution**—hepatic dysfunction, GERD

Maternal Considerations

Ketamine is a rapid-acting general anesthetic agent. There are no adequate reports or well-controlled studies in pregnant women. It is popular in some locales for cesarean delivery of parturients who are either hemorrhaging or have asthma (increased catecholamine release ameliorates bronchospasm) or fetal acidemia. Compared to **thiopental,** women who receive **ketamine** during cesarean delivery have a lower need for supplemental analgesia postoperatively. The incidence of awareness to verbal commands during surgery is lower with **ketamine** compared to **thiopental,** but the frequency of recall of intraoperative events is not different. There is reportedly an increased incidence of dreaming during anesthesia, which may lead to dissatisfaction with the anesthetic experience. **Ketamine** has also been used with neuraxial anesthesia. In women undergoing cesarean section with spinal analgesia, the addition of **ketamine** (0.05mg/kg) intrathecally to 10mg of spinal plain **bupivacaine** (0.5%) led to rapid onset of both sensory and motor blockade and enhanced the segmental spread of spinal block without prolonging the duration of analgesia, while **fentanyl** provided prolonged analgesia. In other studies, IV low-dose **ketamine** combined with intrathecal **bupivacaine** was reported to provide longer analgesia after cesarean section and lower postoperative analgesic consumption than **bupivacaine** alone, suggesting a preemptive effect.
Side effects include increased ICP, laryngospasm, increased intraocular pressure, hypotension, hypertension, bradycardia, myocardial depression, delirium, hypersalivation, N/V, tremor, diplopia, nystagmus, fasciculation, depressed reflexes, and hallucinations.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. A number of rodent studies suggest **ketamine** may alter postnatal behavior and taste appreciation with early exposure. In sheep, **ketamine** attenuates hemodynamic responses to cerebral hypoperfusion and is a potent inhibitor of ACTH and pro-opiomelanocortin/pro-ACTH release.

Breastfeeding Safety

There are no adequate reports or well-controlled studies in nursing women. It is unknown whether **ketamine** enters human breast milk. However, considering its application, it is unlikely a clinically significant amount of drug would remain in breast milk at least 48h postoperatively.

Drug Interactions

Prolonged recovery time may occur if barbiturates and/or narcotics are used concurrently.

References

Gaitini L, Vaida S, Collins G, et al. Can J Anaesth 1995; 42:377-81.
Kee WD, Khaw KS, Ma ML, et al. Anesth Analg 1997; 85:1294-8.
Powers MJ, Wood CE. Am J Physiol Regul Integr Comp Physiol 2007; 292:R1542-9.
Unlugenc H, Ozalevli M, Gunes Y, et al. Eur J Anaesthesiol 2006; 23:1018-24.

Summary

Pregnancy Category: D
Lactation Category: U

- **Ketamine** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Ketoconazole—(Funazole; Fungazol; Fugen; Funginox; Nizoral; Zoralin)

International Brand Name—Akorazol (Mexico); Anfuhex (Indonesia); Antanazol (Singapore); Aquarius (Greece); Beatoconazole (Singapore); Bigazol (Korea); Comozol (Korea); Conazol (Mexico); Cremosan (Mexico); Daktagold (New Zealand); Dezoral (Singapore); Diazon (Hong Kong, Singapore, Thailand); Fazol (Colombia); Formyco (Indonesia); Fugen (Costa Rica, El Salvador, Guatemala, Honduras, Nicaragua, Panama); Funazole Tabs (India); Funet (Indonesia); Fungarest (Spain); Fungaway (Taiwan); Fungazol Tabs (Hong Kong, Thailand); Fungicide (Thailand); Fungicide Tabs (Bahrain, India, Republic of Yemen); Fungiderm-K (Thailand); Funginoc (Bahrain); Funginox Tabs (Thailand); Fungoral (Greece, Norway, Sweden); Kenazol (Thailand); Kenazole (Israel); Kesnazol (Korea); Ketazol (Israel, South Africa); Keto-Comp (Peru); Ketoconazol (Costa Rica, Dominican Republic, El Salvador, Guatemala, Honduras, Nicaragua, Panama); Keto-Crema (Peru); Ketoderm (France); Ketoisdin (Spain); Ketomed (Colombia); Ketomicin (Peru); Ketomicol (Peru); Ketona (China, Taiwan); Keto-Shampoo (Peru); Ketozal (Thailand); Ketozol (India); Kezon (Thailand); Konaturil (Mexico); Lama (Thailand); Larry (Thailand); Lusanoc (Indonesia); Mizole (Korea); Mizoron (Thailand); Mycofebrin (Greece); Nastil (Mexico); Nazole (Korea); Neutrogena T/Sal (Peru); Niz Creme (South Africa); Nizoral 2% Cream (New Zealand, Philippines); Nizoral Cream and Tablets (England, Mexico, Netherlands); Nizoral Shampoo (Germany, New Zealand, Philippines); Nizoral Tablets (Colombia, Costa Rica, Dominican Republic, Ecuador, El Salvador, France, Guatemala, Honduras, Mexico, New Zealand, Nicaragua, Panama, Peru); Nizoral Tabs and Cream (Taiwan); Niz Shampoo (South Africa); Oxonazol (Peru); Panfungol (Spain); Pasalen (Thailand); Picamic (Indonesia); Prenalon (Mexico); Pristine (Hong Kong); Pristinex (Hong Kong); Profungal (Singapore); Sebizole (Australia, Hong Kong); Spike (Korea); Sporium (Colombia); Sporoxyl (Thailand); Sporozol (India); Termizol (Mexico); Triatop Lotion (China); Zoralin Tabs (Indonesia)

Drug Class

Antifungals

Indications

Fungal infections such as tinea versicolor, tinea capitis, tinea corporis, tinea cruris, tinea pedis, and candidiasis

Mechanism

Inhibits cell membrane ergosterol synthesis

Dosage with Qualifiers

Fungal infection—200-400mg PO qd (up to 800mg PO qd for esophageal candida or cavitary histoplasmosis)

NOTE: administer with food; soda increases absorption 50-75%; also available in topical solution and cream.

- **Contraindications**—hypersensitivity to drug or class; achlorhydria; fungal meningitis; use of **astemizole, cisapride,** or **terfenadine**
- **Caution**—hepatotoxic drugs, hepatic dysfunction

Maternal Considerations

There are no adequate reports or well-controlled studies in pregnant women. **Ketoconazole** is a known aromatase inhibitor and may alter sex hormone levels. Although the drug is absorbed when applied topically, the systemic concentration is relatively low. **Ketoconazole** has been used to treat Cushing's syndrome during pregnancy.
Side effects include hepatic failure or toxicity, adrenal insufficiency, N/V, diarrhea, dizziness, headache, lethargy, nervousness, somnolence, hemolytic anemia, thrombocytopenia, leukopenia, increased LFTs, and rash.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. **Ketoconazole** is a P-glycoprotein substrate, though placental transfer has not apparently been studied. Several studies suggest **ketoconazole** interferes with ovarian synthesis of progesterone by inhibiting aromatase. As such, it could interfere with implantation and maintenance of early pregnancy. However, limited epidemiological studies are reassuring. **Ketoconazole** produced maternal toxicity along with syndactyly and oligodactyly in rodents exposed to 10× the MRHD.

Breastfeeding Safety

Only a trace amount of maternally administered **ketoconazole** enters human breast milk, and it is generally considered safe during breastfeeding.

Drug Interactions

A potent inhibitor of CYP3A4. Use with drugs primarily metabolized by CYP3A4 may increase the plasma concentrations of such drugs and increase or prolong both therapeutic and adverse effects. Therefore, unless otherwise specified, appropriate dosage adjustments may be necessary.
Use with **terfenadine** can increase plasma concentration.
Use with **astemizole** may result in elevated plasma levels of **astemizole** and its active metabolite desmethylastemizole, which may prolong QT intervals. Use with **astemizole** is therefore contraindicated.
Use with **cisapride** produces a mean 8-fold increase in the AUC of **cisapride,** which can cause prolongation of the QT interval on the ECG. Therefore, use with **cisapride** is contraindicated.
May increase plasma concentrations of **cyclosporine, tacrolimus,** and **methylprednisolone** to a degree requiring dosage adjustment.
Can increase the concentrations of **midazolam** and **triazolam.** This may potentiate and prolong hypnotic and sedative effects, so these drugs should not be used in women treated with **ketoconazole.**
Rare cases of elevated plasma concentrations of **digoxin** have been reported. It is not clear whether this was due to the combination of therapy. Therefore, it is advisable to monitor **digoxin** concentrations closely.
May enhance the anticoagulant effect of coumarin-like drugs; the anticoagulant effect should be carefully monitored and adjusted as needed.
Severe hypoglycemia has been reported in patients receiving **miconazole** (an imidazole) and oral hypoglycemic agents; such a

potential interaction involving use with **ketoconazole** (an imidazole) cannot be ruled out.
Use with **phenytoin** may alter the metabolism of one or both of the drugs; monitor serum levels closely.
Use with **rifampin** reduces the blood levels of **rifampin.**
Isoniazid is also reported to affect **ketoconazole** concentrations adversely. These drugs should not be given concomitantly.
Rare cases of a **disulfiram**-like reaction to alcohol have been reported. These experiences have been characterized by flushing, rash, peripheral edema, nausea, and headache. Symptoms resolved within a few hours.

References

Amado JA, Pesquera C, Gonzalez EM, et al. Postgrad Med J 1990; 66:221-3.
Ayub M, Stitch SR. J Steroid Biochem 1986; 25:981-4.
Kazy Z, Puho E, Czeizel AE. Congenit Anom (Kyoto) 2005; 45:5-8.
Kragie L, Turner SD, Patten CJ, et al. Endocr Res 2002; 28:129-40.
Moretti ME, Ito S, Koren G. Am J Obstet Gynecol 1995; 173:1625-6.

Summary

Pregnancy Category: C
Lactation Category: S
- **Ketoconazole** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Ketoprofen—(Alrhumat; Kefenid; Orudis; Oruvail)

International Brand Name—Alrheumat (Denmark, England, Ireland); Alrheumun (Germany); Aneol (Japan); Anzema (Indonesia); Apo-Keto (Canada); Arcental (Spain); Bi-Profenid (France); Bi-Rofenid (Belgium); Dolofar (Chile); Dolomax (Colombia); Efiken (Mexico); Epatec (Japan); Fastum (Italy, Spain); Fetik (Indonesia); Floramil (Philippines); Gabrilen (Germany); Gabrilen Retard (Germany); Helenil (Argentina); Kaltrofen (Indonesia); Kebanon (Korea); Keduril (Costa Rica, Dominican Republic, El Salvador, Guatemala, Honduras, Mexico, Nicaragua, Panama); Kefen (New Zealand); Kehancer (Singapore); Kenhancer (Malaysia, Singapore); Kenofen Gel (Korea); Keotsan (Peru); Keprofen (Japan); Ketadom (Hong Kong); Ketin (Taiwan); Ketofen (Taiwan, Thailand); Keto Film (Korea); Ketoflam (South Africa); Ketolgin (Israel); Ketolgin Gel (Israel); Ketolgin SR (Israel); Ketomex (Finland); Ketonal (Israel); Ketorin (Finland); Ketosolan (Spain); Ketum (Colombia); Kevadon (Argentina); Knavon (Greece); Mohrus (Japan); Naxal (Japan); Novo-Keto-EC (Canada); Orucote (South Africa); Orudis (Canada, Costa Rica, Denmark, El Salvador, England, Finland, Germany, Guatemala, Honduras, Italy, Malaysia, Netherlands, Nicaragua, Norway, Panama, Spain, Sweden, Uruguay); Orudis E-100 (Malaysia); Orudis EC (Philippines); Orudis SR (Australia, Switzerland); Oruvail (Canada, China, Denmark, England, Greece, Hong Kong, New Zealand); Oruvail EC (New Zealand); Ostofen (India); Ovurila (Indonesia); Ovurila E (Indonesia); Profecom (Indonesia); Profenid (Austria, Bulgaria, China, Colombia, Czech Republic, Ecuador, Indonesia, Israel, Korea, Mexico, Paraguay, Peru, Poland, Portugal, Russia, Switzerland, Taiwan, Turkey, Venezuela); Profenid 50 (India); Profenil (Italy); Profika (Indonesia); Protofen (Indonesia); Provail CR (Singapore); Rematof (Indonesia); Rhetoflam (Indonesia); Rheuna PAP (Korea); Rofenid (Belgium); Spondylon (Germany); Toprec (France); Treosin (Japan)

Drug Class

Analgesics, non-narcotic; NSAIDs

Indications

Mild to moderate pain, fever, dysmenorrhea, osteoarthritis and rheumatoid arthritis

Mechanism

Inhibits cyclooxygenase and lipoxygenase, leading to reduced prostaglandin synthesis

Dosage with Qualifiers

Mild to moderate pain—25-50mg PO q6-8h; max 75mg/d
Fever—12.5mg PO q4-6h; max 75mg/d
Dysmenorrhea—25-50mg PO q6-8h; max 300mg/d
Osteoarthritis or rheumatoid arthritis—75mg PO tid, or 50mg PO qid; max 300mg/d

NOTE: requires both renal and hepatic dosing; available in SR formulation.

- **Contraindications**—hypersensitivity to drug or class, ASA/NSAID-induced asthma
- **Caution**—hypertension, CHF, history of GI bleeding, nasal polyps, hepatic or renal dysfunction

Maternal Considerations

There are no adequate reports or well-controlled studies in pregnant women. **Ketoprofen** provides effective analgesia after both vaginal and cesarean delivery, but its efficacy is similar to other NSAIDs such as **diclofenac.**
Side effects include renal failure, fluid retention, dyspepsia, GI bleeding, bronchospasm, interstitial nephritis, hepatotoxicity, Stevens-Johnson syndrome, headache, nausea, constipation, abdominal pain, dizziness, rash, agranulocytosis, increased LFTs, thrombocytopenia, tinnitus, and drowsiness.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. **Ketoprofen** rapidly crosses the placenta, reaching an F:M ratio approaching unity. Most other NSAIDs can produce fetal oliguria and ductal constriction in a dose- and gestational age–dependent fashion. One case report suggests **ketoprofen** has the same actions. Another study suggests the active S isomer is preferentially transported across the term placenta. Further, acute renal failure is reported in preterm infants whose mothers received **ketoprofen** prior to delivery. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR.

Breastfeeding Safety

Low concentrations of **ketoprofen** are found in human breast milk, but the breastfed infant would consume less than 1% of the maternal weight adjusted dose.

Drug Interactions

NSAIDs may decrease the antihypertensive effect of ACEIs.
NSAIDs can reduce the natriuetic effect of **furosemide** and thiazides. When given concomitantly with **ketoprofen, hydrochlorothiazide** reduces urinary potassium and chloride excretion compared to **hydrochlorothiazide** alone.
Patients taking diuretics are at a greater risk of developing renal failure secondary to a decrease in renal blood flow caused by NSAIDs.
NSAIDs can reduce the renal clearance and increase the serum levels of **lithium.** Thus, patients receiving both drugs should be observed closely for signs of **lithium** toxicity.
NSAIDs are reported to competitively inhibit **methotrexate** clearance and may increase the risk of toxicity.
Probenecid increases both free and bound **ketoprofen** by reducing the plasma clearance of **ketoprofen** to about ⅓, as well as decreasing its protein binding. This combination is not recommended.
The effects of **warfarin** and NSAIDs on GI bleeding are synergistic, such that users of both drugs together have a risk of serious GI bleeding higher than users of either drug alone. Concurrent therapy with **ketoprofen** and **warfarin** requires close monitoring of patients.

References

De Graeve J, Frankinet C, Gielen JE. Biomed Mass Spectrom 1979; 6:249-52.
Facchinetti F, Casini ML, Costabile L, et al. Acta Obstet Gynecol Scand 2005; 84:951-5.
Fieni S, Gramellini D, Vadora E. Fetal Diagn Ther 2004; 19:224-7.
Gouyon JB, Petion AM, Sandre D, et al. Arch Fr Pediatr 1991; 48:347-8.

Jacqz-Aigrain E, Serreau R, Boissinot C, et al. Ther Drug Monit 2007; 29:815-8.
Lagrange F, Pehourcq F, Bannwarth B, et al. Fundam Clin Pharmacol 1998; 12:286-91.
Sunshine A, Olson NZ. J Clin Pharmacol 1988; 28(12 Suppl): S47-54.

Summary

Pregnancy Category: B
Lactation Category: S

- **Ketoprofen** is an excellent agent for puerperal analgesia. However, there are other NSAIDs for which there is more experience regarding use during pregnancy and lactation.

Ketorolac tromethamine—(Acular; Acular PF; Toradol)

International Brand Name—Acdol (Colombia); Acular (Austria, Brazil, Canada, China, France, Germany, Hong Kong, Korea, Netherlands, Singapore, Thailand, Uruguay, Venezuela); Aculare (Belgium); Acular PF (China); Algipres (Chile); Alidol (Mexico); Burten (Peru); Dolac (Mexico); Dolorex (Peru); Dolten (Argentina, Paraguay); Eleadol (Uruguay); Estopein (Mexico); Kelac (India); Keradol (Dominican Republic, El Salvador, Guatemala, Panama); Kerola (Korea); Ketanov (India, Philippines); Keto (Hong Kong); Ketodrol (Colombia); Ketonic (India); Ketorac (Korea); Ketoracin (Korea); Ketron (Colombia); Kortezor (Philippines); Notolac (Venezuela); Onemer (Mexico); Remopain (Indonesia); Rolesen (Ecuador, Peru); Supradol (Mexico); Tabel (Korea); Tarasyn (Korea); Taresin (Korea); Toloran (Mexico); Tora-Dol (South Africa); Toradol (Australia, Canada, Denmark, England, Finland, Hong Kong, Indonesia, Italy, Norway, Philippines, Poland, Russia, Spain, Sweden, Turkey); Toragesic (Brazil); Toral (Mexico); Torasic (Indonesia); Torolac (India); Torpain (Indonesia); Tradak (Japan); Tromedal (Mexico)

Drug Class

Analgesics, non-narcotic; NSAIDs

Indications

Moderate to severe pain

Mechanism

Inhibits cyclooxygenase and lipoxygenase, leading to reduced prostaglandin synthesis

Dosage with Qualifiers

Moderate to severe pain—begin 60mg IM/30mg IV then repeat q6h as needed, max 120mg or 10mg PO q4-6h prn, max 40mg/d

NOTE: if transitioning from parenteral to PO, begin 20mg PO followed by 10mg PO q4-6h prn, max 40mg/d.
NOTE: do not exceed 5d of therapy; available for ophthalmologic use.

- **Contraindications**—hypersensitivity to drug or class, ASA/NSAID-induced asthma, cerebrovascular hemorrhage, preoperative use
- **Caution**—hypertension, CHF, history of GI bleeding, nasal polyps, hepatic or renal dysfunction

Maternal Considerations

Ketorolac is indicated for the management of pain that usually would require an opioid for relief. There are no adequate reports or well-controlled studies in pregnant women.
Side effects include renal failure, fluid retention, dyspepsia, GI bleeding, bronchospasm, interstitial nephritis, hepatotoxicity, Stevens-Johnson syndrome, nausea, constipation, abdominal pain, headache, dizziness, rash, thrombocytopenia, agranulocytosis, increased LFTs, tinnitus, and drowsiness.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **ketorolac** crosses the placenta. Most other NSAIDs can produce fetal oliguria and ductal constriction in a dose- and gestational age–dependent fashion. It is not known whether **ketorolac** has the same actions.

Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR. The perinatal mortality rate in rodents was increased in association with delayed onset of parturition.

Breastfeeding Safety

Small quantities of **ketorolac** enter human breast milk. An unsupplemented newborn would ingest <0.4% of the daily maternal dose.

Drug Interactions

Reduces the diuretic response to **furosemide** in normovolemic healthy subjects by approximately 20%.
Administration with **probenecid** resulted in decreased clearance of **ketorolac** and significant increases in **ketorolac** plasma levels (total AUC increased approximately 3-fold from 5.4 to 17.8mcg/h/ml). Therefore, concomitant use with **probenecid** is contraindicated.
NSAIDs can reduce renal **lithium** clearance.
Some NSAIDs may reduce the clearance of **methotrexate.**
Concomitant use of ACEIs may increase the risk of renal impairment, particularly in volume-depleted patients.
Hallucinations have been reported when used in patients taking psychoactive drugs (e.g., **alprazolam, fluoxetine, thiothixene**).

References

Wischnik A, Manth SM, Lloyd J. Eur J Clin Pharm 1989; 36:521-4.

Summary

Pregnancy Category: C
Lactation Category: S

- **Ketorolac** is an excellent analgesic, but there are other NSAIDs for which there is more experience regarding use during pregnancy and lactation.

Labetalol—(Coreton; Normadate; Normodyne; Trandate)

International Brand Name—Abetol (Italy); Albetol (Finland); Amipress (Italy); Biascor (Argentina); Hybloc (New Zealand); Ipolab (Italy); Labelol (Argentina); Labesine (Korea); Lamitol (Slovenia); Liondox (Argentina); Presolol (Australia, Taiwan); Pressalolo (Italy); Salmagne (Greece); Trandate (Austria, Belgium, Canada, Chile, Czech Republic, Denmark, England, France, Hong Kong, Hungary, Ireland, Italy, Japan, Korea, Netherlands, Norway, Portugal, Spain, Sweden, Switzerland, Taiwan, Turkey, Venezuela)

Drug Class ..... Adrenergic antagonists; α- and β-Blockers; Antihypertensives

Indications ..... Hypertension

Mechanism ..... Selective α_1- and nonselective β_1- and β_2-adrenergic receptor antagonist

Dosage with Qualifiers .....

Hypertension—begin 100mg PO bid, increase 100mg bid q2-3w; max 2.4g/d

Acute hypertension—if diastolic BP >105mmHg, administer incremental dosing of 5-10mg IV, with a cumulative dose of 40-80mg IV over 20 min; max 300mg IV

- **Contraindications**—hypersensitivity to drug or class, asthma, CHF, AV block, cardiogenic shock, bradycardia, hepatotoxicity, hypoglycemia
- **Caution**—MI, angina, diabetes mellitus, hepatic or renal dysfunction, cocaine, abrupt withdrawal, major surgery

Maternal Considerations .....

Hypertensive disorders complicate 5-10% of pregnancies and are a leading cause of maternal and perinatal morbidity and death. Severe hypertension (systolic BP >170mmHg and/or diastolic BP >110mmHg) should be treated rapidly to reduce the risk of stroke, death, and possibly eclampsia in preeclamptic women. There is no consensus whether mild to moderate hypertension should be treated during pregnancy. The risks of transient severe hypertension, the likelihood of antenatal hospitalization, proteinuria at delivery, and neonatal RDS may be decreased by therapy. **Labetalol** reduces BP more slowly than **nifedipine,** and it does not increase the maternal cardiac index as **nifedipine** does. Thus, **labetalol** is the drug of choice for hypertensive women with tachycardia. **Labetalol** has a lower risk of hypotension than parenteral **hydralazine. Labetalol** is better tolerated than **methyldopa** and provides more efficient BP control. It reduces cerebral pressure without altering cerebral perfusion. IV **labetalol** is equally effective as IV **hydralazine** for the treatment of postpartum hypertension. **Labetalol** may also be useful for the treatment of maternal thyrotoxicosis during labor. ***Side effects*** include hepatic necrosis, SLE, bronchospasm, dizziness, N/V, fatigue, dyspepsia, rhinitis, dyspnea, edema, postural hypotension, pruritus, and increased BUN/Cr.

Fetal Considerations .....

Labetalol crosses the human placenta, yielding an F:M ratio of 0.5 and an AF:M ratio <0.20. Neither **labetalol** nor **hydralazine** vasodilates the perfused human cotyledon. Doppler flow studies reveal no change in umbilical, uterine, and middle cerebral resistances after treatment. IV **labetalol** can cause fetal bradycardia. The available data are inadequate to determine whether **labetalol** adversely affects fetal or neonatal HR and pattern. Until such data are available, FHR changes should not be attributed to a drug effect, but rather to progression of the underlying maternal or placental disease. Hypoglycemia, bradycardia, hypotension, pericardial effusion, and myocardial

hypertrophy are reported after long-term oral **labetalol.**
Fetal death may also occur after a sudden drop in the maternal BP, the risk of which can be minimized by adequate hydration. Overall, neonatal outcome is similar to that achieved with **hydralazine. Labetalol** may be useful for the treatment of fetal thyrotoxicosis. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically. **Labetalol** reduces uteroplacental blood flow selectively in guinea pigs, perhaps explaining the increased frequency of IUGR in this model.

Breastfeeding Safety

There is no consistent relation between maternal plasma and milk concentrations either within or between individuals. The risk of hypoglycemia in breastfed neonates is increased by **labetalol** but may be blunted with glucose-fortified formula.

Drug Interactions

May increase the risk of tremor when taken with TCAs.
May blunt the bronchodilator effect of β-agonists; therefore, greater than normal doses of a β-agonist may be required for the treatment of asthma.
Cimetidine increases the bioavailability of **labetalol.** Special care should be used in establishing the dose required for BP control in such patients.
Synergism with **halothane** has been shown. High concentrations (>3%) should not be used because the degree of hypotension will be increased and because of the possibilities of a large reduction in cardiac output and an increase in the central venous pressure. The anesthesiologist should be informed when a patient is receiving **labetalol.**
Blunts the reflex tachycardia produced by **nitroglycerin** without preventing its hypotensive effect. Additional antihypertensive effects may occur.
Care should be taken if **labetalol** is used concomitantly with calcium antagonists of the **verapamil** type.
Patients with a history of anaphylaxis to a variety of allergens may be more reactive to repeated challenge, either accidental, diagnostic, or therapeutic. Such patients may be unresponsive to the usual doses of **epinephrine** used to treat allergic reaction.

References

Belfort MA, Tooke-Miller C, Allen JC Jr, et al. Hypertens Pregnancy 2002; 21:185-97.
Bowman ML, Bergmann M, Smith JF. Thyroid 1998; 8:795-6.
Crooks BN, Deshpande SA, Hall C, et al. Arch Dis Child Fetal Neonatal Ed 1998; 79:F150-1.
el-Qarmalawi AM, Morsy AH, al-Fadly A, et al. Int J Gynaecol Obstet 1995; 49:125-30.
Gilson GJ, Kramer RL, Barada C, et al. J Matern Fetal Med 1998; 7:142-7.
Harper A, Murnaghan GA. Br J Obstet Gynaecol 1991; 98:453-9.
Hjertberg R, Faxelius G, Belfrage P. Acta Obstet Gynecol Scand 1993; 72:611-5.
Hjertberg R, Faxelius G, Lagercrantz H. J Perinat Med 1993; 21:69-75.
Lunell NO, Kulas J, Rane A. Eur J Clin Pharmacol 1985; 28:597-9.
Munshi UK, Deorari AK, Paul VK, Singh M. Indian Pediatr 1992; 29:1507-12.
Olsen KS, Beier-Holgersen R. Acta Obstet Gynecol Scand 1992; 71:145-7.
Petersen OB, Skajaa K, Svane D, et al. Br J Obstet Gynaecol 1994; 101:871-8.
Pickles CJ, Broughton Pipkin F, Symonds EM. Br J Obstet Gynaecol 1992; 99:964-8.

Pirhonen JP, Erkkola RU, Makinen JI, Ekblad UU. Biol Neonate 1991; 59:204-8.
Rogers RC, Sibai BM, Whybrew WD. Am J Obstet Gynecol 1990; 162:362-6.
Scardo JA, Vermillion ST, Newman RB, et al. Am J Obstet Gynecol 1999; 181:862-6.
Sibai BM, Mabie WC, Shamsa F, et al. Am J Obstet Gynecol 1990; 162:960-6.
Varon J, Marik PE. Chest 2000; 118:214-27.
Vermillion ST, Scardo JA, Newman RB, Chauhan SP. Am J Obstet Gynecol 1999; 181:858-61.
Vigil-De Gracia P, Ruiz E, López JC, et al. Hypertens Pregnancy 2007; 26:163-71.

Summary

Pregnancy Category: C
Lactation Category: S

- **Labetalol** is an effective agent for the treatment of acute hypertension and thyrotoxicosis during labor.
- In many locales, **labetalol** is the preferred drug for the short-term treatment of preeclamptic hypertension.
- Hypoglycemia but not IUGR is the most common adverse neonatal effect.

Lactulose—(Acilac; C-Cephulose; Cephulac; Cholac; Constilac; Constulose; Duphalac; Enulose; Evalose; Generlac; Heptalac; Laxilose)

International Brand Name—Acilac (Canada); Actilax (Australia); Alpha-Lactulose (New Zealand); Avilac (Israel); Bifinorma (Germany); Bifinorma Granulat (Germany); Bifiteral (Belgium, Germany); Danilax (Hong Kong); Dhactulose (Malaysia, Singapore); Dia-Colon (Italy); Duphalac (Austria, Belgium, Bulgaria, Chile, China, Czech Republic, Ecuador, England, Finland, France, Greece, Hong Kong, Hungary, Indonesia, Ireland, Italy, Japan, Korea, Malaysia, Netherlands, Norway, Paraguay, Philippines, Poland, Portugal, South Africa, Spain, Sweden, Switzerland, Taiwan, Thailand, Turkey); Farlac (Brazil); Genlac (Australia); Genocolan (Argentina); Hepalac (Thailand); Lacson (South Africa); Lactocur (Germany); Lactul (Malaysia); Lactulax (El Salvador, Honduras, Indonesia, Israel, Mexico, Panama, Peru, Uruguay); Lactulen (Colombia); Lactumed (Malaysia); Lactus (Singapore); Lactuverlan (Germany); Laevolac (Austria, Czech Republic, Hong Kong, Hungary, Israel, Italy, Portugal, Switzerland, Thailand); Laxette (South Africa); Laxilose (Canada); Laximed (Germany); Levolac (Finland, Norway); Lipebin (Peru); Livo Luk (India); Martulose (Hong Kong); Moderan (Venezuela); Monilac (Japan, Korea); Normolax (Israel); Pralax (Indonesia); Regulact (Mexico); Sirolax (Israel); Tenualax (Argentina); Tulotract (Germany)

Drug Class

Gastrointestinals; Laxatives

Indications

Constipation, hepatic encephalopathy

Mechanism

Increases stool water content, traps ammonium ions

Dosage with Qualifiers

Constipation—15-30ml (10-20g/d) PO qd or bid
Hepatic encephalopathy—30-45ml PO tid or qid (20-30g tid or qid)

- **Contraindications**—hypersensitivity to drug or class, galactosemia
- **Caution**—diabetes mellitus, hypokalemia

Maternal Considerations

Constipation is common during pregnancy. **Lactulose** helps restore normal bowel habits. It is poorly absorbed, and women with **lactose** intolerance tolerate **lactulose** better in the 3rd trimester because of slow transit and bacterial adaptation. It is

used by some to maintain a soft stool after delivery complicated by rectal extension.
Side effects include acidosis, abdominal distention, belching, abdominal pain, diarrhea, anorexia, N/V, electrolyte disorders, hypernatremia, and flatulence.

Fetal Considerations

There are no adequate reports or well-controlled studies of **lactulose** in human fetuses. Because of poor maternal absorption, it is unlikely the maternal systemic concentration will reach a clinically relevant level. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically.

Breastfeeding Safety

There is no published experience in nursing women. It is unknown whether **lactulose** enters human breast milk. Because of poor maternal absorption, it is unlikely the maternal systemic concentration will reach a clinically relevant level. Breastfeeding infants require lactase to metabolize lactose, the major carbohydrate in breast milk. Lactase is located on the small intestinal brush border and is extremely vulnerable to pathogenic damage.

Drug Interactions

There are conflicting reports about use with **neomycin.**
Theoretically, the elimination of certain colonic bacteria by **neomycin** and possibly other anti-infective agents may interfere with the desired breakdown of **lactulose** and thus prevent the acidification of colonic contents.
Use with nonabsorbable antacids may inhibit the desired **lactulose**-induced drop in colonic pH.
Other laxatives should not be used, especially during the initial phase of therapy for portal-systemic encephalopathy, because the loose stools resulting from their use may falsely suggest that adequate **lactulose** dosage has been achieved.

References

Baglioni A, Dubini F. Boll Chim Farm 1976; 115:596-606.
Eogan M, Daly L, Behan M, et al. BJOG 2007; 114:736-40.
Gattuso JM, Kamm MA. Drug Saf 1994; 10:47-65.
Mizuno O. Endocrinol Jpn 1987; 34:449-55.
Northrop-Clewes CA, Lunn PG, Downes RM. J Pediatr Gastroenterol Nutr 1997; 24:257-63.
Signorelli P, Croce P, Dede A. Minerva Ginecol 1996; 48:577-82.
Szilagyi A, Salomon R, Martin M, et al. Clin Invest Med 1996; 19:416-26.

Summary

Pregnancy Category: B
Lactation Category: S

- Most laxatives are relatively safe during pregnancy if used intermittently as directed.

Lamivudine—(Epivir; Epivir HBV; 3 TC)

International Brand Name—3TC (Argentina, Canada, Costa Rica, Dominican Republic, El Salvador, Guatemala, Honduras, Hong Kong, Indonesia, Korea, Malaysia, Mexico, New Zealand, Nicaragua, Panama, South Africa, Uruguay); 3TC-HBV (Indonesia); Epivir (Brazil, Ecuador, Paraguay, Peru, Singapore, Thailand, Venezuela); epivir 3TC (Chile); Heptodin (China); Heptovir (Canada); Inhavir (Colombia); Ladiwin (South Africa); Lamidac (India); Zeffix (Australia, Israel, Philippines, Singapore, Taiwan, Thailand)

Drug Class ..... Antivirals; Nucleoside reverse transcriptase inhibitors

Indications ..... HIV infection, HBV infection

Mechanism ..... Reverse transcriptase inhibitor

Dosage with Qualifiers .....

HIV infection—150mg PO bid
HBV infection—100mg PO qd

- **Contraindications**—hypersensitivity to drug or class
- **Caution**—hepatic or renal dysfunction, pancreatitis, long-term therapy, obesity

Maternal Considerations .....

There are no adequate reports or well-controlled studies of **lamivudine** in pregnant women. **Lamivudine** is rapidly absorbed after oral administration, reaching maximal serum concentrations after 30-90min. Triple therapy (**zidovudine, lamivudine, nevirapine**) is a highly effective regimen. However, there are reports of rapid development of genotypic resistance to **lamivudine.** HIV therapy that reduces the viral load significantly reduces the risk of mother-to-child transmission. Hepatotoxicity, usually within 5mo of beginning therapy, is a major concern during pregnancy. It is most severe when associated with HBV and HCV co-infection. There are presently only 2 drugs for the treatment of hepatitis B during pregnancy—**interferon alfa-2b** and **lamivudine.** The initial response to **lamivudine** is superior to **interferon alfa-2b. Lamivudine** is reportedly safe in pregnant women with chronic HBV infection during the last weeks of pregnancy. However, reduced HBV particle number does not necessarily translate into decreased vertical transmission. Further, resistant HBV strains develop in some patients. US federal government guidelines recommend **zidovudine** plus **lamivudine** for health care personnel exposed to both HBV and HIV. ***Side effects*** include acidosis, hepatic steatosis or toxicity, pancreatitis, neuropathy, neutropenia, thrombocytopenia, rhabdomyolysis, and exacerbation of hepatitis B.

Fetal Considerations .....

The worldwide spread of HIV-1 has resulted in an estimated 1 million children born yearly to HIV-1–infected mothers. In the absence of antiretroviral intervention, about 25% are HIV-1 infected. Maternal **AZT** prophylaxis reduces the rate of neonatal transmission to some 7%, with further reductions with combination therapy including **lamivudine. Lamivudine** readily crosses the human placenta; the AF:M ratio reportedly varies from unity to 4. This level does not necessarily prevent HBV transmission to the perinate despite undetectable maternal viral DNA. Large trials are awaited. Relative and absolute polymerase chain reaction quantification reveals a 3- to 4-fold mean increase in MDR1 placental transcription in HIV-infected women. Further, there is a 2.5-fold increase of immunoreactive P-glycoprotein in placentas from HIV-infected women. This MDR1 overexpression is observed regardless of antiretroviral therapy. This suggests that P-glycoprotein in placentas from

HIV-infected women would modulate the maternofetal transport of antiretrovirals across the placental barrier and consequently decrease fetal exposure to these compounds.
Neonatal prophylaxis with both **zidovudine** and **lamivudine** is typically initiated within 12h of birth. Mitochondrial disorders are described in children exposed *in utero* to some reverse transcriptase enzyme inhibitors (e.g., **zidovudine**). While rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically, embryotoxicity occurs in rabbits. In monkeys, **lamivudine** becomes incorporated into the DNA of multiple fetal organs and telomere shortening occurs. In human infants, **lamivudine** incorporation as well as HPRT and glycophorin A assay (GPA) mutagenesis have been documented in cord blood from infants exposed *in utero* to **zidovudine** and **lamivudine.** Given the risk:benefit ratio, these highly successful drugs will continue to be used for prevention of vertical viral transmission; however, evidence of genotoxicity suggests exposed children should be followed well past adolescence for early detection of potential cancer hazard.

Breastfeeding Safety

There are no adequate reports or well-controlled studies in nursing women. **Lamivudine** is excreted into human breast milk, though the kinetics remain to be elucidated. Breastfeeding is contraindicated in HIV-infected nursing women where formula is available to reduce the risk of neonatal transmission. However, in women receiving **zidovudine, lamivudine,** and **nevirapine** (HAART) from 28w of gestation to 1mo postpartum, median M:P ratios were 1.1, 0.6, and 1.8, respectively. HIV RNA levels in breast milk were significantly lower than in untreated women (median of 2.3 vs. 3.4 log at delivery and 1.9 vs. 3.6 log at day 7; $p < .001$ for both comparisons). Almost 90% of treated women have less than 50 copies/ml compared to only ⅓ of untreated women. DNA loads are unaffected. Thus, antiretroviral agents administered during the 3rd trimester and after delivery reach levels similar to or higher than plasma concentrations in breast milk and can significantly reduce HIV RNA levels, and support the potential role of maternal HAART prophylaxis in reducing the risk of breastfeeding-associated transmission. Further, HIV-1 inhibitory concentrations of **nevirapine** are achieved in breastfeeding infants, exposing infants to the potential beneficial and adverse effects of **nevirapine.**

Drug Interactions

Lamivudine and **zalcitabine** may inhibit the intracellular phosphorylation of one another. Their combined use is not recommended.

References

Bloom SL, Dias KM, Bawdon RE, Gilstrap LC 3rd. Am J Obstet Gynecol 1997; 176:291-3.
Camus M, Deloménie C, Didier N, et al. Placenta 2006; 27:699-706.
Chappuy H, Treluyer JM, Jullien V, et al. Antimicrob Agents Chemother 2004; 48:4332-6.
Clarke JR, Braganza R, Mirza A, et al. J Med Virol 1999; 59:364-8.
Giuliano M, Guidotti G, Andreotti M, et al. J Acquir Immune Defic Syndr 2007; 44:286-91.
Hill JB, Sheffield JS, Zeeman GG, Wendel GD Jr. Obstet Gynecol 2001; 98:909-11.
Johnson MA, Moore KH, Yuen GJ, et al. Clin Pharmacokinet 1999; 36:41-66.
Kazim SN, Wakil SM, Khan LA, et al. Lancet 2002; 359:1488-9.

Lee LM, Henderson DK. Drug Saf 2001; 24:587-97.
Mandelbrot L, Landreau-Mascaro A, Rebacewic ZC, et al. JAMA 2001; 285:2083-93.
Mandelbrot L, Peytavin G, Firtion G, Farinotti R. Am J Obstet Gynecol 2001; 184:153-8.
Moodley D, Pillay K, Naidoo K, et al. J Clin Pharmacol 2001; 41:732-41.
Olivero OA, Fernandez JJ, Antiochos BB, et al. J Acquir Immune Defic Synd 2002; 29:323-9.
Poirier MC, Olivero OA, Walker DM, Walker VE. Toxicol Appl Pharmacol 2004; 199:151-61.
Shapiro RL, Holland DT, Capparelli E, et al. J Infect Dis 2005; 192:720-7.
Shapiro RL, Ndung'u T, Lockman S, et al. J Infect Dis 2005; 192:713-9.
Stojanov S, Wintergerst U, Belohradsky BH, Rolinski B. AIDS 2000; 14:1669.
Trautwein C. Schweiz Rundsch Med Prax 2002; 91:970-6.
van Nunen AB, de Man RA, Heijtink RA, et al. J Hepatol 2000; 32:1040-1.
Yong S, Liu M, Wong L. Zhonghua FuChan Ke Za Zhi 2008; 43:329-31.
Zoulim F. Drug Saf 2002; 25:497-510.

Summary

Pregnancy Category: C
Lactation Category: NS

- A cocktail of **zidovudine, lamivudine,** and **nevirapine** significantly reduces the risk of mother-to-child transmission antenatally and postnatally, and remains a standard for the treatment of adult HIV infection.
- Pregnant women should be monitored closely for hepatotoxicity after initiating therapy.
- Physicians are encouraged to register pregnant women under the Antiretroviral Pregnancy Registry (1-800-258-4263) for a better follow-up of the outcome while under treatment with **lamivudine.**

Lamotrigine—(Lamictal)

International Brand Name—Lamepil (India); Lamictin (South Africa); Lamodex (Israel); Lamogine (Israel); Lamotrix (Malaysia); Neurium (Brazil)

Drug Class ..... Anticonvulsants

Indications ..... Seizures (partial)

Mechanism ..... Unknown

Dosage with Qualifiers .....

Seizures—begin 50mg/d, then increase up to 50-250mg PO bid; max 500mg/d

NOTE: avoid abrupt withdrawal.

- **Contraindications**—hypersensitivity to drug or class, abrupt withdrawal
- **Caution**—hepatic or renal dysfunction, allergy to **valproate**

Maternal Considerations .....

Most pregnancies are uneventful in women with epilepsy, and most babies are delivered healthy with no increased risk of obstetric complications in women. There are no adequate reports

or well-controlled studies of **lamotrigine** during pregnancy. Concerns over teratogenicity of AEDs must be weighed against the risks to the mother and fetus of seizures. Therapeutic drug monitoring has therefore been recommended to control for changes in the disposition of the older generation AEDs during pregnancy. Much less is known about gestation-induced alterations in the pharmacokinetics of the AEDs that have been introduced in the last 15y. Lamotrigine is by far the most extensively studied of the newer AEDs. **Lamotrigine** clearance is increased during pregnancy, and many women require a higher dose to maintain therapeutic levels. Pronounced alterations have been reported, with an increase of >300% from baseline in late pregnancy in some patients on monotherapy. The available data suggest the associated decline in plasma concentrations is associated with loss of seizure control. Limited data indicate a similar decline in late pregnancy in plasma concentrations of the active monohydroxy derivative of **oxcarbazepine.** Adjustments are based on clinical symptoms, not solely on serum drug levels. **Lamotrigine** is an inhibitor of dihydrofolate reductase. Adequate folate supplementation beginning preconception is wise. The impact of pregnancy on clearance reverses quickly postpartum. The most frequent adverse maternal effect is skin rash, typically in the first month of treatment. Planned pregnancy and counseling before conception is crucial. Counseling should cover folate supplementation, the importance medication compliance, the risk of teratogenicity, and the importance of prenatal care. **Lamotrigine** increases the metabolism of **ethinyl estradiol** and progestogens; a preparation containing at least 50mcg of **ethinyl estradiol** is recommended. ***Side effects*** include rash (0.3% and may be life-threatening), dysmenorrhea, dizziness, ataxia, somnolence, diplopia, headache, blurred vision, N/V, dyspepsia, rhinitis, anxiety, insomnia, pain, weight decrease, chest pain, infection, aplastic anemia, hemolytic anemia, thrombocytopenia, hepatic failure, aphasia, confusion, and nystagmus.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. **Lamotrigine** crosses the human placenta, achieving an F:M ratio near unity. Women taking anticonvulsant medication of any type have a 4-8% risk of delivering a child with a birth defect compared to 2-4% in the general population. **Lamotrigine** inhibits dihydrofolate reductase, an enzyme necessary for the biosynthesis of nucleic acids and proteins. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR at doses analogous to human. The highest doses cause maternal and fetal toxicity characterized by IUGR and ventricular dilation. Though some data are conflicting, registry data do not reveal a significant increase in the risk of major malformation (2.8% for 1st trimester exposure with monotherapy, but 4.3% with polytherapy). Use of monotherapy at the lowest effective quantity given in divided doses to minimize the peaks can minimize the risks. Recent pregnancy databases suggest **valproate** is significantly more teratogenic than **carbamazepine,** and the combination of **valproate** and **lamotrigine** is particularly teratogenic.

Breastfeeding Safety

The median M:P ratio ranges from 0.5 to 0.8 2-3w postpartum, and nursed infants maintain plasma concentrations approximating 30% of the mother's plasma level. While no adverse effects have been reported, the infant should be monitored closely if the mother elects to breastfeed, the drug given at the lowest effective dose, and breastfeeding avoided at times of peak drug levels.

Drug Interactions

Limited clinical data suggest there is a higher incidence of dizziness, diplopia, ataxia, and blurred vision in patients receiving **carbamazepine** with **lamotrigine** than in patients receiving other AEDs with **lamotrigine.**

Limited clinical data suggest a higher incidence of headache, dizziness, nausea, and somnolence with co-administration of **lamotrigine** and **oxcarbazepine** compared to **lamotrigine** alone or **oxcarbazepine** alone.

The addition of **valproate** may increase **lamotrigine** steady-state concentrations by slightly more than 2-fold.

The addition of either **carbamazepine, phenobarbital, phenytoin,** or **primidone** can decrease **lamotrigine** steady-state concentrations by approximately 40%.

The AUC and C_{max} of **lamotrigine** were reduced on average by 24% and 20%, respectively, following the addition of **olanzapine** (15mg qd) to **lamotrigine** (200mg qd) in healthy male volunteers (n = 16) compared to healthy male volunteers receiving **lamotrigine** alone (n = 12). This reduction in **lamotrigine** concentration is not expected to be clinically relevant.

In a study in 10 male volunteers, **rifampin** (600mg/d for 5d) increased the apparent clearance of a single 25mg dose of **lamotrigine** by 2-fold (AUC decreased by approximately 40%).

An inhibitor of dihydrofolate reductase. Prescribers should be aware of this action when prescribing other medications that inhibit folate metabolism.

In a study of an oral contraceptive preparation containing 30mcg **ethinyl estradiol** and 150mcg **levonorgestrel,** the apparent clearance of **lamotrigine** (300mg/d) increased some 2-fold with a mean decrease in AUC of 52% and in C_{max} of 39%. Trough serum **lamotrigine** concentrations gradually increased and were 2-fold higher at the end of the week of the inactive preparation. Gradual but transient increases in **lamotrigine** levels will occur during the week of no active hormone preparation (pill-free week) for women not also taking a drug that increases the clearance of lamotrigine (e.g., **carbamazepine, phenobarbital, phenytoin, primidone, rifampin**). The increase in **lamotrigine** levels will be greater if the dose of **lamotrigine** is increased in the few days before or during the pill-free week. Dosage adjustments may be necessary for women receiving oral contraceptive preparations.

Did not affect the pharmacokinetics of the **ethinyl estradiol** component of an oral contraceptive preparation containing 30mcg **ethinyl estradiol** and 150mcg **levonorgestrel.** However, there was a decrease in the AUC and C_{max} of the **levonorgestrel** component of 19% and 12%, respectively. Measurement of serum FSH, LH, and estradiol indicated that there was some loss of suppression of the hypothalamic-pituitary-ovarian axis. The effects of doses of **lamotrigine** other than 300mg/d have not been studied. The possibility of decreased contraceptive efficacy in some patients cannot be excluded, and women should be instructed to promptly report changes in their menstrual pattern (e.g., breakthrough bleeding).

References

Bar-Oz B, Nulman I, Koren G, Ito S. Paediatr Drugs 2000; 2:113-26.

Crawford P. CNS Drugs 2002; 16:263-72.

Crawford P. Epilepsia 2005; 46(Suppl 9):117-24.

Cunnington M, Ferber S, Quartey G; International Lamotrigine Pregnancy Registry Scientific Advisory Committee. Epilepsia 2007; 48:1207-10.

Dolk H, Jentink J, Loane M, et al. Neurology 2008; 71:714-22.

Marchi NS, Azoubel R, Tognola WA. Arq Neuropsiquiatr 2001; 59:362-4.
Ohman I, Vitols S, Tomson T. Epilepsia 2000; 41:709-13.
Sabers A, Gram L. Drugs 2000; 60:23-33.
Tennis P, Eldridge RR; International Lamotrigine Pregnancy Registry Scientific Advisory Committee. Epilepsia 2002; 43:1161-7.
Tran TA, Leppik IE, Blesi K, et al. Neurology 2002; 59:251-5.
Williams J, Myson V, Steward S, et al. Epilepsia 2002; 43:824-31.

Summary

Pregnancy Category: C
Lactation Category: S (likely)

- **Lamotrigine** is well tolerated and drug interaction problems are modest with the possible exception of oral contraceptive failure.
- Physicians are encouraged to register patients, before fetal outcome is known (e.g., ultrasound, results of amniocentesis, birth), and can obtain information from the Lamotrigine Pregnancy Registry (1-800-336-2176).

Lansoprazole—(Lopral; Ogastro; Prevacid; Zoton)

International Brand Name—Agopton (Austria, Germany, Switzerland); Betalans (Indonesia); Compraz (Indonesia); Daxar (Belgium); Digest (Indonesia); Ilsatec (Mexico); Inhipraz (Indonesia); Keval (Mexico); Lancid (Korea); Lancopen (Colombia); Langaton (Korea); Lanpra (Korea); Lanpraz (Colombia); Lanprol (Israel); Lanproton (Colombia); Lansazol (Israel); Lansone (Hungary); Lansop (Korea); Lansopep (Colombia); Lansozole (Korea); Lanster (Korea); Lanston (Korea); Lanvell (Indonesia); Lanximed (Colombia); Lanz (Philippines); Lanzol-30 (India); Lanzopral (Argentina, Costa Rica, Dominican Republic, El Salvador, Guatemala, Honduras, Nicaragua, Panama, Paraguay, Peru, Uruguay, Venezuela); Lanzor (France, Germany, South Africa); Lanzul (Poland); Lapraz (Indonesia); Laproton (Indonesia); Lasgan (Indonesia); Laz (Indonesia); Lopral (Colombia, Peru); Neutron (Colombia); Ogast (France); Ogastro (Brazil, Chile, Colombia, Costa Rica, Dominican Republic, Ecuador, El Salvador, Guatemala, Honduras, Mexico, Nicaragua, Panama, Peru); Praton (Korea); Prevacid (Canada, Malaysia, Philippines, Singapore, Thailand); Prezal (Netherlands); Prolanz (Indonesia); Prosogan (Indonesia); Pysolan (Indonesia); Sopralan-30 (Indonesia); Suprecid (Philippines); Takepron (China, Hong Kong, Japan, South Africa, Taiwan); Takepron OD (Hong Kong); Ulpax (Mexico); Zoton (England, Ireland, Israel, Italy); Zoton Fastab (England, Ireland)

Drug Class

Gastrointestinals; Proton pump inhibitors

Indications

GERD, esophagitis, gastric or duodenal ulcer, *H. pylori* infection, hypersecretory conditions, stress ulcer, ulcer prophylaxis

Mechanism

Hydrogen-potassium ATPase inhibitor

Dosage with Qualifiers

GERD—15-30mg PO qd or bid ×8w
Esophagitis—30mg PO qd or bid ×8w
Gastric ulcer—30mg PO qd or bid ×8w
Duodenal ulcer—15mg PO qd or bid ×8w
H. pylori infection—30mg PO bid ×10-14d
Hypersecretory conditions—60mg PO qd; max 90mg PO bid
Stress ulcer—15-30mg PO, through feeding tube
Ulcer prophylaxis—15-30mg PO qd

- **Contraindications**—hypersensitivity to drug or class
- **Caution**—long-term use, hepatic dysfunction

Maternal Considerations

GERD and/or heartburn occur in 45-85% of women during pregnancy. The effect of estrogen and **progesterone** on lower esophageal sphincter tone is a recognized factor. The treatment of GERD consists of reducing gastric acidity following a step-up algorithm beginning with lifestyle modifications and dietary changes. Antacids or **sucralfate** are first-line medical therapy,

followed by histamine receptor antagonists. **Ranitidine** is probably preferred because of its documented efficacy and safety profile in pregnancy, even in the 1st trimester. Proton pump inhibitors are reserved for the woman with intractable symptoms or complicated reflux disease. However, proton pump inhibitors such as **lansoprazole** are generally considered effective treatment for GERD in pregnant women, and the findings of a recent prospective multicenter trial are reassuring. Adverse effects have not been reported. Further, proton pump inhibitors are first-line agents for the prevention of "aspiration syndrome" during general anesthesia. **Lansoprazole** has also been used with apparent success to treat a woman with Zollinger Ellison syndrome during pregnancy.
Side effects include hepatic failure, blood dyscrasias, Stevens-Johnson syndrome, erythema multiforme, pancreatitis, toxic epidermal necrolysis, headache, diarrhea, asthenia, candidiasis, chest pain, CVA, hypertension/hypotension, MI, and palpitations.

Fetal Considerations

There are no well-controlled studies in human fetuses. It is unknown whether **lansoprazole** crosses the human placenta. Epidemiologic and post-marketing surveillance studies are reassuring. Rodent studies too are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically.

Breastfeeding Safety

There is no published experience in nursing women. It is unknown whether **lansoprazole** enters human breast milk. It is excreted into rodent milk.

Drug Interactions

Metabolized through the CYP3A and CYP2C19 isozymes. When given with **theophylline** (metabolized by CYP1A2, CYP3A), a minor increase (10%) in **theophylline** clearance occurs. Thus, some women may require titration of their **theophylline** dosage when **lansoprazole** is started or stopped.
There have been reports of increased INR and PT in patients receiving proton pump inhibitors such as **lansoprazole** with **warfarin.** Patients treated with proton pump inhibitors and **warfarin** concomitantly may need to be monitored more closely.
In a single-dose crossover study examining **lansoprazole** 30mg and **omeprazole** 20mg each administered alone and concomitantly with **sucralfate** 1g, absorption of the proton pump inhibitors was delayed and their bioavailability was reduced by 17% and 16%, respectively. Therefore, proton pump inhibitors should be taken at least 30min prior to **sucralfate.**
May interfere with the absorption of drugs where gastric pH is an important determinant of bioavailability (e.g., **ampicillin, digoxin, iron, ketoconazole**).

References

Broussard CN, Richter JE. Drug Saf 1998; 19:325-37.
Diav-Citrin O, Arnon J, Shechtman S, et al. Aliment Pharmacol Ther 2005; 21:269-75.
Ramakrishnan A, Katz PO. Curr Treat Options Gastroenterol 2002; 5:301-10.
Richter JE. Gastroenterol Clin North Am 2003; 32:235-61.

Summary

Pregnancy Category: B
Lactation Category: U

- **Lansoprazole** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Latanoprost—(Xalatan)

International Brand Name—Louten (Colombia)

Drug Class	Ophthalmics; Prostaglandins
Indications	Elevated intraocular pressure
Mechanism	Increases aqueous humor outflow
Dosage with Qualifiers	Elevated intraocular pressure—1 gt (1.5mcg) OS/OD qd • **Contraindications**—hypersensitivity to drug or class • **Caution**—asthma
Maternal Considerations	The published experience with **latanoprost** during pregnancy is limited to case reports. ***Side effects*** include epithelial keratitis, blurred vision, eyelid skin darkening, intraocular inflammation, iris pigmentation changes, macular edema, burning, hyperemia, foreign body sensation, itching, dry eyes, tearing, photophobia, ocular pain, discharge, rash, lid crusting, and asthma/exacerbation of asthma.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **latanoprost** crosses the human placenta. Considering the dose and route, it is unlikely the maternal systemic concentration will reach a clinically relevant level. Embryotoxicity was observed in rodents treated with a dosage more than 15× the MRHD.
Breastfeeding Safety	There is no published experience in pregnancy. It is unknown whether **latanoprost** enters human breast milk. However, considering the dose and route, it is unlikely the breastfed neonate would ingest clinically relevant amounts.
Drug Interactions	A precipitate occurs when eyedrops containing **thimerosal** are mixed with **latanoprost.** Such drugs should be administered at least 5min apart.
References	DeSantis M, Lucchese A, Carducci B, et al. Am J Ophthalmol 2004; 138:305-6.
Summary	**Pregnancy Category: C** **Lactation Category: S** (likely) • **Latanoprost** should be used during pregnancy and lactation only if the benefit justifies the potential risk.

Leflunomide—(Arava)

International Brand Name—Arabloc (Australia); Arava (Israel)

Drug Class	Antirheumatics; Immunomodulators
Indications	Rheumatoid arthritis
Mechanism	Pyrimidine synthesis inhibitor with antiproliferative activity
Dosage with Qualifiers	Rheumatoid arthritis—begin 100mg PO qd ×3d, then 10-20mg PO qd *NOTE: check level q14d (normal above 0.02mcg/ml).* • **Contraindications**—hypersensitivity to drug or class, pregnancy • **Caution**—immunodeficiency, blood dyscrasias, bone marrow suppression, infections, HBV or HCV infection
Maternal Considerations	The published literature during pregnancy is limited to case reports of 1st/2nd trimester exposures. Based on animal study (see Fetal Considerations), **leflunomide** is contraindicated during pregnancy and effective contraception is a must. Women desiring pregnancy must discontinue **leflunomide** before conceiving, preferably at least 4mo before. Further, the manufacturer recommends preconception treatment with **cholestyramine** to increase drug elimination with subsequent verification that plasma levels are less than 0.02mg/L. ***Side effects*** include hepatotoxicity, immunosuppression, leukopenia, pancytopenia, Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme, diarrhea, alopecia, N/V, headache, RDS, dyspepsia, rash, back pain, pruritus, asthenia, allergic reactions, dizziness, weight loss, and paresthesias.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. **Leflunomide** likely crosses the human placenta. No pattern of malformations has been reported in infants exposed to **leflunomide,** but the number of reported pregnancy outcomes is small. In an ongoing prospective controlled study of rheumatoid arthritis (RA) medications in pregnancy being conducted by OTIS, 43 **leflunomide**-exposed women were compared to 78 women with RA who did not use **leflunomide** and with a second group of 47 women without RA. Preliminary data indicate rates of major birth defects were similar in all 3 groups. Infants exposed to **leflunomide** were significantly more likely than infants of women without RA to be born prematurely and to be smaller. There were, however, no significant differences in these 2 measures between **leflunomide**-exposed infants and nonexposed infants of women with RA, suggesting that the underlying disease or other medications used to treat RA are likely associated with these adverse outcomes. The incidences of anophthalmia and micropthalmia are increased in rats treated with only 0.1× the concentration recommended in humans. In rabbits, a dose analogous to the human is associated with embryotoxicity and bony abnormalities.
Breastfeeding Safety	There is no published experience in nursing women. It is unknown whether **leflunomide** enters human breast milk. In light of the animal studies, it is best to avoid breastfeeding if **leflunomide** must be prescribed.

Drug Interactions

Cholestyramine or **activated charcoal** produce a rapid and significant decrease in plasma M1 (the active metabolite of **leflunomide**).
The prevalence of side effects increases when **leflunomide** is given with hepatotoxic substances. This is also a risk when **leflunomide** is followed by such drugs. In one small study with **methotrexate,** ⅓ of patients experienced a 2-fold or greater increase in hepatic enzymes. All elevations resolved, 4 despite continuation of both drugs and 6 after discontinuation of **leflunomide.** Three patients met ''ACR criteria'' for liver biopsy (1: Roegnik Grade I, 2: Roegnik Grade IIIa). No pharmacokinetic interaction was identified.
M1 was shown in *in vitro* studies to cause increases ranging from 13% to 50% in the free fraction of **diclofenac** and **ibuprofen** at concentrations in the clinical range. While the clinical significance of this finding is unknown, there was extensive use of NSAIDs in clinical studies and no differential effect was observed.
M1 was shown in *in vitro* studies to increase the free fraction of **tolbutamide** 13-50% at concentrations in the clinical range. The clinical significance of this finding is unknown.
M1 peak levels were increased (~40%) after concomitant administration of a single dose of **leflunomide** to subjects receiving multiple doses of **rifampin.** Because of the potential for **leflunomide** levels to continue to increase with multiple dosing, caution should be used if patients are to be receiving both **leflunomide** and **rifampin.**
Increased INR has been rarely reported when **leflunomide** and **warfarin** are co-administered.

References

Brent RL. Teratology 2001; 63:106-12.
Chambers C, Koren G, Tutuncu ZN, et al. Can Fam Physician 2007; 53:409-12.
DeSantis M, Shaface G, Cavaliere A, et al. Ann Rheum Dis 2005; 64:1096-7.
Kraemer B, Abele H, Hahn M, et al. Hypertens Pregnancy 2008; 27:247-52.
Neville CE, McNally J. Rheumatology 2007; 46:1506.
Prakash A, Jarvis B. Drugs 1999; 58:1137-64.

Summary

Pregnancy Category: X
Lactation Category: U

- **Leflunomide** is a potent teratogen in some rodents; human data are less clear.
- Health care providers are encouraged to register patients by calling 1-877-311-8972 to improve knowledge of fetal outcomes of pregnant women exposed to **leflunomide.**
- There are alternative agents for which there is more experience during pregnancy and lactation.

Lepirudin—(Refludan)

International Brand Name—Refludin (South Africa)

Drug Class

Anticoagulants; Thrombin inhibitors

Indications

Thrombocytopenia, heparin-induced

Mechanism

Direct inhibitor of thrombin independent of ATIII

Dosage with Qualifiers

Heparin-induced thrombocytopenia/thrombosis—begin 0.4mg/kg, then 0.15mg/kg/h IV; max 44mg

- **Contraindications**—hypersensitivity to drug or class
- **Caution**—bleeding; renal dysfunction; increased risk of bleeding, including AV malformations; hypertension; recent surgery

Maternal Considerations

Heparin-induced thrombocytopenia is a rare but potentially life-threatening reaction to both **heparin** and LMWH. It is the most common drug-induced immune-mediated thrombocytopenia. **Lepirudin** effectively treats the thrombocytopenia by inhibiting thrombin. Many patients develop antibodies (40%), and the aPTT should be monitored during long-term therapy. The published experience during pregnancy is limited to a few case reports, including 1st trimester treatment.
Side effects include bleeding, anemia, hematuria, intracranial hemorrhage, fever, GI bleeding, increased LFTs, and epistaxis.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **lepirudin** crosses the human placenta; it does cross the rat placenta. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically.

Breastfeeding Safety

There is no published experience in nursing women. It is unknown whether **lepirudin** enters human breast milk.

Drug Interactions

Use with thrombolytics (e.g., rt-PA, **streptokinase**) may increase the risk of bleeding complications and considerably enhance the effect of **lepirudin** on aPTT prolongation.
Use with coumarin derivatives (vitamin K antagonists) and drugs that affect platelet function may also increase the risk of bleeding.

References

Dager WE, White RH. Ann Pharmacother 2002; 36:489-503.
Furlan A, Vianello F, Clementi M, Prandoni P. Haematologica 2006; 91(8 Suppl):ECR40.
McCrae KR, Bussel JB, Mannucci PM, et al. Hematology (Am Soc Hematol Educ Program) 2001; 282-305.
Young SK, Al-Mondhiry HA, Vaida SJ, et al. Pharmacotherapy 2008; 28:1531-6.

Summary

Pregnancy Category: B
Lactation Category: S (likely)

- Heparin-induced thrombocytopenia is the most frequently encountered drug-induced immune-mediated adverse thrombocytopenia. Therapeutic options are limited.

Letrozole—(Femara)

International Brand Name—None identified.

Drug Class

Antineoplastics, aromatase inhibitor

Indications

Breast cancer

Mechanism

Inhibits aromatase

Dosage with Qualifiers

Breast cancer—2.5mg PO qd

- **Contraindications**—hypersensitivity to drug or class
- **Caution**—renal dysfunction

Maternal Considerations

Letrozole is a nonsteroidal aromatase inhibitor that significantly lowers **estradiol** and estrone. It is used mostly for adjuvant therapy. **Letrozole** has also been used to treat infertility associated with poor response to FSH stimulation. There is no published experience during pregnancy.
Side effects include thromboembolism, muscular pain, N/V, fatigue, arthralgia, cough, chest pain, hot flashes, diarrhea, abdominal pain, viral infection, edema, hypertension, and anorexia.

Fetal Considerations

There are no well-controlled studies in human fetuses. It is unknown whether **letrozole** crosses the human placenta.
The scant human study is reassuring. There is no difference in the overall rates of major and minor congenital malformations among newborns of women who conceived after **letrozole** or **clomiphene** treatments. However, it appears that congenital cardiac anomaly is less frequent in the **letrozole** group.
Letrozole is embryotoxic, fetotoxic, and teratogenic in rodents even at low doses. Since in the primate estrogen modulates placental vascular endothelial growth/permeability factor expression and angiogenesis, **letrozole** could conceptually impact placentation.

Breastfeeding Safety

There is no published experience in nursing women. It is unknown whether **letrozole** enters human breast milk.

Drug Interactions

Use with **tamoxifen** (20mg daily) reduced **letrozole** plasma levels by 38%. There is no clinical experience to date on the use of **letrozole** in combination with other anticancer agents.

References

Albrecht ED, Robb VA, Pepe GJ. J Clin Endocrinol Metab 2004; 89:5803-9.
Forman R, Gill S, Moretti M, et al. J Obstet Gynaecol Can 2007; 29:668-71.
Mitwally MF, Casper RF. Fertil Steril 2002; 77:776-80.

Summary

Pregnancy Category: D
Lactation Category: U

- **Letrozole** is an adjuvant agent for the treatment of breast cancer.
- **Letrozole** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Leucovorin—(Calcium folinate; citrovorum factor; Lerderfoline; Ledervorin-Calcium; Wellcovorin)

International Brand Name—Antrex (Finland); Asovorin (Argentina); Calciumfolinat-Ebewe (Taiwan); Calcium Leucovorin (Australia); Citrec (Sweden); Folina 15 (Thailand); Folinoxan (Philippines); Lederfolin (England, Italy, Spain); Lederfoline (France); Lederle Leucovorin (Canada); Ledervorin Calcium (Belgium, Netherlands); Leucocalcin (Paraguay); Leucovorin (Austria, Bulgaria, Czech Republic, Denmark, England, Finland, Germany, Greece, Hungary, Ireland, New Zealand, Norway, Sweden, Switzerland, Thailand, Uruguay); Leucovorina Calcica (Peru); Leucovorine Abic (Netherlands); Litacor (Philippines); Lovorin (Philippines); Medsavorin (Mexico); Nyrin (Korea, Malaysia); Oncofolic (Germany); Refolinon (England); Rescufolin (Norway); Rescuvolin (Belgium, Denmark, Germany, Greece, Indonesia, Israel, Korea, Philippines, Sweden, Switzerland, Thailand); Robin (Korea); Rontafur (Argentina); Tecnovorin (Brazil, Ecuador)

Drug Class

Antidotes; Toxicology; Vitamins/minerals

Indications

Leucovorin rescue after folate inhibition

Mechanism

Counteracts folate antagonists

Dosage with Qualifiers

Leucovorin rescue—15mg IV/IM/PO q6h 24h after last methotrexate dose

- **Contraindications**—hypersensitivity to drug or class, vitamin B_{12} deficiency, pernicious anemia, megaloblastic anemia
- **Caution**—seizure disorder

Maternal Considerations

Gestational trophoblastic disease is a spectrum of disorders ranging from the benign complete or partial hydatidiform mole to malignant choriocarcinoma. While the preponderance of women are cured by surgery, the occasional patient requires chemotherapy. **Methotrexate,** an inhibitor of dihydrofolate reductase, is the first-line agent. It can persist in human tissue for long periods. **Leucovorin** is a derivative of tetrahydrofolate and as such circumvents the block. Supplementation minimizes toxicity and can counteract inadvertent overdose. **Methotrexate** may be given as a single dose IM, which usually does not require **leucovorin,** or in a multiple-dose regimen, which does require **leucovorin** rescue. **Methotrexate** with **leucovorin** rescue is a highly effective, well-tolerated, nonsurgical treatment for patients with ectopic pregnancy.
Side effects include anaphylactic reaction, seizures, syncope, urticaria, and N/V.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses (see **folic acid**). Folate is quickly transferred across the placenta. Rodent teratogenicity studies have not been conducted. Periconceptional folate supplementation increases fertility (higher cumulative rates and of multiple births). A deficiency of **folic acid** increases the incidence of NTDs, and randomized studies reveal that 4mg/d of **folic acid** prior to conception prevents their recurrence. It is not known whether **leucovorin** supplementation would have the same effect.

Breastfeeding Safety

There is no published experience in nursing women. It is unknown whether **leucovorin** enters human breast milk.

Drug Interactions

Large amounts of **folic acid** may counteract the antiepileptic effect of **phenobarbital, phenytoin,** and **primidone,** and increase the frequency of seizures in susceptible patients.
May enhance the toxicity of **5-fluorouracil.**
Preliminary animal and human studies reveal that small quantities of systemically administered **leucovorin** enter the CSF primarily as 5-methyltetrahydrofolate and, in humans, remain 1-3 orders of magnitude lower than the usual **methotrexate** concentration following intrathecal administration. High doses of **leucovorin** may reduce the efficacy of intrathecally administered **methotrexate.**

References

Barnhart K, Coutifaris C, Esposito M. Expert Opin Pharmacother 2001; 2:409-17.
Bruno MK, Harden CL. Curr Treat Options Neurol 2002; 4:31-40.
Czeizel AE, Dudas I, Metneki J. Arch Gynecol Obstet 1994; 255:131-9.
Elit L, Covens A, Osborne R, et al. Gynecol Oncol 1994; 54:282-7.
Gillespie AM, Kumar S, Hancock BW. Br J Cancer 2000; 82:1393-5.
Homesley HD. J Reprod Med 1994; 39:185-92.
Kendall A, Gillmore R, Newlands E. Curr Opin Obstet Gynecol 2002; 14:33-8.
Kwon JS, Elit L, Mazurka J, et al. Gynecol Oncol 2001; 82:367-70.

Larson DM, Tipping SJ, Mulligan GM, et al. Wis Med J 1995; 94:664-7.
McNeish IA, Strickland S, Holden L, et al. J Clin Oncol 2002; 20:1838-44.
Newlands ES, Bower M, Holden L, et al. J Reprod Med 1998; 43:111-8.
Wegner C, Nau H. Neurology 1992; 42:17-24.

Summary

Pregnancy Category: C
Lactation Category: U

- **Leucovorin** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Leuprolide—(Lupron; Procren)

International Brand Name—Carcinil (Germany); Enanton Depot (Denmark, Finland, Norway, Sweden); Enantone (Austria, France, Germany); Enantone Depot (Italy); Enantone LP (Thailand); Enantone SR (China, Hong Kong); Leuplin (Korea); Leuplin Depot (Taiwan); Lorelin Depot (Hong Kong, Korea); Lucrin (France, Hong Kong, Korea, Malaysia, Mexico, Portugal, Singapore); Lucrin Depot (Belgium, Costa Rica, Dominican Republic, El Salvador, Guatemala, Honduras, Hungary, Israel, Korea, Mexico, Netherlands, Nicaragua, Panama, Singapore, Switzerland, Turkey); Lupride (India); Lupride Depot (India); Luprolex (Philippines); Luprolex Depot (Philippines); Lupron (Argentina, Brazil, Canada, Chile, Colombia, Ecuador, Paraguay, Uruguay, Venezuela); Lupron Depot (Argentina, Brazil, Canada, Chile, Colombia, Ecuador, Paraguay, Peru, Uruguay, Venezuela); Procren Depot (Denmark, Finland, Norway, Sweden); Procrin (Spain); Prostap (England, Ireland); Reliser (Mexico); Tapros (Indonesia)

Drug Class

Antineoplastics, hormone modifier

Indications

Endometriosis, uterine fibroids

Mechanism

Inhibits the release of the gonadotropins by suppressing ovarian steroidogenesis

Dosage with Qualifiers

Endometriosis—3.75mg IM qmo
Uterine fibroids—3.75mg IM qmo

NOTE: administer iron and check the bone mineral density if treatment extends longer than 3mo.

- **Contraindications**—hypersensitivity to drug or class, undiagnosed vaginal bleeding
- **Caution**—bone metastases, osteoporosis, psychiatric disorder, depression

Maternal Considerations

Gonadotropin-releasing agonists are important for the treatment of infertility and are often used with IVF. There are no adequate reports or well-controlled studies of **leuprolide** during pregnancy, nor is there an indication for its use.
Side effects include angina, cardiac arrhythmias, MI, pulmonary emboli, spinal cord compression, paralysis, bone density loss, erythema multiforme, libido decrease, thyroid enlargement, anxiety, blurred vision, lethargy, memory disorder, mood swings, itching, nervousness, numbness, paresthesias, cough, pleural rub, pneumonia, dry skin, ecchymosis, hair loss, local skin reactions, pigmentation, skin lesions, pulmonary fibrosis, dysuria, incontinence, leukopenia, hemoptysis, pelvic fibrosis, hair growth, and hypoproteinemia.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **leuprolide** crosses the human placenta. No malformations are reported in women inadvertently exposed to **leuprolide** during pregnancy.

However, early exposure of a male fetus may lead to micropenis. Rodent studies reveal a dose-dependent increase in the incidence of major malformations and IUGR.

Breastfeeding Safety — There is no published experience in nursing women. It is unknown whether **leuprolide** enters human breast milk.

Drug Interactions — No clinically relevant interactions identified.

References

McMahon DR, Kramer SA, Husmann DA. J Urol 1995; 154:825-9.
Tan HH, Yeong CT, Loh KE. Aust N Z J Obstet Gynaecol 2006; 46:336-40.
Tay CC. Hum Fertil 2002; 5:G35-7.

Summary

Pregnancy Category: X
Lactation Category: U

- **Leuprolide** is currently contraindicated during pregnancy.
- Barrier contraception is recommended if therapy is initiated for indications other than infertility.
- No malformations are described in women inadvertently exposed to **leuprolide.**

Levalbuterol—(Xopenex)

International Brand Name—None identified.

Drug Class — Adrenergic agonists; β_2-Agonists; Bronchodilators

Indications — Bronchospasm

Mechanism — Stimulates β_2-adrenergic receptors

Dosage with Qualifiers

Bronchospasm—0.63-1.25mg NEB q6-8h prn

NOTE: avoid mixing with other nebulizers.

- **Contraindications**—hypersensitivity to drug or class, MAOI <14d
- **Caution**—arrhythmias, CAD, hypertension, hypokalemia

Maternal Considerations — **Levalbuterol** is at least as effective as other β_2-adrenergic agonists for the treatment or prevention of bronchospasm. There is no published experience with **levalbuterol** during pregnancy. ***Side effects*** include paradoxical bronchospasm, angioedema, cardiac arrest, arrhythmia, hypokalemia, palpitation, dizziness, tremor, nervousness, headache, chest pain, and dry mouth.

Fetal Considerations — There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **levalbuterol** crosses the human placenta. Maternal systemic plasma levels are low after inhalation. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically. In contrast, other β_2-adrenergic agonists (e.g., **albuterol, isoproterenol**) have been associated with cleft palate and NTDs.

Breastfeeding Safety — There is no published experience in nursing women. It is unknown whether **levalbuterol** enters human breast milk. However, considering the indication and dosing, occasional **levalbuterol** use is unlikely to pose a clinically significant risk to the breastfeeding neonate.

Drug Interactions

Other short-acting sympathomimetic aerosol bronchodilators or **epinephrine** should be used with caution to avoid adverse CV effects.
β-Adrenergic receptor blocking agents block or reduce the pulmonary effect of β-agonists such as **levalbuterol,** and may produce severe bronchospasm in asthmatic patients. Therefore, patients with asthma should not normally be treated with β-blockers. However, under certain circumstances (e.g., as prophylaxis after MI), there may be no acceptable alternatives to the use of β-adrenergic blocking agents in patients with asthma. In this setting, cardioselective β-blockers could be considered, although they should be administered with caution.
The ECG changes and/or hypokalemia that can result from non–potassium-sparing diuretics (such as loop or thiazide) can be acutely worsened by β-agonists, especially when the recommended dose of the β-agonist is exceeded.
Digoxin levels decrease 16% and 22% after single doses of racemic **albuterol** to normal volunteers who had received **digoxin** for 10 days. Thus, it is prudent to carefully evaluate the **digoxin** levels in patients who are currently receiving **digoxin** and **levalbuterol.**
Should be administered with extreme caution to patients being treated with MAOIs or TCAs, or within 2w of discontinuation of such agents, because the action of **levalbuterol** on the vascular system may be potentiated.

References

Chowdhury BA. J Allergy Clin Immunol 2002; 110:324.
Wendel PJ, Ramin SM, Barnett-Hamm C, et al. Am J Obstet Gynecol 1996; 175:150-4.

Summary

Pregnancy Category: C
Lactation Category: S (likely)
- **Levalbuterol** is an effective agent for the control and prevention of bronchospasm.
- There are alternative agents for which there is more experience during pregnancy and lactation.

Levamisole—(Ascaryl; Decas; Dewormis; Ergamisol; Immunol)

International Brand Name—Ascaridil (Indonesia); Decaris (Bulgaria, Czech Republic, Hong Kong, Hungary, Israel, Mexico, Russia, South Africa, Taiwan); Detrax 40 (South Africa); Dewormis 50 (India); Ketrax (India, Ireland); Newkentax (South Africa); Solaskil (France); Vermisol (India)

Drug Class

Antineoplastics; Immunomodulators

Indications

Colon cancer

Mechanism

Unknown

Dosage with Qualifiers

Colon cancer—50mg PO q8h ×3d beginning 7-30d after surgery; repeat medication q14d ×1y

- **Contraindications**—hypersensitivity to drug or class
- **Caution**—alcohol ingestion

Maternal Considerations

Levamisole is an immunomodulator often used as adjuvant treatment for colon cancer. It is also used as an antirheumatic and anthelmintic drug. There is limited use in pregnancy, mostly as a deworming agent in developing countries. One post-marketing report is reassuring.

Side effects include agranulocytosis, leukopenia, thrombocytopenia, dermatitis, N/V, diarrhea, fatigue, fever, rigors, arthralgia, dizziness, headache, paresthesias, somnolence, taste change, infection, hyperpigmentation, ataxia, tearing, forgetfulness, blurred vision, conjunctivitis, and hyperbilirubinemia.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **levamisole** crosses the human placenta. One post-marketing report is reassuring. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically. Embryotoxicity was noted in some studies.

Breastfeeding Safety

There is no published experience in nursing women. It is unknown whether **levamisole** enters human breast milk. **Levamisole** is excreted into cow's milk and reportedly stimulates production.

Drug Interactions

No clinically relevant interactions identified.

References

Block E, McDonald WA, Jackson BA. J Dairy Sci 1987; 70:1080-5.
da Costa-Macedo LM, Rey L. Rev Inst Med Trop Sao Paulo 1990; 32:351-4.
Gyorkos TW, Larocque R, Casapia M, Gotuzzo E. Pediatr Infect Dis J 2006; 25:791-4.
Osterdahl BG, Nordlander I, Johnsson H. Food Addit Contam 1986; 3:161-5.

Summary

Pregnancy Category: C
Lactation Category: U

- **Levamisole** should be used during pregnancy and lactation only if the benefit justifies the potential risk.

Levetiracetam—(Keppra)

International Brand Name—Keppra (Argentina, Australia, Hong Kong, Malaysia, Mexico, Peru, Philippines, Singapore, Taiwan, Thailand); Kopodex (Chile)

Drug Class

Anticonvulsants

Indications

Partial-onset seizure disorder

Mechanism

Unknown

Dosage with Qualifiers

Seizure disorder—begin 500mg PO q12h, increasing 1g/d every 2w; max 3000mg/d

- **Contraindications**—hypersensitivity to drug or class
- **Caution**—renal dysfunction, abrupt withdrawal, depression

Maternal Considerations

Levetiracetam is unrelated to other AEDs, and is used for the treatment for partial-onset seizures. Case series suggest it is well-tolerated during pregnancy. Maternal clearance increases such that 3rd trimester levels are only 40%-50% of baseline absent a dose adjustment. Those women who become or who are planning to become pregnant while taking **levetiracetam** should supplement their **folic acid** intake. Once pregnant, dosage

readjustments may be necessary and should be based on clinical symptoms, and not exclusively on serum drug concentrations. A specific drug registry for women exposed to **levetiracetam** during pregnancy has been established by the manufacturer (1-888-537-7734).
Side effects include N/V, suicide attempts, psychosis, leukopenia, neutropenia, pancytopenia, somnolence, asthenia, dizziness, ataxia, agitation, anxiety, behavior changes, anemia, cough, rhinitis, and diplopia.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. In one series of 11 exposed pregnancies, there were 3 neonates with IUGR. **Levetiracetam** crosses the human placenta, achieving an F:M ratio of 0.56-2.0. *In vitro,* **carbamazepine** and **topiramate** alone did not induce neuronal death; both drugs exacerbate **phenytoin**-induced cell death. In contrast, co-treatment with **levetiracetam** and **carbamazepine** did not enhance cell death in the developing brain. Thus, it may be possible to avoid proapoptotic effects, even in polytherapy, by choosing appropriate drugs. **Levetiracetam,** as monotherapy or in combination, may be a promising candidate for the treatment of women during pregnancy and for preterm and neonatal infants. Rodent studies conducted using doses in excess of the MRHD reveal embryotoxicity and an increased prevalence of skeletal malformations.

Breastfeeding Safety

Levetiracetam enters human breast milk. In two small studies of 11 women, the mean M:P ratio approximated 1. The calculated neonatal dose was estimated to be 2.4mg/kg/d, equivalent to 8.0% of the weight-normalized maternal dose. Plasma concentrations in breastfed newborns were approximately 13% of the mother's level.

Drug Interactions

In vitro data indicate that **levetiracetam** is unlikely to produce, or be subject to, pharmacokinetic interactions.

References

Crawford P. CNS Drugs 2002; 16:263-72.
Faught E. Epilepsia 2001; 42(Suppl 4):19-23.
Kim J, Kondratyev A, Gale K. J Pharmacol Exp Ther 2007; 323:165-73.
Pennell PB. Epilepsy Curr 2006; 6:22-4.
ten Berg K, Samren EB, van Oppen AC, et al. Reprod Toxicol 2005; 20:175-8.
Tomson T, Battino D. Clin Pharmacokinet 2007; 46:209-19.
Tomson T, Palm R, Källén K, et al. Epilepsia 2007; 48:1111-6.
Westin AA, Reimers A, Helde G, et al. Seizure 2008; 17:192-8.

Summary

Pregnancy Category: C
Lactation Category: U

- **Levetiracetam** should be used during pregnancy and lactation only if the benefit justifies the potential risk.
- Though the early experience is encouraging, there are alternative agents for which there is more experience during pregnancy and lactation.
- Physicians are encouraged to register patients, before fetal outcome is known (e.g., ultrasound, results of amniocentesis), in the Keppra Pregnancy Registry (1-888-537-7734).

Levocabastine—(Livostin)

International Brand Name—Histimet (Argentina, Poland); Levophta (France, Germany); Livocab (Netherlands); Livostin (Austria, Belgium, Brazil, Bulgaria, Chile, China, Colombia, Costa Rica, Czech Republic, Denmark, Dominican Republic, Ecuador, El Salvador, England, Finland, Greece, Guatemala, Honduras, Hungary, Ireland, Italy, Korea, Mexico, Nicaragua, Norway, Panama, Paraguay, Sweden, Switzerland, Uruguay, Venezuela); Livostin ED (South Africa)

Drug Class	Allergy; Antihistamines, H_1; Ophthalmics
Indications	Allergic conjunctivitis
Mechanism	Selective H_1-receptor antagonist
Dosage with Qualifiers	Allergic conjunctivitis—1 gt OS/OD qid; max 2w • **Contraindications**—hypersensitivity to drug or class, contact lenses • **Caution**—unknown
Maternal Considerations	There is no published experience with **levocabastine** during pregnancy. Approximately ⅓ of childbearing-age women have allergic rhinitis. Immunotherapy, **cromolyn,** and **beclomethasone** are first-line agents because of their safety record. ***Side effects*** include dry mouth, dyspnea, somnolence, eye burning, eyelid edema, and rash.
Fetal Considerations	There are no adequate reports or well-controlled studies of **levocabastine** in human fetuses. Considering the dose and route, it is unlikely the maternal systemic concentration reaches a clinically relevant level. In rodents, **levocabastine** caused polydactyly at doses 16,500× the ocular MRHD; polydactyly, hydrocephaly, brachygnathia, and embryo and maternal toxicities occur at doses 66,000× the ocular MRHD.
Breastfeeding Safety	There is no published experience with **levocabastine** in nursing women. The manufacturer's reports suggest a trace amount is excreted. However, considering the dose and route, it is unlikely the breastfed neonate would ingest clinically relevant amounts.
Drug Interactions	No clinically relevant interactions identified.
References	Mazzotta P, Loebstein R, Koren G. Drug Saf 1999; 20:361-75.
Summary	**Pregnancy Category: C** **Lactation Category: S** (likely) • **Levocabastine** is an effective agent for the treatment of allergic conjunctivitis. • **Levocabastine** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Levodopa—(Dopar; Dopastral; Laradopa; Larodopa; L-Dopa; Levotrifar; Medidopa; Prolopa)

International Brand Name—Bidopal (India); Brocadopa (England); Ceredopa (Austria); Dopaflex (Czech Republic, Germany, Hungary, Puerto Rico); Doparkin (Finland); Doparkine (Argentina); Doparl (Japan); Dopasol (Japan); Dopastan (Japan); Dopaston (Taiwan); Eldopal (Netherlands); Levopa (India)

Drug Class	Antiparkinson agents; Dopaminergics
Indications	Parkinson's disease
Mechanism	Dopamine precursor
Dosage with Qualifiers	Parkinson's disease—0.5-1g PO qd; max 8g/d; therapy is individualized and changed gradually • **Contraindications**—hypersensitivity to drug or class, glaucoma, MAOI <14d, undiagnosed skin lesion • **Caution**—severe renal and hepatic disease, CV disease, pulmonary disease
Maternal Considerations	Parkinson's disease is characterized by neuronal degeneration in the corpora nigra. Evidence suggests the symptoms are related to depletion of striatal dopamine. Parkinson's disease manifests before age 40y in about 5% of patients. Limited experience suggests symptoms often worsen during pregnancy, and may not return to baseline postpartum. **Levodopa** is the first-line agent and is usually combined with **carbidopa.** There are no adequate reports or well-controlled studies of **levodopa** in pregnant women. Several case reports describe successful outcomes without obvious adverse effect on the pregnancy. Early reports suggested a relationship between **levodopa** during pregnancy and fulminant hepatitis. ***Side effects*** include anorexia, N/V, hallucinations, abdominal pain, dry mouth, dysphagia, sialorrhea, ataxia, numbness, hand tremor, headache, dizziness, weakness and faintness, bruxism, confusion, insomnia, nightmares, agitation and anxiety, malaise, fatigue, euphoria, oculogyric crises, hiccups, edema, hair loss, hoarseness, dystonic reactions, and orthostatic hypotension.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. **Levodopa** crosses the human placenta, and limited study suggests it achieves an F:M ratio approaching unity. While some studies show that **levodopa** concentrates in the fetal brain and thus has the potential to affect fetal neuronal development, the majority of studies reveal no evidence of teratogenicity. Rodent studies are generally reassuring, without evidence of teratogenicity, though IUGR occurs at high doses.
Breastfeeding Safety	There are no adequate reports or well-controlled studies in nursing women. **Levodopa** is excreted into human breast milk, but the kinetics remain to be elucidated. While it suppresses prolactin release and thus, theoretically, may interfere with lactation, the suckling stimulus seems to override any inhibitory effect on prolactin release.
Drug Interactions	MAOIs may trigger a hypertensive crisis. **Olanzapine, fluoxetine, isoniazid,** and **rifampin** may decrease the dopaminergic effect, while **metoclopramide** may have antagonistic effects.

Antiacids may increase bioavailability. Give 2h apart.
Multivitamins may decrease efficacy.

References

Deis RP, Kann G, Martinet J. Reprod Nutr Dev 1990; 30:605-10.
Merchant CA, Cohen G, Mytilineou C, et al. J Neural Transm Park Dis Dement Sect 1995; 9:239-42.
Nomoto M, Kaseda S, Iwata S, et al. Mov Disord 1997; 12:261.
Routiot T, Lurel S, Denis E, Barbarino-Monnier P. J Gynecol Obstet Biol Reprod 2000; 29:454-7.
Scott M, Chowdhury M. Mov Disord 2005; 20:1078-9.
Shulman LM, Minagar A, Weiner WJ. Mov Disord 2000; 15:132-5.
Thulin PC, Woodward WR, Carter JH, Nutt JG. Neurology 1998; 50:1920-1.

Summary

Pregnancy Category: C
Lactation Category: U

- **Levodopa** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Levofloxacin—(Cravit; Lesacin; Levaquin; Quixin)

International Brand Name—Cravit (China, Indonesia, Japan, Korea, Singapore, Thailand); Cravit Ophthalmic (Hong Kong); Elequine (Mexico); Floxel (Philippines); Leroxacin (Korea); Lesacin (Korea); Levokacin (Korea); Levox (Philippines); Levoxacin (Korea); Mosardal (Indonesia); Nofaxin (Korea); Reskuin (Indonesia); Tavanic (Colombia, England, France, Germany, India, Ireland, Israel, Peru, South Africa); Volequin (Indonesia)

Drug Class

Antibiotics; Quinolones

Indications

Bacterial infections (aerobic gram-positive: *Enterococcus faecalis, S. aureus* [methicillin-susceptible], *S. saprophyticus, S. pneumoniae, S. pyogenes;* aerobic gram-negative: *Enterobacter cloacae, E. coli, H. influenzae, H. parainfluenzae, Klebsiella pneumoniae, Legionella pneumophila, Moraxella catarrhalis, P. mirabilis, Pseudomonas aeruginosa;* other microorganisms: *Chlamydia pneumoniae, Mycoplasma pneumoniae*)

Mechanism

Inhibits bacterial topoisomerase IV and DNA gyrase, required for DNA replication, transcription, repair, and recombination

Dosage with Qualifiers

Bacterial infections—250-500mg PO/IV qd

- **Contraindications**—hypersensitivity to drug or class, prolongation of the QT interval, concomitant usage of antiarrhythmic drugs
- **Caution**—hepatic or renal dysfunction (CrCl <50ml/min), seizure disorder, dehydration, hypokalemia, sun exposure, diabetes mellitus, bradycardia, cardiomyopathy, anemia

Maternal Considerations

Levofloxacin is indicated for the treatment of mild, moderate, and severe infections caused by a wide variety of susceptible microorganisms. There are no adequate reports or well-controlled studies of **levofloxacin** in pregnant women. Compared to other quinolones, **levofloxacin** has fewer adverse GI or CNS events and is minimally phototoxic. **Levofloxacin** should not be used for the treatment of gonorrhea because of the growing prevalence of resistant strains. Recent studies report increased sensitivity of *Chlamydia trachomatis* to quinolone medication. Vaginal candidiasis is more frequently associated with quinolone use than with other antibiotics.

Side effects include tendonitis, tendon rupture, N/V, vaginitis, phototoxicity, pseudomembranous colitis, seizures, psychosis, arthropathy, restlessness, light-headedness, anxiety, agitation, confusion, elevated LFTs, dyspepsia, and taste perversion.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. Less than 4% of maternal **levofloxacin** and **ofloxacin** crosses the isolated perfused human placenta. Intracompartmental clearance has not been detailed to date. Animal studies (mice, dogs, rabbits) reveal that several quinolones are associated with a juvenile arthropathy, and it is this toxicity that has lead to their restricted use in pregnant women. However, not all quinolones have the same potency on cartilage growth. Further, the use of quinolones during the 1st trimester of human pregnancy has not been associated with an increased risk of malformations or musculoskeletal conditions. Rodent studies with **levofloxacin** are reassuring, revealing no evidence of teratogenicity despite the use of doses higher than those used clinically. IUGR was noted.

Breastfeeding Safety

At steady state, peak **levofloxacin** exposure in breast milk approximates 8mcg/ml 5h after dosing. Elimination pharmacokinetics followed the anticipated pattern. Thus, peak **levofloxacin** concentrations in human breast milk are similar to levels attained in plasma. However, breastfeeding mothers who take **levofloxacin** will expose their infants to **levofloxacin** in concentrations below those being studied in the pediatric population.

Drug Interactions

Antacids containing magnesium or aluminum, as well as **sucralfate,** metal cations such as iron, and multivitamin preparations with zinc, may reduce GI absorption, resulting in systemic levels considerably lower than desired. These agents should be taken at least 2h before or 2h after **levofloxacin.**
Administration of other quinolones with **theophylline** has resulted in a prolonged elimination t/2, elevated serum **theophylline** levels, and a subsequent increase in the risk of **theophylline**-related adverse reactions in the patient population.
Prolongation of the PT in the setting of concurrent **warfarin** and **levofloxacin** use have been associated with bleeding. PT, INR, or other suitable anticoagulation tests should be closely monitored if **levofloxacin** is used with **warfarin.**
Quinolones may cause an increase in the serum levels of **cyclosporine.** No dosage adjustment is required.
Use of NSAIDs with a quinolone, including **levofloxacin,** may increase the risk of CNS stimulation and convulsive seizures.
Both hyperglycemia and hypoglycemia are reported in patients treated with both quinolones and an antidiabetic agent. Careful monitoring of blood glucose is recommended.
Some quinolones, including **levofloxacin,** may produce false-positive urine screening results for opiates. Confirmation of positive opiate screens by more specific methods may be necessary.

References

Berkovitch M, Pastuszak A, Gazarian M, et al. Obstet Gynecol 1994; 84:535-8.
Cahill JB Jr, Bailey EM, Chien S, Johnson GM. Pharmacotherapy 2005; 25:116-8.
Centers for Disease Control and Prevention. JAMA 2001; 286:2396-7.
Centers for Disease Control and Prevention. MMWR Morb Mortal Wkly Rep 2002; 51:1041-4.

Connell W, Miller A. Drug Saf 1999; 21:311-23.
Koul PA, Wani JI, Wahid A. Lancet 1995; 346:307-8.
Lipsky BA, Baker CA. Clin Infect Dis 1999; 28:352-64.
Loebstein R, Addis A, Ho E, et al. Antimicrob Agents Chemother 1998; 42:1336-9.
McDuffie RS Jr, Eskens JL, Gibbs RS. Obstet Gynecol 1998; 92:28-30.
Polachek H, Holcberg G, Sapir G, et al. Eur J Obstet Gynecol Reprod Biol 2005; 122:61-5.
Shakibaei M, Baumann-Wilschke I, Rucker M, Stahlmann R. Arch Toxicol 2002; 75:725-33.
Siefert HM, Maruhn D, Maul W, et al. Arzneimittelforschung 1986; 36:1496-502.
Weber JT, Johnson RE. Clin Infect Dis 1995; 20(Suppl 1):S66-71.
Wilton LV, Pearce GL, Mann RD. Br J Clin Pharmacol 1996; 41:277-84.

Summary

Pregnancy Category: C
Lactation Category: S (likely)

- **Levofloxacin** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.
- Although quinolones appear safe during the 1st trimester, their widespread use during the 2nd and 3rd trimesters should await further study because of the potential for juvenile arthropathy.
- There are alternative agents for which there is more experience during pregnancy and lactation.

Levorphanol—(Levo-Dromoran)

International Brand Name—Dromoran (Japan)

Drug Class

Analgesics, narcotic

Indications

Pain

Mechanism

Binds to opiate receptors

Dosage with Qualifiers

Pain—2mg PO q6-8h, or 1-2mg IV q3-6h

*NOTE: **naloxone** should be administered immediately in the event of overdosage.*

- **Contraindications**—hypersensitivity to drug or class, depressed respiratory function, MI, hypotension
- **Caution**—hepatic or renal dysfunction, drug dependency, seizure disorder

Maternal Considerations

Levorphanol has properties similar to **morphine,** but is 4-6× more potent. There is no published experience during pregnancy. ***Side effects*** include N/V, respiratory distress, bronchospasm, diplopia, mood disturbance, pruritus, flushing, rash, constipation, biliary spasm, and dry mouth.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. Its chemical structure suggests **levorphanol** will rapidly cross the placenta. Adolescent rodents exposed prenatally to **morphine** are tolerant to its analgesic effect. This tolerance also occurs when the rats are exposed to **levorphanol**, a morphine congener, but not by its analgesically inactive isomer, **dextromethorphan.**

Breastfeeding Safety — There is no published experience in nursing women. It is unknown whether **levorphanol** enters human breast milk.

Drug Interactions — See **Morphine.**

References

O'Callaghan JP, Holtzman SG. J Pharmacol Exp Ther 1977; 200:255-62.

Summary

Pregnancy Category: C
Lactation Category: U

- **Levorphanol** should be used during pregnancy and lactation only if the benefit justifies the potential risk.
- There are alternative agents for which there is more experience during pregnancy and lactation.

Levothyroxine—(Levo-T; Levothroid; Levoxyl; L-Thyroxine; Novothyrox; Synthroid; Synthrox; Throxinique; Thyradin; Thyroxine)

International Brand Name—Berlthyrox (Germany); Eferox (Germany); Elthyrone (Belgium); Eltroxin (Canada, Czech Republic, Denmark, England, Hungary, Indonesia, Ireland, Israel, Korea, Malaysia, Netherlands, Pakistan, South Africa, Switzerland); Euthyrox (Argentina, Austria, Belgium, Brazil, Bulgaria, China, Czech Republic, Germany, Hungary, Netherlands, Philippines, Poland, Singapore, Thailand, Venezuela); Eutirox (Chile, Costa Rica, El Salvador, Guatemala, Honduras, Ireland, Italy, Mexico, Nicaragua, Panama, Peru); Eutroxsig (Australia); Levaxin (Sweden); Levothroid (Spain); Levothyrox (France); Levotirox (Italy); Levotiroxina (Ecuador); L-Thyroxine (France); Narval (Uruguay); Oroxine (Australia, Malaysia, Singapore); Pondtroxin (Thailand); Synthroid (Brazil, Canada, Korea); T4KP (Thailand); Thevier (Germany); Thyradin S (Japan); Thyrax (Belgium, Czech Republic, Hungary, Indonesia, Netherlands, Philippines, Portugal, Spain); Thyrex (Austria); Thyro-4 (Bulgaria, Greece); Thyrosit (Thailand); Thyroxin (Finland); Thyroxin-Natrium (Norway); Tiroidine (Mexico); Tiroxin (Colombia)

Drug Class — Hormones, thyroid

Indications — Hypothyroidism, myxedema coma

Mechanism — Unknown (increases metabolism)

Dosage with Qualifiers

Hypothyroidism—50-200mcg PO qd; usual dose 75-125mcg/d

NOTE: levels should be checked q2-4w until stable, then yearly.
Myxedema coma—300-500mcg IV

- **Contraindications**—hypersensitivity to drug or class, thyrotoxicosis, adrenal insufficiency
- **Caution**—hypertension, CV disease

Maternal Considerations

Hypothyroidism affects 4-10% of women. Many of the signs and symptoms of typical hypothyroidism are a normal part of pregnancy. The diagnosis of hypothyroidism (and hyperthyroidism) should be always confirmed by laboratory tests and not by symptoms. **Levothyroxine** is the standard for the treatment of hypothyroidism during pregnancy. Women with isolated hypothyroxinemia are neither at increased risk for adverse perinatal outcome nor have an increased prevalence of thyroid peroxidase antibodies; it may well be biologically insignificant. In contrast, up to ⅓ of women with asymptomatic hypothyroidism diagnosed because of an elevated TSH have thyroid peroxidise antibodies. It has been suggested that asymptomatic maternal hypothyroidism is associated with an increased prevalence of neurodevelopmental abnormalities, but is unknown whether **levothyroxine** supplementation of these

women alters that risk. Asymptomatic hypothyroidism is more common in multiple gestation. Be aware that the TSH of women chronically hyper- or hypothyroid may respond much more slowly to replacement than the free T_4 level.
Side effects include weight loss, increased appetite, palpitations, nervousness, diarrhea, arrhythmias, CHF, hypertension, angina, abdominal cramps, sweating, tachycardia, tremors, insomnia, heat intolerance, fever, menstrual irregularities, and alopecia.

Fetal Considerations

Thyroid hormones are essential for normal brain development. Both maternal and fetal thyroid hormones contribute. Though maternal thyroid hormone transport across the placenta is low, its importance is illustrated by the fact that most athyrotic newborns have no sign of hypothyroidism, and the degree of maternal hypothyroidism early and midgestation correlates with the severity of fetal neural damage. The children of women with subclinical hypothyroidism in the first half of pregnancy have lower mean Mental Developmental Index scores during the 1st year of life. Fetal hypothyroidism can be diagnosed by cordocentesis. Hypothyroid fetuses are treated by weekly intra-amniotic injections of **levothyroxine.** The adequacy of therapy is determined by periodic measurement of free T_4, free T_3, and TSH compared to gestational age–appropriate norms. Most fetuses whose mothers are being treated with **propylthiouracil** are not euthyroid and should be monitored directly. Ultrasonographic evaluation of the fetus by biparietal diameter, cranial and abdominal circumference, and both humerus and femur length is recommended. Craniosynostosis is associated with iatrogenic hyperthyroidism in infants receiving thyroid hormone replacement therapy.

Breastfeeding Safety

There are no adequate reports or well-controlled studies in nursing women. **Levothyroxine** is excreted at low concentrations into human breast milk. The neonatal effect is controversial. Some reports suggest that the levels in breast milk are sufficient to treat neonatal hypothyroidism. It is unknown whether maternal supplementation increases excretion.

Drug Interactions

Antacids (aluminum and magnesium), hydroxides (e.g., **simethicone**), bile acid sequestrants (e.g., **cholestyramine, colestipol**), calcium carbonate, cation exchange resins (e.g., **kayexalate**), **ferrous sulfate, sucralfate,** and soybean flour (e.g., infant formula) each may reduce the efficacy of **levothyroxine** by binding and delaying or preventing absorption, potentially resulting in hypothyroidism. Calcium carbonate may form an insoluble chelate with **levothyroxine,** and ferrous sulfate likely forms a ferric-thyroxine complex. Administer **levothyroxine** at least 4h apart from these agents.
Androgens and related anabolic hormones, **asparaginase, clofibrate,** estrogens and estrogen-containing compounds, **5-fluorouracil, furosemide,** glucocorticoids, **meclofenamate, mefenamic acid, methadone, perphenazine, phenylbutazone, phenytoin,** salicylates, and **tamoxifen** each may bind **levothyroxine,** decreasing availability.
Aminoglutethimide, *para*-aminosalicylic acid, amiodarone, androgens and related anabolic hormones, complex anions (e.g., **perchlorate, pertechnetate, thiocyanate**), antithyroid drugs, β-adrenergic blocking agents, **carbamazepine, chloral hydrate, diazepam, dopamine** and dopamine agonists, **ethionamide,** glucocorticoids, **heparin,** hepatic enzyme inducers, insulin, iodinated cholestographic agents, iodine-containing compounds, **levodopa, lovastatin, lithium, 6-mercaptopurine,**

metoclopramide, mitotane, nitroprusside, phenobarbital, phenytoin, resorcinol, rifampin, somatostatin analogs, sulfonamides, sulfonylureas, and thiazide diuretics may alter thyroid hormone or TSH levels, by affecting either thyroid hormone synthesis, secretion, distribution, metabolism, action, or elimination, or altering TSH secretion.

Metabolic clearance of adrenocorticoids is decreased in hypothyroid patients and increased in hyperthyroid patients, and may therefore change with changing thyroid status.

Amiodarone can cause hypothyroidism or hyperthyroidism.

Oral cholecystographic agents and **amiodarone** are slowly excreted, producing more prolonged hypothyroidism than parenterally administered iodinated contrast agents. **Amiodarone** and iodide (including iodine-containing radiographic contrast agents) may cause hyperthyroidism in euthyroid patients with Graves' disease previously treated with antithyroid drugs or in euthyroid patients with thyroid autonomy (e.g., multinodular goiter or hyperfunctioning thyroid adenoma). Hyperthyroidism may develop over several weeks and may persist for several months after therapy discontinuation. **Amiodarone** may induce hyperthyroidism by causing thyroiditis.

Long-term **lithium** therapy can result in goiter in up to 50% of patients, and either subclinical or overt hypothyroidism, each in up to 20% of patients.

The fetus, neonate, elderly, and euthyroid patients with underlying thyroid disease (e.g., Hashimoto's thyroiditis or Graves' disease previously treated with radioiodine or surgery) are among those individuals who are particularly susceptible to iodine-induced hypothyroidism.

The hypoprothrombinemic effect of anticoagulants may be potentiated, apparently by increased catabolism of vitamin K–dependent clotting factors. Concomitant use of these agents impairs the compensatory increases in clotting factor synthesis. The PT should be carefully monitored in patients taking **levothyroxine** and oral anticoagulants and the dose of anticoagulant therapy adjusted accordingly.

Hypoglycemic agent requirements may be reduced in hypothyroid patients with diabetes mellitus and may increase with the initiation of thyroid hormone replacement.

Actions of some of β-blocking agents may be impaired when hypothyroid patients become euthyroid.

Serum digitalis levels may be decreased in hyperthyroidism or when a hypothyroid patient becomes euthyroid.

Marked hypertension and tachycardia have been reported in association with concomitant use of **levothyroxine** and **ketamine.**

Maprotiline may increase the risk of cardiac arrhythmias.

Uptake of radiolabeled iodide (^{123}I and ^{131}I) and sodium pertechnetate Tc-99m may be decreased.

Excessive **levothyroxine** may accelerate epiphyseal closure.

Untreated hypothyroidism may interfere with the growth response to somatrem or somatropin.

Theophylline clearance may be decreased in hypothyroid patients and return toward normal when a euthyroid state is achieved.

Concurrent use of TCAs may increase the therapeutic and toxic effects of both drugs, possibly due to increased catecholamine sensitivity. Toxic effects may include increased risk of arrhythmias and CNS stimulation; onset of action of tricyclics may be accelerated. Administration of **sertraline** in patients stabilized on **levothyroxine** may result in increased **levothyroxine** requirements.

There is a possible increased risk of coronary insufficiency in patients with CAD.

Furosemide (>80mg IV), **heparin**, hydantoins, NSAIDs (e.g., fenamates, **phenylbutazone**), and salicylates (>2g/d) each may cause protein-binding site displacement, resulting in an initial transient increase in free T_4. Continued administration results in a decrease in serum T_4 and normal free T_4 and TSH concentrations and, therefore, patients are clinically euthyroid. Salicylates inhibit binding of T_4 and T_3 to thyroid-binding globulin (TBG) and transthyretin. An initial increase in serum free T_4 is followed by return of free T_4 to normal levels with sustained therapeutic serum salicylate concentrations, although total T_4 levels may decrease by as much as 30%.

Carbamazepine, hydantoins, **phenobarbital,** and **rifampin** stimulate hepatic microsomal drug-metabolizing enzyme activity and may increase hepatic degradation of **levothyroxine,** resulting in increased **levothyroxine** requirements. **Phenytoin** and **carbamazepine** reduce serum protein binding of **levothyroxine,** and total and free T_4 may be reduced by 20-40%, but most patients have normal serum TSH levels and are clinically euthyroid.

Amiodarone, β-adrenergic antagonists (e.g., **propranolol** >160mg/d), glucocorticoids (e.g., **dexamethasone** 4mg/d), and **propylthiouracil** may decrease the peripheral conversion of T_4 to T_3, leading to decreased T_3 levels. However, serum T_4 levels are usually normal but may occasionally be slightly increased. In patients treated with large doses of **propranolol** (>160mg/d), T_3 and T_4 levels change slightly, TSH levels remain normal, and patients are clinically euthyroid. Short-term administration of large doses of glucocorticoids may decrease serum T_3 concentrations by 30% with minimal change in serum T_4 levels. However, long-term glucocorticoid therapy may result in slightly decreased T_3 and T_4 levels due to decreased TBG production.

Interferon-alfa has been associated with the development of antithyroid microsomal antibodies in 20% of patients, and some have transient hypothyroidism, hyperthyroidism, or both. Patients who have antithyroid antibodies before treatment are at higher risk for thyroid dysfunction during treatment. IL-2 has been associated with transient painless thyroiditis in 20% of patients.

References

Abalovich M, Gutierrez S, Alcaraz G, et al. Thyroid 2002; 12:63-8.

Abbassi V, Steinour TA. J Pediatr 1980; 97:259-61.

Casey BM, Dashe JS, Spong CY, et al. Obstet Gynecol 2007; 109:1129-35.

Glinoer D. Thyroid 2001; 11:471-81.

Gruner C, Kollert A, Wildt L, et al. Fetal Diagn Ther 2001; 16:47-51.

Letarte J, Guyda H, Dussault JH, Glorieux J. Pediatrics 1980; 65:703-5.

Neto LV, De Almeida CA, Da Costa SM, Vaisman M. Gynecol Endocrinol 2007; 23:138-41.

Olivieri A, Medda E, De Angelis S, et al; Study Group for Congenital Hypothyroidism. J Clin Endocrinol Metab 2007; 92:3141-7.

Radetti G, Zavallone A, Gentili L, et al. Minerva Pediatr 2002; 54:383-400.

Redmond GP. Int J Fertil Womens Med 2002; 47:123-7.

Rotondi M, Caccavale C, Di Serio C, et al. Thyroid 1999; 9:1037-40.

Smit BJ, Kok JH, Vulsma T, et al. Acta Paediatr 2000; 89:291-5.

van Wassenaer AG, Stulp MR, Valianpour F, et al. Clin Endocrinol (Oxf) 2002; 56:621-7.

Varma SK, Collins M, Row A, et al. J Pediatr 1978; 93:803-6.

Summary

Pregnancy Category: A
Lactation Category: S

- **Levothyroxine** is the standard treatment of hypothyroidism during pregnancy.
- Abnormalities of maternal and fetal thyroid function affect long-term neonatal neurologic development.
- Screening for thyroid deficiency during pregnancy may be warranted.

Lidocaine—(Alphacaine; Leostesin; Rucaina; Xylocaina; Xylocaine)

International Brand Name—Aeroderm (Spain); After Burn Spray (Israel); Cuivasil Spray (Israel); Dube Spray (Singapore); Dynexan (France); Esracain Jelly (Israel); Esracain Ointment (Israel); Farmacaina (Colombia); Gesicain Jelly (India); Gesicain Ointment (India); Gesicain Viscous (India); Lecasin (Korea); Leostesin Jelly (Israel); Leostesin Ointment (Israel, South Africa); Lidocain Gel (Bulgaria, Finland, Germany, Hungary); Lidocain Ointment (Bulgaria); Lidocain Spray (Bulgaria, Hungary); Lidonest (Indonesia); Ora (Taiwan); Remicaine Gel (South Africa); Roxicaina (Colombia); Rucaina Pomada (Mexico); Solarcaine (Hong Kong); Xilocaina Viscosa (Portugal); Xilonest Pomada (Peru); Xilotane Gel (Portugal); Xilotane Oral (Portugal); Xylocaina Aerosol (Spain); Xylocain Aerosol (Denmark, Sweden); Xylocaina Gel (Spain); Xylocaina Ointment (Italy, Mexico, Spain); Xylocaina Pomada (Peru); Xylocaina Spray (Italy, Mexico); Xylocain Creme (Denmark, Norway); Xylocaine Adhesive Ointment (New Zealand); Xylocaine Aerosol (Australia, Canada, France, Hong Kong, Netherlands); Xylocaine Gel (Belgium, England, France, Greece, Ireland, Israel); Xylocaine Heavy (Israel); Xylocaine Jelly (Hong Kong, India, Indonesia, Israel, New Zealand, Philippines, South Africa, Taiwan); Xylocaine Ointment (Greece, India, Malaysia, Netherlands, Philippines, South Africa, Taiwan, Thailand); Xylocaine Solution (France); Xylocaine Spray (Belgium, France, Greece, Hong Kong, Indonesia, Israel, Korea, Malaysia, Netherlands, New Zealand, Philippines, Taiwan, Thailand); Xylocaine Topical Solution (Canada, Israel); Xylocaine Viscous (England, India, Ireland, Malaysia, Taiwan, Thailand); Xylocaine Viscous Topical Solution (Australia, Canada, England); Xylocaine Viscus (Greece); Xylocaine Viskeus Topical Solution (Netherlands); Xylocaine Visquese (France); Xylocaine Visqueuse (Belgium); Xylocain Gargle (Finland, Sweden); Xylocain Gel (Austria, Denmark, Finland, Germany, Norway, Sweden, Switzerland); Xylocain Liniment (Denmark); Xylocain Ointment (Austria, Finland, Germany, Sweden, Switzerland); Xylocain Salve (Denmark); Xylocain Spray (Austria, Germany, Norway, Switzerland); Xylocain Viscous (Austria, Switzerland); Xylocain Viskos (Germany, Sweden); Xylocain Visks (Finland); Xylocard (Israel); Xyloctin (Germany)

Drug Class — Anesthetics, local; Anesthetics, topical; Antiarrhythmics, class IB

Indications — Arrhythmia (ventricular), local anesthesia, postherpetic neuralgia

Mechanism — Depress action potential phase 0, stabilizes membranes

Dosage with Qualifiers

Ventricular arrhythmia—begin 1-1.5mg/kg IV; may repeat bolus in 5min, then begin infusion 1-4mg/min IV; max 300mg ×1h
Local anesthesia—infiltrate IM/SC; max 300mg
Postherpetic neuralgia—apply topically q12h

NOTE: available in parenteral (with and without preservatives), ointment, patch, oral spray, and gel formats.

- **Contraindications**—hypersensitivity to drug or class, Wolff-Parkinson-White syndrome, sinoatrial or AV block, Stokes-Adams syndrome
- **Caution**—hepatic or renal dysfunction, bradycardia, CHF, hypertension

Maternal Considerations

Lidocaine has been used for decades for paracervical/pudendal blocks and perineal infiltration prior to episiotomy. Buffered products reduce the pain of infiltration. However, sprayed **lidocaine** is not effective for perineal anesthesia. Allergies are rare. It is often used for spinal anesthesia (saddle block) without **epinephrine** or epidural anesthesia with **epinephrine.** The prevalence of maternal hypotension may be higher with **lidocaine** than with **bupivacaine.** Both the quality and the duration of

anesthesia are improved by the addition of **fentanyl.** The topical application of 2% **lidocaine** gel decreases perineal pain in women with genital herpes. **Lidocaine** is a second option for the treatment of ventricular arrhythmias after failed electrical cardioversion.
Side effects include tinnitus, blurred vision, light-headedness, impaired swallowing, seizures, respiratory arrest, arrhythmia, heart block, bradycardia, asthma, coma, tremor, confusion, hypotension, hallucinations, agitation, N/V, and cardiovascular collapse.

Fetal Considerations

Lidocaine rapidly crosses the human placenta, and its elimination t/2 after birth approximates 3h. **Lidocaine** administered by the perineal route has a T_{max} of 15min, significantly lower than when the drug is administered peridurally; M:F ratios in this instance approximate 1:2 at the time of delivery. It is not placenta-bound. The results of neurobehavioral exams of newborns whose mothers received continuous epidural analgesia are conflicting. Some suggest a decrease in muscle strength and tone, while others find no effect. **Lidocaine** can potentially produce neonatal CNS depression and seizures. There are no reports of associated malformations. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically.

Breastfeeding Safety

Lidocaine is excreted into breast milk, but the maternal systemic levels are low. Considering the dose and route, it is unlikely the breastfed neonate would ingest clinically relevant amounts.

Drug Interactions

Should be used with caution in patients receiving class I antiarrhythmic drugs (e.g., **mexiletine, tocainide**) since the toxic effects are additive and potentially synergistic.

References

Ala-Kokko TI, Pienimaki P, Herva R, et al. Pharmacol Toxicol 1995; 77:142-8.
Banzai M, Sato S, Tezuka N, et al. Can J Anaesth 1995; 42:338-40.
Brown WU, Bell GC, Lurie AO, et al. Anesthesiology 1975; 42:698-707.
Browne IM, Birnbach DJ. Am J Obstet Gynecol 2001; 185:1253-4.
Carvalho B, Fuller A, Brummel C, Cohen SE. Int J Obstet Anesth 2007; 16:116-21.
Cavalli R de C, Lanchote VL, Duarte G, et al. Eur J Clin Pharmacol 2004; 60:569-74.
Collins MK, Porter KB, Brook E, et al. Obstet Gynecol 1994; 84:335-7.
Connelly NR, Parker RK, Lucas T, et al. Anesth Analg 2001; 93:1001-5.
Connelly NR, Parker RK, Vallurupalli V, et al. Anesth Analg 2000; 91:374-8.
Guay J, Gaudreault P, Boulanger A, et al. Acta Anaesthesiol Scand 1992; 36:722-7.
Joglar JA, Page RL. Drug Saf 1999; 20:85-94.
Kuhnert BR, Philipson EH, Pimental R, et al. Anesth Analg 1986; 65:139-44.
Lam DT, Ngan Kee WD, Khaw KS. Anaesthesia 2001; 56:790-4.
Lawrie D. Aust NZ J Obstet Gynaecol 1997; 37:485-6.
Levy BT, Bergus GR, Hartz A, et al. J Fam Pract 1999; 48:778-84.
Ng EH, Tang OS, Chui DK, Ho PC. Hum Reprod 2000; 15:2148-51.
Ortega D, Viviand X, Lorec AM, et al. Acta Anaesthesiol Scand 1999; 43:394-7.

Philipson EH, Kuhnert BR, Syracuse CD. Am J Obstet Gynecol 1984; 149:403-7.
Puente NW, Josephy PD. J Anal Toxicol 2001; 25:711-5.
Sanders J, Campbell R, Peters TJ. BMJ 2006; 333:117.
Scanlon JW, Brown WU Jr, Weiss JB, Alper MH. Anesthesiology 1974; 40:121-8.
Shahriari A, Khooshideh M. Middle East J Anesthesiol 2007; 19:397-406.
Trappe HJ, Pfitzner P. Z Kardiol 2001; 90(Suppl 4):36-44.
Wiebe ER, Rawling M. Int J Gynaecol Obstet 1995; 50:41-6.

Summary

Pregnancy Category: B
Lactation Category: S

- **Lidocaine** is considered safe and effective during pregnancy and lactation when used as directed.

Lincomycin—(Lincocin; Lincoject; Lincorex; L-Mycin)

International Brand Name—Albiotic (Germany); Biolincom (Indonesia); Cillimicina (Italy); Cillimycin (Israel); Frademicina (Argentina); Libiocid (Mexico); Linco ANB (Thailand); Lincobiotic (Indonesia); Lincocine (France); Lincofan (Peru); Lincomec (Indonesia); Lincomed (Israel); Lincono (Thailand); Lincophar (Indonesia); Lincoplus (Peru); Linmycin (Thailand); Lintropsin (Indonesia); Medoglycin (Hong Kong); Princol (Mexico); Zumalin (Indonesia)

Drug Class

Antibiotics; Lincosamides

Indications

Bacterial infections (aerobic gram-positive cocci: *S. pyogenes,* viridans group streptococci; aerobic gram-positive bacilli: *Corynebacterium diphtheria;* anaerobic gram-positive bacteria: *Propionibacterium acnes, C. tetani, C. perfringens)*

Mechanism

Inhibits protein synthesis

Dosage with Qualifiers

Bacterial infection—600-1000mg q8-12h

- **Contraindications**—hypersensitivity to drug or class, pseudomembranous colitis
- **Caution**—hepatic or renal dysfunction, asthma, GI disease

Maternal Considerations

There are 2 main antibiotics in the lincosamide family: **lincomycin** and **clindamycin.** Because **lincomycin** has been associated with severe colitis that may end fatally, it should be reserved for serious infections where less toxic antimicrobial agents are ineffective. There are no adequate reports or well-controlled studies of **lincomycin** in pregnant women, in whom **clindamycin** is commonly used.
Side effects include pseudomembranous colitis, diarrhea, colitis, vaginitis, glossitis, stomatitis, N/V, neutropenia, leukopenia, agranulocytosis, tinnitus, thrombocytopenia, aplastic anemia, angioneurotic edema, serum sickness, urticaria, rash, azotemia, oliguria, and vertigo.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **lincomycin** crosses the human placenta. Rodent teratogen studies have not been performed.

Breastfeeding Safety

There are no adequate reports or well-controlled studies in nursing women. **Lincomycin** is excreted into human breast milk, achieving concentrations of 0.5-2.4mcg/ml. Even if a term

	breastfed newborn had 100% absorption, the daily dose would be <2mg.
Drug Interactions	May enhance the action of neuromuscular blocking agents, and should thus be used with caution in patients taking these drugs. Kaolin-pectin mixtures inhibit the absorption of orally administered **lincomycin.** Antagonism between **lincomycin** and **erythromycin** *in vitro* has been demonstrated. Because of possible clinical significance, the two drugs should not used together.
References	Czeizel AE, Rockenbauer M, Sorensen HT, Olsen J. Scand J Infect Dis 2000; 32:579-80. Pechere JC. Pathol Biol (Paris) 1986; 34:119-28.
Summary	**Pregnancy Category: C** **Lactation Category: S** • **Lincomycin** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk. • There is more experience with **clindamycin** during pregnancy and lactation.

Lindane—(Aphtiria; Hexicid; Kwell; Lorexane; Scabex)

International Brand Name—Acaricida (Peru); Benhex Cream (New Zealand); Bicide (Israel); Davesol (Ecuador); Delice (Taiwan); Delitex (Germany); GAB (India); Gambex (South Africa); Herklin (Costa Rica, Dominican Republic, El Salvador, Guatemala, Honduras, Nicaragua, Panama); Hexit (Canada); Jacutin (Germany); Lencid (Belgium); Linden Lotion (Korea); PMS Lindane (Canada); Quellada (Belgium, South Africa); Quellada Cream (Australia); Quellada Creme Rinse (Australia); Quellada-H (Germany); Quellada Head Lice Treatment (Australia); Quellada Lotion (New Zealand); Sarconyl (Ecuador); Scabecid (France); Scabexyl (Costa Rica, Dominican Republic, El Salvador, Guatemala, Honduras, Panama); Scabi (Taiwan); Scabisan (Mexico); Varsan (Japan)

Drug Class	Anti-infectives; Dermatologics; Scabicides/pediculicides
Indications	Scabies, pediculosis
Mechanism	Ectoparasiticide and ovicide against *Sarcoptes scabiei* (scabies)
Dosage with Qualifiers	Scabies—apply from neck to the feet and bathe after 8-12h; repeat treatment 1w; max 30ml per application Pediculosis—apply 20-30ml shampoo to dry hair, wait 5min and rinse; comb hair and remove nits; may repeat in 1w • **Contraindications**—hypersensitivity to drug or class, inflamed skin, seizure disorder, pregnancy, breastfeeding • **Caution**—genitalia contact
Maternal Considerations	**Lindane** (γ-hexachlorocyclohexane) is a popular OTC treatment for scabies. The number of suspected adverse reactions is small considering over 10 million ounces of 1% **lindane** are sold yearly. Almost all suspected adverse drug reactions involve misuse. There are no adequate reports or well-controlled studies of **lindane** in pregnant women. However, **lindane** is stored in fat, and rodent studies describe a reduction in uterine gap junction synthesis and, as a result, incoordination of uterine contractions. ***Side effects*** include seizures, neurotoxicity, dizziness, eczema, dermatitis, anxiety, insomnia, and myelosuppression.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. **Lindane** likely crosses and is stored in the human placenta. It is a known neurotoxin. One report describes a suicide attempt with oral ingestion at 16w followed immediately by fetal death and vaginal bleeding. Fortunately, the maternal systemic concentrations after topical application (cream or shampoo) are low. An increased prevalence of IUGR has been suggested. Transfer across the rabbit placenta occurs but is inefficient. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically. **Lindane** transiently reduces fetal serum T_4 in sheep.

Breastfeeding Safety

There are no adequate reports or well-controlled studies in nursing women. **Lindane** is excreted into human milk at low concentrations (0-113ppb) and may also be present due to environmental contamination; it is unlikely the neonate would ingest a clinically relevant amount. However, if this is a concern, the neonate may be bottle fed for 2d.

Drug Interactions

Oils may enhance absorption; therefore, simultaneous use of creams, ointments, or oils should be avoided. If an oil-based hair dressing is used, it is recommended that the hair be shampooed, rinsed, and dried before application of **lindane** shampoo.

References

Beard AP, Rawlings NC. J Toxicol Environ Health A 1999; 58:509-30.
Criswell KA, Loch-Caruso R. Reprod Toxicol 1999; 13:481-90.
Folster-Holst R, Rufli T, Christophers E. Hautarzt 2000; 51:7-13.
Karmaus W, Wolf N. Environ Health Perspect 1995; 103:1120-5.
Konje JC, Otolorin EO, Sotunmbi PT, Ladipo OA. J Reprod Med 1992; 37:992-4.
Lopez-Espinosa MJ, Granada A, Carreno J, et al. Placenta 2007; 28:631-8.
Pompa G, Fadini L, Di Lauro F, Caloni F. Pharmacol Toxicol 1994; 74:28-34.
Rasmussen JE. J Am Acad Dermatol 1981; 5:507-16.

Summary

Pregnancy Category: B
Lactation Category: S (likely)

- 1% **Lindane** continues as the agent of choice for nearly all patients with scabies and lice during pregnancy and lactation when used as directed.

Linezolid—(Zyvox)

International Brand Name—Linox (India); Zyvox (England, Hong Kong, Ireland, Korea, Singapore); Zyvoxam (Canada, Mexico); Zyvoxid (Colombia, France, Germany, Israel)

Drug Class

Antibiotics; Oxalodinones

Indications

Bacterial infections (gram-positive bacteria: *Enterococcus fecalis* and *E. faecium* [vancomycin-resistant], *S. aureus, S. agalactiae, S. pneumoniae, S. pyogenes,* viridans group streptococci; gram-negative bacteria: *P. multocida* and anaerobic bacteria)

Mechanism

Inhibits bacterial protein synthesis

Dosage with Qualifiers

Vancomycin-resistant enterococcal infections—600mg IV/PO q12h ×10-28d
Pneumonia—600mg IV/PO q12h ×10-28d
Skin infection—400mg PO q12h ×10-14d

NOTE: avoid tyramine-containing foods (keep tyramine content <100mg/meal); monitor the CBC count weekly.

- **Contraindications**—hypersensitivity to drug or class
- **Caution**—hypertension, pheochromocytoma, carcinoid syndrome, thyroid disease, MAOIs, thrombocytopenia, phenylketonuria, severe hepatic disease, myelosuppression

Maternal Considerations

Linezolid is a member of a new class of synthetic antibiotics, the oxazolidinones. It is also a nonselective MAOI. This family of drugs is useful in the treatment of aerobic gram-positive and -negative bacteria infections. There is no published experience with **linezolid** during pregnancy.
Side effects include thrombocytopenia, pseudomembranous colitis, leukopenia, pancytopenia, anemia, diarrhea, headache, N/V, dyspepsia, localized abdominal pain, pruritus, tongue discoloration, and rash.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **linezolid** crosses the human placenta. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically. Embryotoxicity is noted only at doses causing maternal toxicity.

Breastfeeding Safety

There is no published experience in nursing women. It is unknown whether **linezolid** enters human breast milk. It is excreted into rat milk, achieving an M:P ratio near unity.

Drug Interactions

A reversible, nonselective MAOI, **linezold** may interact with adrenergic and serotonergic agents. Some individuals experience a reversible enhancement of the pressor response to indirect-acting sympathomimetic agents, vasopressors, or dopaminergic agents. Initial doses of adrenergic agents (e.g., **dopamine, epinephrine**) should be reduced and titrated.
The serotonin syndrome may manifest after co-administration of **linezolid** and serotonergic agents, including antidepressants such as SSRIs. Patients should be closely observed for signs and symptoms of serotonin syndrome (e.g., cognitive dysfunction, hyperpyrexia, hyperreflexia, incoordination).

References

Chin KG, Mactal-Haaf C, McPherson CE. J Hum Lact 2000; 16:351-8.

Summary

Pregnancy Category: C
Lactation Category: U

- **Linezolid** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.
- There are alternative agents for which there is more experience during pregnancy and lactation.

Liothyronine—(Cytomel; Triostat)

International Brand Name—Cynomel (Costa Rica, Dominican Republic, El Salvador, France, Guatemala, Honduras, Mexico, Nicaragua, Panama, South Africa); Cytomel 25 (Israel); T3 (Greece); Tertroxin (South Africa); Thyronine (Japan); Trijodthyronin (Austria, Bulgaria); Trijodthyronin BC N (Germany)

Drug Class	Hormones, thyroid
Indications	Myxedema coma
Mechanism	Unknown (increases metabolism)
Dosage with Qualifiers	Myxedema coma—25-50mcg IV ×1; then 25mcg/d PO, increase 12.5-25mcg q1-2w; usual dose 25-75mcg/d • **Contraindications**—hypersensitivity to drug or class, MI, thyrotoxicosis, adrenal insufficiency • **Caution**—angina, hypertension, diabetes mellitus, renal failure
Maternal Considerations	**Liothyronine** is synthetic T_3. Myxedema coma is a potentially lethal manifestation of hypothyroidism. Patients with suspected myxedema coma should be immediately admitted to an ICU for aggressive pulmonary and CV support. Most authorities recommend treatment with IV **levothyroxine** rather than IV **liothyronine. Hydrocortisone** is also administered until coexisting adrenal insufficiency is excluded. Advanced age, cardiac complications, and high-dose thyroid hormone replacement (>500mcg/d) are associated with a fatal outcome within 1mo of treatment. **Amiodarone**-induced hypothyroidism may also be life-threatening, and thyroid function should be tested before and during **amiodarone** therapy. There are no adequate reports or well-controlled studies of **liothyronine** in pregnant women. There are no reports of myxedema coma during pregnancy. ***Side effects*** include headache, irritability, nervousness, sweating, tachycardia, increased bowel motility, menstrual irregularities, shock, insomnia, tremor, arrhythmia, weight loss, heat intolerance, and diaphoresis.
Fetal Considerations	There are no adequate reports or well-controlled studies of **liothyronine** in human fetuses. Transfer of natural T_3 across the human placenta is low but physiologically relevant.
Breastfeeding Safety	It is unknown whether **liothyronine** enters human breast milk. However, several studies conclude the amount of thyroid hormone present in human milk is too low to clinically affect the neonate. It is unknown whether supplementation increases the level.
Drug Interactions	Thyroid hormones increase the catabolism of vitamin K–dependent clotting factors. Normal compensatory increases in clotting factor synthesis are impaired when oral anticoagulants are also given. Patients stabilized on oral anticoagulants found to require thyroid replacement therapy should be closely watched when thyroid hormone is begun. If a patient is truly hypothyroid, it is likely a reduction in anticoagulant dosage will be required. No special precautions appear necessary when oral anticoagulant therapy is begun in a patient already stabilized on maintenance thyroid replacement therapy. Initiating thyroid replacement may increase insulin or oral hypoglycemic requirements. Patients receiving insulin or oral

hypoglycemics should be closely watched during the initiation of thyroid replacement.
Estrogens increase serum thyroid-binding globulin, and free **levothyroxine** may be decrease when estrogens are begun. If the patient's thyroid gland has sufficient function, the decreased free T_4 will trigger a compensatory increase in T_4 release. However, patients without a functioning thyroid gland may need an increased dose if estrogens or estrogen-containing oral contraceptives are given.
Imipramine and other TCAs may increase receptor sensitivity and enhance antidepressant activity; transient cardiac arrhythmias are reported. Thyroid hormone activity may also be enhanced. May potentiate the toxic effects of digitalis. Thyroid hormone replacement increases the metabolic rate, which requires an increase in digitalis dosage.
Ketamine may cause hypertension and tachycardia. Use with caution and be prepared to treat hypertension.
May increase adrenergic effects of catecholamines such as **epinephrine** and norepinephrine. Use of vasopressors in patients receiving thyroid hormone preparations may increase the risk of coronary insufficiency, especially in those with CAD. Use caution when administering vasopressors with **liothyronine.**
Cholestyramine binds both T_4 and T_3 in the intestine, thus impairing absorption of these thyroid hormones. *In vitro* studies indicate that the binding is not easily removed. Allow at least 4-5h between administration of **cholestyramine** and thyroid hormones.

References

Mazonson PD, Williams ML, Cantley LK, et al. Am J Med 1984; 77:751-4.
Pereira VG, Haron ES, Lima-Neto N, Medeiros-Neto GA. J Endocrinol Invest 1982; 5:331-4.
van Wassenaer AG, Stulp MR, Valianpour F, et al. Clin Endocrinol (Oxf) 2002; 56:621-7.
Wall CR. Am Fam Physician 2000; 62:2485-90.
Yamamoto T, Fukuyama J, Fujiyoshi A. Thyroid 1999; 9:1167-74.

Summary

Pregnancy Category: A
Lactation Category: S
- **Liothyronine** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Liotrix—(Euthroid; Thyrolar)

International Brand Name—Cynoplus 3 (Mexico); Euthroid 2 (Colombia); Eutroid (Peru); Proloid S-1 (Mexico); Proloid S-2 (Mexico); Thyreotom (Cyprus, Egypt, Iraq, Jordan, Libya, Syria); Thyreotom Forte (Israel)

Drug Class

Hormones, thyroid

Indications

Hypothyroidism

Mechanism

Unknown (increases metabolism)

Dosage with Qualifiers

Hypothyroidism—begin 50mcg PO qd, increase 25mcg every 2-3w until replacement adequate

- **Contraindications**—hypersensitivity to drug or class, MI, thyrotoxicosis, adrenal insufficiency
- **Caution**—angina, hypertension, diabetes mellitus, renal failure

Maternal Considerations

Liotrix is synthetic microcrystalline **levothyroxine** (T_4) and synthetic microcrystalline liothyronine (T_3) combined in a 4:1 ratio. There are no adequate reports or well-controlled studies of **liotrix** in pregnant women (see **Levothyroxine, Liothyronine**). ***Side effects*** include headache, irritability, nervousness, sweating, tachycardia, increased bowel motility, menstrual irregularities, shock, insomnia, tremor, arrhythmia, weight loss, heat intolerance, and diaphoresis.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses (see **Levothyroxine, Liothyronine**).

Breastfeeding Safety

There are no adequate reports or well-controlled studies in nursing women. It is unknown whether **liotrix** enters human breast milk. (See **Levothyroxine, Liothyronine.**)

Drug Interactions

Thyroid hormones increase the catabolism of vitamin K–dependent clotting factors. Normal compensatory increases in clotting factor synthesis are impaired when oral anticoagulants are also given. Patients stabilized on oral anticoagulants found to require thyroid replacement therapy should be closely watched when thyroid hormone is begun. If a patient is truly hypothyroid, it is likely a reduction in anticoagulant dosage will be required. No special precautions appear necessary when oral anticoagulant therapy is begun in a patient already stabilized on maintenance thyroid replacement therapy.

Initiating thyroid replacement may increase insulin or oral hypoglycemic requirements. Patients receiving insulin or oral hypoglycemics should be closely watched during the initiation of thyroid replacement.

Estrogens increase serum thyroid-binding globulin, and free **levothyroxine** may be decreased when estrogens are begun. If the patient's thyroid gland has sufficient function, the decreased free T_4 will trigger a compensatory increase in T_4 release. However, patients without a functioning thyroid gland may need an increased dose if estrogens or estrogen-containing oral contraceptives are given.

Imipramine and other TCAs may increase receptor sensitivity and enhance antidepressant activity; transient cardiac arrhythmias are reported. Thyroid hormone activity may also be enhanced. May potentiate the toxic effects of digitalis. Thyroid hormone replacement increases the metabolic rate, which requires an increase in digitalis dosage.

Ketamine may cause hypertension and tachycardia. Use with caution and be prepared to treat hypertension.

May increase adrenergic effects of catecholamines such as **epinephrine** and norepinephrine. Use of vasopressors in patients receiving thyroid hormone preparations may increase the risk of coronary insufficiency, especially in those with CAD. Use caution when administering vasopressors with **liothyronine.**

Cholestyramine binds both T_4 and T_3 in the intestine, thus impairing absorption of these thyroid hormones. *In vitro* studies indicate that the binding is not easily removed. Allow at least 4-5h between administration of **cholestyramine** and thyroid hormones.

References

See **Levothyroxine, Liothyronine.**

Summary

Pregnancy Category: A
Lactation Category: S

- **Liotrix** should be used during pregnancy and lactation only if the benefit justifies the potential risk.

Lisinopril—(Prinivil; Zestril)

International Brand Name—Acepril (Hong Kong); Acerbon (Germany); Alapril (Italy); Alfaken (Mexico); Carace (England, Ireland); Cipril (India); Coric (Germany); Dapril (China, South Africa); ES (India); Fibsol (Australia); Inopril (Israel); Linopril (Israel); Linvas (India); Lipril (India); Lisi ABZ (Germany); Lisibeta (Germany); Lisigamma (Germany); Lisihexal (Germany); Lisipril (Colombia, Dominican Republic); Lisodur (Australia); Lisopril (Israel); Lisoril (India, Singapore); Lispril (Thailand); Listril (India); Noperten (Indonesia); Novatec (Belgium, Netherlands); Presiten (Dominican Republic); Prinil (Switzerland); Sinopril (Israel); Tensopril (Israel); Tensyn (Colombia); Vivatec (Denmark, Finland, Norway, Sweden); Zestomax (South Africa)

Drug Class	ACEI/A2R-antagonists; Antihypertensives
Indications	Hypertension, CHF, MI
Mechanism	ACE inhibition
Dosage with Qualifiers	Hypertension—10-40mg PO qd CHF—5-20mg PO qd; max 40mg/d MI—5-10mg PO qd ×6w • **Contraindications**—hypersensitivity to drug or class, history of angioedema, pregnancy • **Caution**—renal artery stenosis, hepatic or renal dysfunction, hyponatremia, CHF, collagen vascular disease
Maternal Considerations	There are no adequate reports or well-controlled studies of **lisinopril** in pregnant women. In general, inhibitors of the renin-angiotensin system are contraindicated throughout pregnancy. The lowest dose effective should be used when **lisinopril** is required during pregnancy for BP control. ***Side effects*** include fetal and neonatal morbidity and death, hypovolemia, asthenia, fever, paresthesias, vertigo, dyspepsia, gastroenteritis, tachycardia, palpitation, leukopenia, hepatotoxicity, neutropenia, hyperkalemia, agranulocytosis, edema, diarrhea, chest pain, cough, elevated LFTs, pruritus, and rash.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. **Lisinopril** crosses the human placenta. No adverse fetal effects are reported following 1st trimester exposure. However, such adverse events are well-documented after the ingestion of other ACEIs. Later exposure is associated with cranial hypoplasia, anuria, reversible or irreversible renal failure, death, oligohydramnios, prematurity, IUGR, and PDA. The mechanism of renal dysfunction is likely related to fetal hypotension and prolonged decreased glomerular filtration. If oligohydramnios is detected, **lisinopril** should be discontinued unless lifesaving for the mother. Antenatal surveillance should be initiated (e.g., BPP) if the fetus is potentially viable. Oligohydramnios may not appear until after the fetus has irreversible injury. Neonates exposed *in utero* to ACEIs should be observed closely for hypotension, oliguria, and hyperkalemia. If oliguria occurs despite adequate pressure and renal perfusion, exchange transfusion or peritoneal dialysis may be required.
Breastfeeding Safety	There is no published experience in nursing women. It is unknown whether **lisinopril** enters human breast milk. Other ACEIs (e.g., **captopril**) are excreted in the milk at low concentrations.
Drug Interactions	Patients on diuretics, especially those recently started, may occasionally become hypotensive after the initiation of **lisinopril.**

The risk of hypotension can be reduced by either discontinuing the diuretic or increasing salt intake prior to starting the **lisinopril.** If it is necessary to continue the diuretic, initiate therapy with **lisinopril** at a dose of 5mg daily, and provide close medical supervision after the initial dose until BP has stabilized.
An additional antihypertensive effect is typically observed when a diuretic is added to the therapy of a patient receiving **lisinopril.**
In some patients with comprised renal function who are being treated with NSAIDs, **lisinopril** may trigger a further deterioration of renal function. These effects are usually reversible. Further, the antihypertensive effect of **lisinopril** may be reduced by **indomethacin.**
Attenuates potassium loss caused by thiazide-type diuretics. Use of **lisinopril** with potassium-sparing diuretics (e.g., **amiloride, spironolactone, triamterene**), potassium supplements, or potassium-containing salt substitutes may lead to hyperkalemia. Therefore, this combination should be used with caution and with frequent monitoring of serum potassium. Potassium-sparing agents should generally not be used in patients with heart failure who are receiving **lisinopril.**
Lithium toxicity has been reported in patients receiving ACEIs. It is usually reversible upon discontinuation of **lithium** and the ACEI. Monitor **lithium** levels frequently if **lisinopril** is administered concomitantly.

References

Bhatt-Mehta V, Deluga KS. Pharmacotherapy 1993; 13:515-8.
Filler G, Wong H, Condello AS, et al. Arch Dis Child Fetal Neonatal Ed 2003; 88:F154-6.
Noble TA, Murray KM. Clin Pharm 1988; 7:659-69.
Parish RC, Miller LJ. Drug Saf 1992; 7:14-31.
Tomlinson AJ, Campbell J, Walker JJ, Morgan C. Ann Pharmacother 2000; 34:180-2.

Summary

Pregnancy Category: C (1st trimester), **D** (2nd and 3rd trimesters)
Lactation Category: U

- ACE inhibitors are well-established in the treatment of arterial hypertension, heart failure, and diabetic and/or hypertensive nephropathy with albuminuria.
- **Lisinopril** and other ACEIs are to be avoided throughout pregnancy if possible.
- When mother's disease requires treatment with **lisinopril,** the lowest dose should be used followed by close monitoring of the fetus.

Lithium carbonate-citrate—(Calith; Eskalith; Eskalith CR; Hypnorex; Hyponrex; Lilipin; Lilitin; Lithane; Litheum; Lithobid; Lithocarb; Lithonate; Lithotabs; Manialit; Phasal)

International Brand Name—Camcolit (Belgium, England, Hong Kong, Ireland, Israel, Netherlands, Puerto Rico, Singapore, Taiwan); Carbolit (Colombia, Mexico); Carbolith (Canada); Ceglution (Argentina); Ceglution 300 (Ecuador); Duralith (Canada); Hynorex Retard (Germany, Switzerland); Lentolith (South Africa); Licab (India); Licarb (Thailand); Licarbium (Israel); Lidin (Taiwan); Limas (Japan); Liskonum (Israel, South Africa); Litheum 300 (Mexico); Lithicarb (Malaysia); Lithionate (Taiwan); Lithocap (India); Litilent (Argentina); Litocarb (Peru); Maniprex (Belgium); Phanate (Thailand); Plenur (Spain); Priadel (Belgium, England, Netherlands, New Zealand, Singapore); Priadel Retard (Greece, Switzerland); Quilonium-R (Philippines); Quilonorm Retardtabletten (Switzerland); Quilonum Retard (Czech Republic, Germany, South Africa); Quilonum SR (Australia); Teralithe (France); Theralite (Colombia)

Drug Class	Antipsychotics
Indications	Bipolar disorder, acute mania, schizoaffective disorder, neutropenia (chemotherapy)
Mechanism	Unknown; alters Na^+ transport at the neuronal level
Dosage with Qualifiers	Bipolar disorder—900-1200mg/d PO; max 1800mg qd Acute mania—600mg PO tid Schizoaffective disorder—300mg PO tid or qid Neutropenia (chemotherapy)—300-1000mg PO qd (SR: 600-900mg PO bid) *NOTE: serum lithium levels should not exceed 2.0mEq/L.* • **Contraindications**—hypersensitivity to drug or class, inability to monitor **lithium** level, pregnancy • **Caution**—hepatic or renal dysfunction, hypovolemia, thyroid disorder, CAD
Maternal Considerations	**Lithium** is used for the treatment of psychiatric disorders. It is typically inadequate for the rapid control of acute mania; antipsychotics, **divalproex,** or sedatives are commonly used, with or without **lithium** in these instances. The usefulness of **lithium** lies in the long-term prevention of recurrent mania and bipolar depression and in reducing risk of suicidal behavior. Among patients treated for a bipolar disorder, the risk of a suicide attempt is lower during treatment with **lithium** than it is with **divalproex.** Pregnancy and especially the puerperium are times high risk for recurrence of bipolar disease. Recommendations during pregnancy include discontinuing therapy for at least the 1st trimester, switching to an agent with a less controversial profile (e.g., tricyclics), using smaller doses of **lithium,** and avoiding sodium restriction or diuretics while under treatment. However, discontinuation during pregnancy of mood stabilizer, particularly abruptly, carries a high risk for new morbidity in women with bipolar disease, especially for early depressive and dysphoric states. This risk is reduced markedly by continued mood stabilizer treatment. Treatment planning for pregnant women with bipolar disease should consider not just the relative risks of fetal exposure but also the high risk of recurrence and morbidity associated with stopping therapy. The dose used should be titered to maintain a serum level between 0.5-1.2mEq/L. Toxicity develops between 1.5 and 2.0mEq/L. Ideally, the drug should be tapered gradually over a month. **Lithium** levels should be monitored weekly after 35w gestation, and therapy either discontinued or decreased by ¼ 2-3d before delivery.

Side effects include tremor, muscle fasciculations, twitching, clonic movements, hypertonicity, ataxia, choreoathetotic movements, hyperactive DTR, blackout spells, epileptiform seizures, acute dystonia, cogwheel rigidity, slurred speech, dizziness, vertigo, downbeat nystagmus, incontinence of urine or feces, somnolence, psychomotor retardation, restlessness, confusion, stupor, coma, tongue movements, tics, tinnitus, hallucinations, poor memory, slowed intellectual functioning, startled response, polyuria, diarrhea, vomiting, gastritis, salivary gland swelling, abdominal pain, excessive salivation, flatulence, drowsiness, arrhythmia, hypotension, circulatory collapse, bradycardia, glycosuria, albuminuria, oliguria, nephrogenic diabetes insipidus, alopecia, anesthesia of skin, acne, chronic folliculitis, xerosis cutis, psoriasis, goiter, myxedema, ECG changes, and hyperparathyroidism.

Fetal Considerations

Lithium crosses the placenta; the F:M ratio approximates 1 across a wide range of maternal concentrations (0.2-2.6mEq/L). Infants with higher **lithium** concentrations (>0.64mEq/L) at delivery have significantly lower Apgar scores, longer hospital stays, and higher rates of CNS and neuromuscular complications. Withholding **lithium** therapy for 24-48h before delivery decreases the maternal **lithium** concentration an average of 0.28mEq/L. Several studies note an increased prevalence of Ebstein's anomaly, though this was not confirmed in a prospective, multicenter study. The main effects attributable to **lithium** are cardiac malformations and increased birth weight. A targeted ultrasound performed by a fetal medicine expert is suggested. Fetuses of depressed mothers are more active during midgestation and exhibit lower baseline HRs and move less during late-term vibratory stimulation. Midgestation heightened activity and late-term diminished responsivity may be a prenatal manifestation of the "general adaptation syndrome." SSRIs increase middle cerebral artery velocity while **lithium** decreases it. Neonatal complications often attributed to **lithium** include poor respiratory effort and cyanosis, rhythm disturbances, nephrogenic diabetes insipidus, thyroid dysfunction and goiter, hypoglycemia, hypotonia and lethargy, polyhydramnios, hyperbilirubinemia, and large-for-gestational-age infant. As a result, the delivery of a mother taking **lithium** should be considered a high-risk delivery. However, the results of long-term follow-up studies are reassuring as are the most recent epidemiologic studies. Animal studies using doses producing serum levels similar to therapeutic human levels have not reported any abnormalities, though higher doses have produced exencephaly, skeletal and craniofacial defects, and abnormalities of blood vessel development. Experiments with other vertebrates suggest **lithium** affects dorsoventral specification and inhibition of vasculogenesis. Both these effects can be prevented by pretreatment with myoinositol, indicating that **lithium** interferes with the phosphatidylinositol cycle.

Breastfeeding Safety

Lithium is excreted into human milk and can be measured in the nursing newborn. Maternal serum, breast milk, and infant serum daily trough levels of **lithium** are reported to average 0.76, 0.35, and 0.16mEq/L, respectively, each level lower than the preceding by approximately ½. In this study, no serious adverse events were observed, and elevations of TSH and BUN/Cr were few, minor, and transient.

Drug Interactions

An encephalopathic syndrome (characterized by weakness, lethargy, fever, tremulousness and confusion, extrapyramidal symptoms, leukocytosis, and elevated serum enzymes, BUN, and

fasting blood sugar) followed by irreversible brain damage has occurred in a few patients treated with **lithium** plus **haloperidol.** A causal relationship has not been established

May prolong the effects of neuromuscular blocking agents.

Sodium loss secondary to diuretic use may reduce the renal clearance of **lithium** and increase the risk of toxicity. When such combinations are used, the **lithium** dosage may need to be decreased, and frequent monitoring of plasma levels is recommended.

Toxicity has resulted from interactions with NSAIDs. **Indomethacin** and **piroxicam** have been reported to increase steady-state plasma **lithium** concentrations. There is evidence other NSAIDs, including selective COX-2 inhibitors, have the same effect.

Use of **metronidazole** may trigger **lithium** toxicity due to reduced renal clearance. Patients receiving such combined therapy should be monitored closely.

ACEIs (e.g., **captopril, enalapril**) and angiotensin II receptor antagonists (e.g., **losartan**) can increase steady-state plasma **lithium** levels, sometimes causing in **lithium** toxicity. **Lithium** dosage may need to be decreased, and plasma **lithium** levels measured more often.

Use with calcium channel blocking agents may increase the risk of neurotoxicity in the form of ataxia, tremors, N/V, diarrhea, and/or tinnitus. Caution is recommended.

Use with SSRIs should be undertaken cautiously as the combination may cause diarrhea, confusion, tremor, dizziness, and agitation.

Acetazolamide, urea, xanthine preparations, and alkalinizing agents such as **sodium bicarbonate** may lower serum **lithium** concentrations by increasing urinary lithium excretion.

Extended use of iodide preparations, especially **potassium iodide,** may produce hypothyroidism.

May impair mental and/or physical abilities. Patients should be cautioned about activities requiring alertness (e.g., operating vehicles or machinery).

References

Ang MS, Thorp JA, Parisi VM. Obstet Gynecol 1990; 76:517-9.

Chaudron LH, Jefferson JW. J Clin Psychiatry 2000; 61:79-90.

Cohen LS, Friedman JM, Jefferson JW, et al. JAMA 1994; 271:146-50.

Emory EK, Dieter JN. Ann N Y Acad Sci 2006; 1094:287-91.

Giles JJ, Bannigan JG. Curr Pharm Des 2006; 12:1531-41.

Goodwin FK, Fireman B, Simon GE, et al. JAMA 2003; 290:1467-73.

Grof P, Robbins W, Alda M, et al. Affect Disord 2000; 61:31-9.

Jacobson SJ, Jones K, Johnson K, et al. Lancet 1992; 339:530-3.

Kellner CH, Beale MD, Pritchett JT. JAMA 1994; 271:1828-9.

Maher JE, Colvin EV, Samdarshi TE, et al. Am J Perinatol 1994; 11:334-6.

Newport DJ, Viguera AC, Beach AJ, et al. Am J Psychiatry 2005; 162:2162-70.

Pinelli JM, Symington AJ, Cunningham KA, Paes BA. Am J Obstet Gynecol 2002; 187:245-9.

Schou M. Bipolar Disord 1999; 1:5-10.

Schou M. J Clin Psychiatry 1990; 51:410-3.

Silverman JA, Winters RW, Strande C. Am J Obstet Gynecol 1971; 109:934-6.

Stothers JK, Wilson DW, Royston N. Br Med J 1973; 3:233-4.

Teixeira NA, Lopes RC, Secoli SR. Braz J Med Biol Res 1995; 28:230-9.

Troyer WA, Pereira GR, Lannon RA, et al. J Perinatol 1993; 13:123-7.
Vander Zanden JA. J Hum Lact 1991; 7:195.
Viguera AC, Newport DJ, Ritchie J, et al. Am J Psychiatry 2007; 164:342-5.
Viguera AC, Whitfield T, Baldessarini RJ, et al. Am J Psychiatry 2007; 164:1817-24.
Yacobi S, Ornoy A. Isr J Psychiatry Relat Sci 2008; 45:95-106.

Summary

Pregnancy Category: D
Lactation Category: S

- **Lithium** is the preferred agent for patients with typical bipolar disorder and in patients who are at high risk for suicide (severe depressions or depression combined with persistent suicidal ideas).
- **Lithium** levels should be monitored during pregnancy.
- Controversy continues regarding the potential teratogenic effect of **lithium.** Prospective studies suggest **lithium** is at worst a very weak human teratogen.
- Women of childbearing potential should be informed of the teratogenic potential and advised of the need for adequate contraception and the protective role of folate.
- Serum **lithium** levels in nursing infants are low and well-tolerated.

Lodoxamide tromethamine—(Alomide; Lomide)

International Brand Name—Alconmide (Philippines); Almide (France); Alomide (Argentina, Austria, Belgium, Brazil, Bulgaria, Canada, Chile, China, Colombia, Czech Republic, Denmark, Ecuador, England, Germany, Greece, Hong Kong, Hungary, India, Indonesia, Israel, Italy, Malaysia, Paraguay, Peru, Poland, Singapore, Taiwan, Thailand, Uruguay, Venezuela); Alomide SE (Germany)

Drug Class

Allergy; Mast cell stabilizers; Ophthalmics

Indications

Vernal keratoconjunctivitis, vernal conjunctivitis, vernal keratitis

Mechanism

Inhibits the type I immediate hypersensitivity reaction of mast cells

Dosage with Qualifiers

Vernal keratoconjunctivitis—1-2 gtt OS/OD qid
Vernal conjunctivitis—1-2 gtt OS/OD qid
Vernal keratitis—1-2 gtt OS/OD qid

NOTE: treatment can last up to 3mo.

- **Contraindications**—hypersensitivity to drug or class
- **Caution**—contact lenses

Maternal Considerations

There is no published experience with **lodoxamine** during pregnancy.
Side effects include ocular itching, pruritus, blurred vision, dry eye, tearing, discharge, hyperemia, foreign body sensation, corneal ulcer, eye pain, ocular edema, ocular swelling, corneal abrasion, anterior chamber cells, keratitis, blepharitis, and allergy.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **lodoxamine** crosses the human placenta. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically. Considering the dose and route,

it is unlikely the maternal systemic concentration will reach a clinically relevant level.

Breastfeeding Safety — There is no published experience in nursing women. It is unknown whether **lodoxamine** enters human breast milk. However, considering the dose and route, it is unlikely the breastfed neonate would ingest clinically relevant amounts.

Drug Interactions — No clinically relevant interactions identified.

References — There is no published experience in pregnancy or during lactation.

Summary

Pregnancy Category: B
Lactation Category: S

- **Lodoxamine** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Lomefloxacin—(Maxaquin)

International Brand Name—Decalogiflox (France); Lofloquin (Peru); Logiflox (France); Lomaday (Malaysia); Lomaxacin (Korea); Lomebact (Taiwan); Lomeflon (Japan); Lomeflox (Hong Kong); Lomflox (India, Singapore); Mahaquin (China); Maxaquin (Brazil, Czech Republic, Ecuador, Hong Kong, Italy, Mexico, Portugal, Russia, Switzerland, Venezuela); Meflox (Brazil); Okacin (Malaysia, Philippines, Singapore); Omniquin (Indonesia); Ontop (India); Uniquin (South Africa)

Drug Class — Antibiotics; Quinolones

Indications — Bacterial infections (gram-positive bacteria: *S. saprophyticus;* gram-negative bacteria: *E. coli, H. influenzae, Klebsiella pneumoniae, Moraxella catarrhalis, P. mirabilis, Pseudomonas aeruginosa, Citrobacter diversus, Enterobacter cloacae)*

Mechanism — Inhibits DNA synthesis

Dosage with Qualifiers

Bacterial infection—400mg PO qd ×10-14d
Gonorrhea—400mg PO ×1

NOTE: drink fluids liberally; renal dosing.

- **Contraindications**—hypersensitivity to drug or class, prolongation of QT interval, concomitant use of antiarrhythmic drugs
- **Caution**—hepatic or renal dysfunction (CrCl <50ml/min), seizures, dehydration, hypokalemia, sun exposure, diabetes mellitus, bradycardia, cardiomyopathy, anemia

Maternal Considerations — This quinolone has poor efficacy against anaerobic infections. There are no studies of **lomefloxacin** in pregnant women. Superior agents are usually available.
Side effects include tendonitis, tendon rupture, convulsions, coma, vaginitis, leukorrhea, intermenstrual bleeding, perineal pain, Stevens-Johnson syndrome, hyperkinesia, tremor, vertigo, paresthesias, fatigue, back pain, malaise, asthenia, chest pain, chills, allergic reaction, facial edema, flu-like symptoms, decreased heat tolerance, hypotension, hypertension, edema, syncope, tachycardia, bradycardia, arrhythmia, extrasystole, cyanosis, cardiac failure, angina pectoris, MI, PE, cerebrovascular disorder, cardiomyopathy, vomiting, flatulence, constipation, abdominal

pain, dyspepsia, pseudomembranous colitis, GI inflammation, dysphagia, GI bleeding, pruritus, urticaria, eczema, dysuria, hematuria, and anuria.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **lomefloxacin** crosses the human placenta. Animal studies (mice, dogs, rabbits) report that several quinolones lead to arthropathy, and this toxicity resulted in the recommended restricted use in pregnant women. However, not all quinolones have the same potency on cartilage growth. Further, the use of quinolones during the 1st trimester of pregnancy is not associated with an increased risk of malformations or musculoskeletal conditions. Rodent and monkey studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically. There was evidence of embryo and fetal toxicity at high doses.

Breastfeeding Safety

There is no published experience with **lomefloxacin** in nursing women. Other quinolones are excreted into human breast milk.

Drug Interactions

Sucralfate given within 2h decreased absorption (C_{max} decreased by 30% and T_{max} increased by 1h).
Magnesium- and aluminum-containing antacids significantly decrease bioavailability (48%). Allow at least 4h before administering **lomefloxacin.**
Cimetidine interferes with the elimination of other quinolones. Elevated levels of **cyclosporine** have been reported with other members of the quinolone class.
Probenecid slows the renal elimination and increases by some ⅔ the mean AUC and by 50% the mean T_{max}.
Quinolones may enhance the effects of **warfarin** or its derivatives.

References

Shakibaei M, Baumann-Wilschke I, Rucker M, Stahlmann R. Arch Toxicol 2002; 75:725-33.
Tesh JM, McAnulty PA, Willoughby CR, et al. Jpn J Antibiot 1988; 41:1370-84.

Summary

Pregnancy Category: C
Lactation Category: U

- **Lomefloxacin** should be used during pregnancy and lactation only if the potential benefit justifies the perinatal risk.
- While quinolones appear safe during the 1st trimester, their use during the 2nd and 3rd trimesters should await further study because of the potential for juvenile arthropathy.
- There are alternative agents for which there is more experience during pregnancy and lactation.

Loperamide—(Arret; Beamodium; Chisen; Hocular; Imode; Imodium; Lorico; Motilen)

International Brand Name—Acanol (Mexico); Amerol (Indonesia); Arestal (France); Betaperamide (South Africa); Binaldan (Switzerland); Brek (Italy); Colifilm (Argentina); Colodium (Hong Kong); Desitin (Peru); Diacure (Netherlands); Diadium (Indonesia); Diamide (Philippines); Diapen (Israel); Diarent (Thailand); Diarin (Philippines); Diarlop (India); Diarodil (Thailand); Diarr-Eze (Canada); Diarstop-L (Germany); Diasolv (Philippines); Dicap (New Zealand); Dissenten (Italy); Donafan (Peru); Elcoman (Argentina); Ercestop (France); Fortasec (Spain); Gastron (South Africa); Gastro-Stop (Australia); Glubemide (Philippines); IMD (Singapore); Imosec (Spain); Imosen (Taiwan); Imossel (France); Imotril (Israel); Lenide-T (South Africa); Lodia (Indonesia); Lomy (Thailand); Loniper (Philippines); Lop (Germany); Lopamid (Korea); Lopamide (India); Lop-Dia (Germany); Lopedin (Taiwan); Lopemid (Italy); Lopemin (Japan); Loperacap (Canada); Loperamil (Singapore); Loperastat (South Africa); Loperhoe (Germany); Loperid (Israel); Loperium (Puerto Rico); Lopermide (China, Hong Kong); Loperol (South Africa); Loperyl (Italy); Loridin (Ecuador); Lorpa (Singapore); Motilex (Indonesia); Nabutil (France); Nimaz (France); Oramide (Indonesia); Orulop (Spain); Pangetan NF (Colombia); Perasian (Thailand); Pramidal (Mexico); Prodium (South Africa); Raxedin (Mexico); Regulane (Argentina); Rexamide (Israel); Sanpo (Taiwan); Seldiar (Slovenia); Stopit (Israel); Suprasec (Argentina); Tanitril (Indonesia); Tebloc (Italy); Top-Dal (Mexico); Undiarrhea (Taiwan); Vacontil (Hong Kong, Iran, Israel, Malaysia, South Africa)

Drug Class	Antidiarrheals; Gastrointestinals
Indications	Diarrhea
Mechanism	Inhibits bowel peristalsis
Dosage with Qualifiers	Diarrhea—begin 4mg PO ×1, then 2mg PO after each loose stool; max 16mg/d *NOTE: available in liquid or tablet forms.* • **Contraindications**—hypersensitivity to drug or class, bloody diarrhea, pseudomembranous colitis • **Caution**—diarrhea >48h, hepatic or renal disease, inflammatory bowel disease
Maternal Considerations	**Loperamide** is a popular and effective agent for the treatment of diarrhea (''traveler's diarrhea'') and associated symptoms. It reduces the incidence of side effects (diarrhea, nausea) in women undergoing 2nd trimester termination. One recent registry study noted an increased risk of previa, LGA and cesarean delivery. ***Side effects*** include necrotizing enterocolitis, paralytic ileus, drowsiness, dizziness, dry mouth, abdominal pain, abdominal distention, constipation, N/V, fatigue, and skin rash.
Fetal Considerations	Prospective human studies suggest that the use of **loperamide** during pregnancy is not associated with an increased risk of major malformations. However, a recent registry report observed an increase in hypospadias when used during early pregnancy.
Breastfeeding Safety	Although there are no adequate reports or well-controlled studies in nursing women, **loperamide** is generally considered safe for breastfeeding women.
Drug Interactions	No evidence of clinically relevant interactions identified.
References	Daugherty LM. Am Pharm 1990; 30:45-8. Einarson A, Mastroiacovo P, Arnon J, et al. Can J Gastroenterol 2000; 14:185-7. Hagemann TM. J Hum Lact 1998; 14:259-62. Jain JK, Harwood B, Meckstroth KR, Mishell DR. Contraception 2001; 63:217-21.

Kallen B, Nilsson E, Otterblad Olausson P. Acta Pediatr 2008; 97:541-5.
Nikodem VC, Hofmeyr GJ. Eur J Clin Pharmacol 1992; 42:695-6.

Summary

Pregnancy Category: B
Lactation Category: S

- **Loperamide** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk. It is best to avoid first trimester exposure.

Loracarbef—(Lorabid)

International Brand Name—Carbac (Mexico); Karbef (Poland); Lorabid (Austria, Finland, France, Hungary, Indonesia, Korea, Malaysia, Mexico, Philippines, South Africa, Sweden, Taiwan, Thailand); Lorafem (Germany); Lorax (Netherlands)

Drug Class

Antibiotics; Cephalosporins, 2nd-generation

Indications

Bacterial infections (gram-positive aerobes: *S. aureus, S. pneumoniae, S. pyogenes;* gram-negative anaerobes: *H. influenzae*)

Mechanism

Bactericidal—inhibits cell wall synthesis

Dosage with Qualifiers

Bacterial infections—200-400mg PO bid

NOTE: best taken on empty stomach.

- **Contraindications**—hypersensitivity to drug or class, pseudomembranous colitis
- **Caution**—unknown

Maternal Considerations

Loracarbef is used to treat lower respiratory tract infections, GU tract infections, skin infections, and septicemia, and for surgical prophylaxis. Though cephalosporins are usually considered safe during pregnancy, there is no published experience with **loracarbef** during pregnancy.
Side effects include penicillin allergy, renal dysfunction, antibiotic-associated colitis, and seizure.

Fetal Considerations

There are no adequate reports or well-controlled studies of **loracarbef** in human fetuses. Other cephalosporins cross the human placenta. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically.

Breastfeeding Safety

There is no published experience in nursing women. It is unknown whether **loracarbef** enters human breast milk. Most cephalosporins are excreted into breast milk.

Drug Interactions

As with other β-lactam antibiotics, renal excretion is inhibited by **probenecid,** resulting in an approximate 80% increase in the AUC.

References

There is no published experience in pregnancy or during lactation.

Summary

Pregnancy Category: B
Lactation Category: S (likely)

- **Loracarbef** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.
- There are alternative antibiotics for which there is more experience during pregnancy and lactation.

Loratadine—(Alavert; Claritin; Claritin RediTabs)

International Brand Name—Aerotina (Argentina); Alerfast (Peru); Alernitis (Indonesia); Alertadin (Peru); Allerta (Philippines); Allertyn (Hong Kong, Singapore); Allohex (Indonesia); Ambrace (Hong Kong); Analergal (Mexico); Anhissen (Indonesia); Anlos (Indonesia); Ardin (Singapore); Bonalerg (Guatemala); Caradine (Thailand); Carin (Malaysia); Civeran (Spain); Clalodine (Thailand); Claratyne (New Zealand); Clarid (Thailand); Claritin (Brazil, Bulgaria, Canada, Indonesia, Philippines); Claritine (Belgium, Czech Republic, Hungary, Netherlands, Poland, Portugal, Russia, Switzerland, Turkey); Clarityn (Austria, Denmark, England, Finland, Ireland, Italy, Norway, Sweden); Clarityne (Argentina, Chile, China, Colombia, Costa Rica, Dominican Republic, Ecuador, El Salvador, France, Greece, Guatemala, Honduras, Hong Kong, Korea, Malaysia, Mexico, Panama, Paraguay, Peru, South Africa, Spain, Taiwan, Thailand, Uruguay, Venezuela); Cronitin (Indonesia); Cronopen (Peru); Curyken (Mexico); Demazin Anti-Allergy (South Africa); Eclaran (Peru); Ezasmin (Korea); Ezede (Singapore); Finska (Taiwan); Frenaler (Chile); Fristamin (Italy); Genadine (Taiwan); Halodin (Thailand); Hislorex (Indonesia); Histalor (Singapore); Histaloran (Ecuador); J-Tadine (Korea); Klarihist (Israel); Klinset (Indonesia); Lergia (Indonesia); Lertamine (Mexico); Lindine (Thailand); Lisino (Germany); Lobeta (Germany); Lodain (Korea); Lora (Taiwan); Lorabasics (Germany); Loracert (Colombia); Loraclar (Germany); Loraderm (Germany); Loradex (Philippines); Loradin (Hong Kong); Lorahist (Philippines); Loralerg (Germany); Lora-Lich (Germany); Lorano (Germany, Philippines); Loranox (Thailand); Lorastine (Israel); Lora-Tabs (New Zealand); Loratadura (Germany); Loraton (Hong Kong); Loratrim (Israel); Loratyne (Philippines, South Africa); Lorazin (Korea); Loreen (Israel); Lorfast (India, Singapore); Loridin (Singapore, South Africa); Lorihis (Indonesia); Lorin (India); Lorita (Thailand); Lotadine (Hong Kong); Lotarin (Taiwan); Lowadina (Mexico); Mosedin (Israel); Noratin (Korea); Notamin (Korea); Onemin (Philippines); Optimin (Spain); Polaratyne (South Africa); Proactin (Peru); Pylor (Indonesia); Restamine (Israel); Ridamin (Singapore, Thailand); Rihest (Indonesia); Rinityn (Philippines, Singapore); Rityne (Thailand); Roletra (Singapore); Rotifar (Hong Kong); Sensibit (Mexico); Sohotin (Indonesia); Tidilor (Israel); Tirlor (Thailand); Toradine (Thailand); Velodan (Spain); Voratadine (Hong Kong); Zeos (Indonesia)

Drug Class

Antihistamines, H_1

Indications

Allergic rhinitis, urticaria

Mechanism

Antagonizes peripheral H_1 receptors

Dosage with Qualifiers

Allergic rhinitis—10mg PO qd
Urticaria—10mg PO qd

NOTE: available in orally disintegrating tablets.

- **Contraindications**—hypersensitivity to drug or class
- **Caution**—hepatic or renal dysfunction

Maternal Considerations

Loratadine is a 2nd-generation antihistamine with minimal sedating effect. It is a first-line agent for the treatment of allergic rhinorrhea. There are no adequate reports or well-controlled studies of **loratadine** in pregnant women.
Side effects include bronchospasm, hepatitis, fatigue, headache, somnolence, dry mouth, nervousness, and abdominal pain.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **loratadine** crosses the human placenta. Prospective human studies reveal no adverse outcomes. In 2002, a Swedish study observed that, among male infants born to women who took **loratadine** for seasonal allergies, the prevalence of hypospadias was twice that of the general population. However, the CDC recently analyzed data from the National Birth Defects Prevention Study and determined there was no increased risk for 2nd or 3rd degree hypospadias in the

male offspring of women who used **loratadine** in early pregnancy. This conclusion is confirmed by a recent Danish study. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically.

Breastfeeding Safety

Loratadine and its active metabolite, descarboethoxyloratadine, pass easily into human breast milk, achieving concentrations almost equivalent to maternal plasma. However, the total dose absorbed by the breastfeeding neonate is <1%.

Drug Interactions

No clinically relevant interactions identified.

References

Centers for Disease Control and Prevention. MMWR Morb Mortal Wkly Rep 2004; 53:219-21.
Hilbert J, Radwanski E, Affrime MB, et al. J Clin Pharmacol 1988; 28:234-9.
Horak F, Stubner UP. Drug Saf 1999; 20:385-401.
Mazzotta P, Loebstein R, Koren G. Drug Saf 1999; 20:361-75.
Moretti ME, Caprara D, Coutinho CJ, et al. J Allergy Clin Immunol 2003; 111:479-83.
Pedersen L, Nørgaard M, Skriver MV, et al. Am J Ther 2006; 13:320-4.
Simons FE, Simons KJ. Clin Pharmacokinet 1991; 21:372-93.

Summary

Pregnancy Category: B
Lactation Category: S

- **Loratadine** is considered safe for the noted indications during pregnancy and lactation.

Lorazepam—(Almazine; Aplacassee; Ativan; Bonton; Lorat; Lozepam; Nervistopl; Sedizepan; Wintin)

International Brand Name—Anxiedin (Taiwan); Anxira (Thailand); Anzepam (Taiwan); Aplacasse (Argentina); Apo-Lorazepam (Canada); Aripax (Greece); Azurogen (Japan); Bonatranquan (Germany); Control (Italy); Duralozam (Germany); Efasedan (Argentina); Emotion (Argentina); Emotival (Argentina); Kalmalin (Argentina); Larpose (India); Laubeel (Germany); Lonza (Thailand); Lopam (Taiwan); Lorabenz (Denmark); Loram (Slovenia); Lorans (Hong Kong, Israel, Italy); Lorapam (New Zealand, Thailand); Loravan (Korea); Lorax (Brazil); Lorazene (Thailand); Lorazep (Thailand); Lorazin (Taiwan); Lorazon (Taiwan); Lorenin (Portugal); Loridem (Belgium); Lorivan (Hong Kong, Israel); Lorsedal (Portugal); Lorzem (New Zealand); Merlit (Austria, Russia); Nervistop L (Argentina); NIC (Argentina); Novhepar (Greece); Novo-lorazem (Canada); Orfidal (Spain); Punktyl (Germany); Renaquil (Indonesia); Rocosgen (Japan); Sedatival (Argentina); Sidenar (Argentina); Silence (Taiwan); Sinestron (Dominican Republic, El Salvador, Guatemala, Honduras, Nicaragua); Stapam (Taiwan); Tavor (Czech Republic, Germany, Greece, Italy); Temesta (Austria, Belgium, Denmark, Finland, France, Netherlands, Sweden, Switzerland); Titus (Greece); Tranqipam (South Africa); Trapax (Argentina); Trapex (India); Upan (Japan); Wypax (Japan)

Drug Class

Anticonvulsants; Anxiolytics; Benzodiazepines

Indications

Anxiety, insomnia, status epilepticus

Mechanism

Stimulates benzodiazepine receptors

Dosage with Qualifiers

Anxiety—0.5-2mg PO IM/IV q6-8h; max 10mg/d
Insomnia—2-4mg PO qhs
Status epilepticus—4mg IV ×1, may be repeated in 10-15min; max 8mg/12h

- **Contraindications**—hypersensitivity to drug or class, glaucoma, alcohol intoxication, depressive disorder, psychosis
- **Caution**—hepatic, pulmonary, or renal dysfunction; drug abuse

Maternal Considerations

There is a growing appreciation that the purported risks of **lorazepam** during pregnancy are smaller than first thought. Women in need of the therapy should not be denied it solely because of the pregnancy. Although nonpharmacologic approaches to the treatment of insomnia are first-line therapy, intermediate-acting benzodiazepines such as **lorazepam** and **temazepam** may be useful in some circumstances. **Lorazepam** reverses the hypothermia associated with neuraxial anesthesia utilizing **bupivacaine, morphine,** and **fentanyl.**
Side effects include CV collapse, respiratory depression, withdrawal syndrome, blood dyscrasias, gangrene, dependency, sedation, dizziness, weakness, ataxia, depression, N/V, antegrade amnesia, headache, sleep disturbances, diplopia, nystagmus, agitation, urinary incontinence, change in appetite, delirium, and pain at the injection site.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. **Lorazepam** crosses the human placenta. High peak concentrations are avoided by dividing the daily dose into 2 or 3. While there are many studies of benzodiazepine use in human pregnancy, data on teratogenicity and effects on postnatal development and behavior are limited and conflicting. Early studies suggested that 1st trimester exposure to benzodiazepines was associated with an increased risk of facial clefts and cardiac malformations. Subsequent studies contradicted that conclusion, finding no clear evidence of an increase in either the overall incidence of malformations or any particular type of defect. Benzodiazepine use in the 3rd trimester or during labor may cause the floppy infant syndrome or neonatal withdrawal. There is no increase in jaundice at term. Rodent studies are for the most part reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically. In other rodent studies, prenatal exposure to some benzodiazepines is associated with behavioral and neurochemical alterations in the early postnatal period that may persist into adulthood. Studies in humans document an effect at least up to 18mo of age.

Breastfeeding Safety

Lorazepam is excreted into human breast milk. It has been estimated the breastfed neonate ingests <1% of the maternal dose, a dose that should be clinically insignificant. Using the lowest effective quantity in divided doses to minimize drug peaks could further minimize any theoretic risk.

Drug Interactions

Enhances CNS depression when administered with ethyl alcohol, phenothiazines, barbiturates, MAOIs, and other antidepressants. There is an increased incidence of sedation, hallucinations, and irrational behavior when **scopolamine** is used.

References

Hess PE, Snowman CE, Wang J. Int J Obstet Anesth 2005; 14:279-83.
Humpel M, Stoppelli I, Milia S, Rainer E. Eur J Clin Pharmacol 1982; 21:421-5.
Iqbal MM, Sobhan T, Ryals T. Psychiatr Serv 2002; 53:39-49.
Jurand A, Martin LV. Pharmacol Toxicol 1994; 74:228-35.
Kanto JH. Drugs 1982; 23:354-80.
Koff JM, Miller LG. Pharmacol Biochem Behav 1995; 51:721-4.
Laegreid L, Hagberg G, Lundberg A. Neuropediatrics 1992; 23:60-7.
McElhatton PR. Reprod Toxicol 1994; 8:461-75.
Sanchis A, Rosique D, Catala J. DICP 1991; 25:1137-8.
Summerfield RJ, Nielsen MS. Br J Anaesth 1985; 57:1042-3.

Whitelaw AG, Cummings AJ, McFadyen IR. Br Med J (Clin Res Ed) 1981; 282:1106-8.

Summary

Pregnancy Category: D
Lactation Category: S

- Benzodiazepines historically have been prescribed in excess. They should be avoided where possible during pregnancy.
- **Lorazepam** may be an appropriate choice for women with a clear indication.
- There are alternative agents for which there is both more experience and a clearer safety profile during pregnancy and lactation.

Lovastatin—(Altocor; Lofacol; Mevacor)

International Brand Name—Belvas (Indonesia); Birotin (Korea); Cholestra (Indonesia); Cysin (Taiwan); Ellanco (Hong Kong); Elstatin (Singapore); Lipdip (India); Lipivas (Ecuador); Lipovas (Indonesia); Lofacol (Hong Kong); Lomar (Hong Kong); Lostatin (Singapore); Lovacel (Korea, Peru); Lovalip (Israel); Lovalord (Korea); Lovastan (Colombia); Lovasterol (Colombia); Lovastin (Taiwan); Lovatadin (Korea); Lowachol (Taiwan); Lozutin (Taiwan); Medostatin (Israel, Singapore); Meverstin (Korea); Mevinacor (Costa Rica, El Salvador, Germany, Guatemala, Honduras, Nicaragua, Panama, Portugal); Nergadan (Spain); Ovasta (Korea); Rodatin (Taiwan); Rovacor (India, Singapore); Taucor (Spain)

Drug Class

Antihyperlipidemics; HMG-CoA reductase inhibitors; Statins

Indications

Hypercholesterolemia, prevention of CV events

Mechanism

Inhibits HMG-CoA reductase

Dosage with Qualifiers

Hypercholesterolemia—begin 20mg PO with food, increase until desired effect; max 80mg PO qpm
Prevention of CV events—10-80mg PO qpm

NOTE: monitor hepatic transaminases at baseline, 6w after initiation, and 1mo after each increase.

- **Contraindications**—hypersensitivity to drug or class, active hepatic disease, elevated transaminases, pregnancy, lactation
- **Caution**—hepatic or renal dysfunction, alcoholism

Maternal Considerations

There are no adequate reports or well-controlled studies of **lovastatin** in pregnant women. The limited information available on the effect of HMG-CoA reductase inhibitors on pregnancy suggests similar outcomes as the general, nonexposed population. Hypercholesterolemia is a chronic problem. Discontinuation of **lovastatin** during pregnancy is unlikely to increase maternal morbidity.
Side effects include rhabdomyolysis, hepatotoxicity, dyspepsia, constipation, flatulence, abdominal pain, rash, asthenia, myalgias, and elevated CPK and LFTs.

Fetal Considerations

Cholesterol and other products of the cholesterol biosynthesis are essential components for fetal development. There are no adequate reports or well-controlled studies of **lovastatin** in human fetuses. It is unknown whether it crosses the human placenta, and there is limited follow-up study. **Lovastatin** is lipophilic and should equilibrate between maternal and fetal compartments. Retrospective series tend to raise the most suspicion. For example, one review of 214 pregnancy exposures to one of several statins with 70 informative cases noted 31 adverse outcomes, including 22 cases with structural defects, 4 cases of

IUGR, and 5 fetal deaths. **Cerivastatin** and **lovastatin** were associated with 4 reports of severe midline CNS defects; **simvastatin, lovastatin,** and **atorvastatin** were each associated with reports of limb deficiencies. None were reported after exposure to **pravastatin,** which is poorly transported across the placenta. These authors concluded that statins may have secondary effects on sterol-dependent morphogens such as Sonic Hedgehog. A more recent survey included 225 prospective outcomes reported for **lovastatin** specifically: 154 live-born infants, 49 elective abortions, 18 spontaneous abortions, and 4 fetal deaths. Six congenital anomalies were reported: chromosomal translocation, trisomy 18, hypospadias, duodenal atresia, cleft lip, and skin tag. The rate of congenital anomalies (congenital anomalies/live births plus fetal deaths) was 3.8%, which is similar to the background population rate (3.2%; relative ratio, 1.21; 95% 1-sided upper CI, 2.02). Skeletal abnormalities were also noted when the administered dose of **lovastatin** exceeded 40× the MRHD. Some animal studies suggest the statin drugs might be neuroprotective against hypoxic/ischemic stroke.

Breastfeeding Safety

There is no published experience in nursing women. Small quantities of **lovastatin** apparently enter human breast milk, but the kinetics are unknown. Statin drugs inhibit prolactin release in the rat brain, and theoretically could interfere with the initiation of lactation.

Drug Interactions

Metabolized by CYP3A4 but has no CYP3A4 inhibitory activity.
Potent inhibitors of CYP3A4 (e.g., **clarithromycin, erythromycin,** large quantities of grapefruit juice [>1quart daily], HIV protease inhibitors**, itraconazole, ketoconazole, nefazodone, telithromycin**) increase the risk of myopathy by reducing the elimination of **lovastatin.**
The risk of myopathy is also increased by the following lipid-lowering drugs that are not potent CYP3A4 inhibitors, but can cause myopathy themselves: **gemfibrozil,** other fibrates, and **niacin** (nicotinic acid) (=1g/d).
The risk of myopathy/rhabdomyolysis is increased by use with **cyclosporine** or **danazol** particularly with higher doses of **lovastatin.**
The risk of myopathy/rhabdomyolysis is increased when either **amiodarone** or **verapamil** is used concomitantly with a closely related member of the HMG-CoA reductase inhibitor class.
In one small clinical trial in which **lovastatin** was administered to **warfarin**-treated patients, no effect on PT was detected. However, another HMG-CoA reductase inhibitor has been found to produce a <2sec increase in PT in healthy volunteers. Also, bleeding and/or increased PT have been reported in a few patients taking coumarin anticoagulants with **lovastatin.** The PT should be determined before starting **lovastatin** and frequently enough during early therapy to ensure that no significant alteration occurs.

References

Balduini W, De Angelis V, Mazzoni E, Cimino M. Stroke 2001; 32:2185-91.
Edison RJ, Muenke M. Am J Med Genet A 2004; 131:287-98.
Freyssinges C, Ducrocq MB. Therapie 1996; 51:537-42.
Manson JM, Freyssinges C, Ducrocq MB, Stephenson WP. Reprod Toxicol 1996; 10:439-46.
Pollack PS, Shields KE, Burnett DM, et al. Birth Defects Res A Clin Mol Teratol 2005; 73:888-96.

Summary	**Pregnancy Category: X** **Lactation Category: U** • Pending the availability of reassuring studies, **lovastatin** is not recommended during pregnancy or lactation. • Placental transport studies are desperately needed.

Loxapine—(Loxitane)

International Brand Name—Desconex (Spain); Loxapac (Belgium, Canada, Denmark, England, France, Greece, India, Ireland, Netherlands, Portugal, Spain, Taiwan)

Drug Class	Antipsychotics
Indications	Psychosis
Mechanism	Unknown; selectively antagonizes the dopamine D_2 receptors
Dosage with Qualifiers	Psychosis—30-50mg PO bid • **Contraindications**—hypersensitivity to drug or class, depression • **Caution**—CV diseases, glaucoma, hepatic disease
Maternal Considerations	**Loxapine** is a tranquilizer indicated for the management of the manifestations of psychotic disorders. Galactorrhea is a common complication. There are no adequate reports or well-controlled studies of **loxapine** in pregnant women. ***Side effects*** include drowsiness, sedation, dizziness, faintness, staggering or shuffling gait, muscle twitching, weakness, insomnia, agitation, tension, seizures, akinesia, slurred speech, numbness, confusional states, parkinsonian-like symptoms, dystonic reaction, tachycardia, hypotension, hypertension, orthostatic hypotension, light-headedness, syncope, agranulocytosis, thrombocytopenia, leukopenia, dry mouth, nasal congestion, constipation, blurred vision, urinary retention, weight gain or loss, dyspnea, ptosis, hyperpyrexia, flushed facies, headache, paresthesia, polydipsia, and N/V.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **loxapine** crosses the human placenta. Rodent studies are reassuring, but are limited.
Breastfeeding Safety	There are no adequate reports or well-controlled studies in nursing women. **Loxapine** is excreted into human breast milk, but the kinetics have yet to be elucidated.
Drug Interactions	There are rare reports of significant respiratory depression, stupor, and/or hypotension when used with **lorazepam.**
References	Gelenberg AJ. J Nerv Ment Dis 1979; 167:635-6.
Summary	**Pregnancy Category: C** **Lactation Category: U** • **Loxapine** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk. • There are alternative agents for which there is more experience during pregnancy and lactation.

Lypressin—(Diapid; Syntopressin)

International Brand Name—Syntopressin (England, Ireland)

Drug Class	Antidiuretics; Hormones
Indications	Diabetes insipidus
Mechanism	Stimulates vasopressin receptors
Dosage with Qualifiers	Diabetes insipidus—1-2 spray IN prn • **Contraindications**—hypersensitivity to drug or class, history of CV diseases (angina, MI) • **Caution**—nasal congestion, allergic rhinitis, URIs
Maternal Considerations	**Lypressin** is indicated for the treatment of diabetes insipidus. It is a synthetic version of the natural porcine compound. There is no published experience with **lypressin** during pregnancy. It is a powerful vasoconstrictor when applied to isolated vessels and induces contractions in isolated myometrium from humans. ***Side effects*** include rhinorrhea, nasal congestion, irritation, nasal ulceration, headache, conjunctivitis, heartburn, periorbital edema, chest tightness, and dyspnea.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **lypressin** crosses the human placenta. Rodent teratogenicity studies have not been conducted.
Breastfeeding Safety	There is no published experience in nursing women. It is unknown whether **lypressin** enters human breast milk. **Lypressin** stimulates mammary ejection pressure in sheep.
Drug Interactions	No clinically relevant interactions identified.
References	Landstrom G, Wallin A, Lundmark K, et al. Hum Reprod 1999; 14:151-5. Sala NL. Acta Physiol Lat Am 1965; 15:191-9.
Summary	**Pregnancy Category: C** **Lactation Category: U** • **Lypressin** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Magnesium chloride—(Chlor-3)

International Brand Name—None identified.

Drug Class	Electrolyte replacements; Vitamins/minerals
Indications	Hypomagnesemia
Mechanism	Replacement
Dosage with Qualifiers	Hypomagnesemia—4g mixed in 250ml of 5% dextrose IV no faster than 3ml/min, dose range 1-40g qd *NOTE: serum magnesium measurements should guide replacement; keep calcium gluconate readily available to counteract potentially serious signs of magnesium intoxication.* • **Contraindications**—hypersensitivity to drug or class, renal failure, impaired myocardial function • **Caution**—electrolyte disturbances, renal dysfunction
Maternal Considerations	There are no adequate reports or well-controlled studies of **magnesium chloride** in pregnant women. ***Side effects*** include flushing and sweating.
Fetal Considerations	There are no adequate reports or well-controlled studies of **magnesium chloride** in human fetuses. Magnesium administered parenterally to the mother crosses the placenta. Rodent studies are reassuring.
Breastfeeding Safety	Magnesium is normally present in human breast milk, and its concentration stable throughout the 1st year of lactation. It is unknown whether **magnesium chloride** increases the magnesium content of breast milk. Considering the indications, limited use is unlikely to pose a clinically significant risk to the breastfeeding neonate.
Drug Interactions	Calcium channel–blocking agents should be avoided. **Doxercalciferol** may increase the risk of hypermagnesemia.
References	Oorschot DE. Magnes Res 2000; 13:265-73. Martin RW, Perry KG Jr, Martin JN Jr, et al. J Miss State Med Assoc 1998; 39:180-2. Meirowitz NB, Ananth CV, Smulian JC, Vintzileos AM. J Matern Fetal Med 1999; 8:177-83. Nagra SA. J Trop Pediatr 1989; 35:126-8. Usami M, Sakemi K, Tsuda M, Ohno Y. Eisei Shikenjo Hokoku 1996; 114:16-20.
Summary	**Pregnancy Category: B** **Lactation Category: S** • **Magnesium chloride** should be used during pregnancy and lactation only for the treatment of hypomagnesemia.

Magnesium citrate

International Brand Name—None identified.

Drug Class	Laxatives
Indications	Constipation
Mechanism	Unknown
Dosage with Qualifiers	Constipation—120-240ml PO prn • **Contraindications**—hypersensitivity to drug or class, appendicitis, acute abdomen, GI obstruction • **Caution**—renal dysfunction, electrolyte disturbances
Maternal Considerations	**Magnesium citrate** reduces the frequency of night leg cramps in nonpregnant patients. There are no adequate reports or well-controlled studies of **magnesium citrate** in pregnant women. Its use during pregnancy increases serum magnesium. ***Side effects*** include abdominal cramps, flatulence, diarrhea, hypotension, hypermagnesemia, and respiratory disturbances.
Fetal Considerations	There are no adequate reports or well-controlled studies of **magnesium citrate** in human fetuses. Magnesium ions freely cross the placenta.
Breastfeeding Safety	**Magnesium** is normally present in human breast milk, and its concentration stable throughout the 1st year of lactation. It is unknown whether **magnesium citrate** increases the magnesium content of breast milk. Considering the indications and dosing, limited use is unlikely to pose a clinically significant risk to the breastfeeding neonate.
Drug Interactions	Calcium channel–blocking agents should be avoided. **Doxercalciferol** may increase the risk of hypermagnesemia.
References	Ajayi GO, Fadiran EO. Clin Exp Obstet Gynecol 1998; 25:64-6. Roffe C, Sills S, Crome P, Jones P. Med Sci Monit 2002; 8:CR326-30.
Summary	**Pregnancy Category: B** **Lactation Category: S** (likely) • **Magnesium citrate** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Magnesium oxide

International Brand Name—None identified.

Drug Class	Electrolyte replacements; Vitamins/minerals
Indications	Hypomagnesemia
Mechanism	Replacement
Dosage with Qualifiers	Hypomagnesemia—1-2 tab PO bid or tid *NOTE: 400mg tab = 241.3mg of elemental magnesium.* • **Contraindications**—hypersensitivity to drug or class, renal failure, impaired myocardial function • **Caution**—electrolyte disturbances, renal dysfunction
Maternal Considerations	There are no adequate reports or well-controlled studies of **magnesium oxide** in pregnant women. Obstetricians have used oral magnesium as a tocolytic agent without demonstrable efficacy. It has also been advocated as a neuroprotectant for the acutely hypoxic fetus and to prevent preeclampsia. Neither indication can be substantiated. ***Side effects*** include flushing and sweating.
Fetal Considerations	There are no adequate reports or well-controlled studies of **magnesium oxide** in human fetuses.
Breastfeeding Safety	Magnesium is normally present in human breast milk, and its concentration stable throughout the 1st year of lactation. It is unknown whether **magnesium oxide** increases the magnesium content of breast milk.
Drug Interactions	Calcium channel–blocking agents should be avoided. **Doxercalciferol** may increase the risk of hypermagnesemia.
References	Andreassi S, Teso A. Riv Eur Sci Med Farmacol 1992; 14:309-12. D'Almeida A, Carter JP, Anatol A, Prost C. Womens Health 1992; 19:117-31. Martin RW, Perry KG Jr, Martin JN Jr, et al. J Miss State Med Assoc 1998; 39:180-2. Nagra SA. J Trop Pediatr 1989; 35:126-8. Ridgway LE 3rd, Muise K, Wright JW, et al. Am J Obstet Gynecol 1990; 163:879-82.
Summary	**Pregnancy Category: B** **Lactation Category: S** • **Magnesium oxide** should be used during pregnancy and lactation for the treatment of hypomagnesemia. The efficacy of other applications cannot currently be substantiated.

Magnesium sulfate—(Tis U Sol)

International Brand Name—None identified.

Drug Class ..... Anticonvulsants; Electrolyte replacements; Tocolytics

Indications ..... Ventricular arrhythmia, eclampsia, tocolysis, hypomagnesemia

Mechanism ..... Inhibits Ca^{2+} release from the intracytoplasmic storage deposits, blocks Ca^{2+} influx through glutamate channels or through the NMDA receptor

Dosage with Qualifiers .....

Ventricular arrhythmia—3-20mg/min continuous IV ×6-48h
Eclampsia, prevention and treatment—begin 4g IV ×1 over 30min; then 1g/h IV maintenance rate for at least 24h postpartum, or during diuresis >200ml/h; alternatively, 10g IM loading dose followed by 5g IM q4h until at least 24h postpartum
Tocolysis—begin 6g IV ×1 over 30min, then 2-4g/h IV ×48h
Hypomagnesemia—1g IM q4-6h; alternative 5g mixed in 1L NS IV over 3h

NOTE: renal dosing; measure serum magnesium every 4-6h if infusion >2g/h or oliguria or maternal symptoms of toxicity; maintain between 4-7mEq/L (4.8-8.4mg/dl).

- **Contraindications**—hypersensitivity to drug or class, renal failure, impaired myocardial function
- **Caution**—renal dysfunction, electrolyte disturbances

Maternal Considerations .....

Magnesium sulfate is excreted by the kidney, with 90% of the dose excreted during the first 24h after an IV infusion. The pharmacokinetic profile of **magnesium sulfate** after IV administration is best described by a 2-compartment model with a rapid distribution (alpha) phase, followed by a relatively slow beta phase of elimination. The clinical effect and toxicity of magnesium is linked to its plasma concentration. A decreased GFR may lead to toxicity if not monitored closely. Use only ½ the usual load when the plasma Cr exceeds 1.3mg/dl. DTRs are decreased as the concentration exceeds 4mEq/L; they are lost as the level approaches 10mEq/L. Potentially, lethal respiratory depression may occur at 12-15mEq/L. Recent investigation suggests the measurement of total magnesium is not adequate for titration in women with either preeclampsia or preterm labor as there is poor correlation between total magnesium and the physiologically active ionized magnesium. **Calcium gluconate** should always be readily available to counteract potential serious signs of magnesium intoxication.
Preeclampsia remains a leading cause of maternal and perinatal morbidity and death. Randomized trials demonstrate **magnesium sulfate** infusion halves the risk of eclampsia and is superior to both **phenytoin** and **diazepam** for the prevention of recurrent eclamptic seizures. The anticonvulsant effect is probably exerted on the cerebral cortex. It is also the drug of choice for the control of seizures. **Magnesium sulfate** is *NOT* an effective antihypertensive, though Mg^{2+} concentrations between 2 and 4mmol/L produce greater than half the maximal lowering of systolic and diastolic pressures. There remains controversy as to whether **magnesium sulfate** is beneficial for the treatment of mild preeclampsia. A recent analysis concluded that the risks and benefits of magnesium in this patient population counterbalance each other. Although a no-magnesium strategy results in a 15%

reduction in neonatal mortality and avoids maternal drug toxicity, it leads to a 2-fold increase in maternal death and more neurologically compromised neonates compared to empiric magnesium. The clinical decision to use magnesium in women with mild preeclampsia for seizure prophylaxis should be determined by the physician or institution, considering patient values or preferences and the unique risk:benefit trade-off of each strategy. However, **magnesium sulfate** treatment clearly does not prevent the worsening of preeclampsia during labor.
Approximately 10-15% of eclamptic women convulse despite prophylaxis. An additional 2g loading dose is recommended if a woman convulses while receiving **magnesium sulfate** for the prevention of eclampsia. **Magnesium sulfate** may also be administered IM. Prospective studies comparing magnesium levels achieved with continuous IV infusion and IM reveal that therapeutically effective levels are achieved with both. **Magnesium sulfate** neither prolongs labor nor increases the oxytocin requirement in preeclamptic women. **Magnesium sulfate** is often continued for at least 24h postpartum, but there is little scientific support for the practice. The duration of therapy may be individualized using maternal diuresis (>200ml/h for at least 2h) as evidence the associated vasospasm has resolved. In one study, women with mild preeclampsia received shorter courses of **magnesium sulfate** (mean 9.5 ± 4.2h) than those with severe preeclampsia alone (mean 16 ± 5.9h), superimposed preeclampsia (mean 16 ± 5.8h), or atypical preeclampsia (hemolysis, elevated liver enzymes, and low platelet count) (mean 20 ± 6.7h). There was no eclampsia, and recovery room time was reduced 50%.
Preterm labor: No tocolytic agent has been proven to stop preterm labor and improve perinatal outcome. The demonstrable benefit of tocolysis is the time gained to administer corticosteroids. **Magnesium sulfate** depresses uterine contractility both *in vitro* and *in vivo.* Although it has no effect on the labor of preeclamptic women, it is the most commonly used parenteral tocolytic in the US, believed effective in stopping contractions in 60-80% of patients for 48-72h. Unfortunately, the scientific support for this belief is weak, and several in-depth analyses conclude there is stronger evidence for the use of other agents with fewer side effects. The most recent Cochrane Review noted that >2000 women participated in 23 trials but that only 9 trials adequately concealed allocation. In the **magnesium sulfate** vs. control (all studies) comparisons, there was no difference for the risk of birth <48h (relative risk [RR] 0.85, 95% CI 0.58-1.25, 11 trials, 881 women). There was also no reduction in the risk of giving birth at <37w or <34w. The risk of perinatal death was higher for the **magnesium sulfate** group (RR 2.82, 95% CI 1.20-6.62, 7 trials, 727 infants). These reviewers conclude that **magnesium sulfate** is *ineffective* in delaying birth or preventing preterm birth, and its use may even be associated with an increased perinatal mortality. While smaller trials have variously concluded that **magnesium sulfate** is as effective as one of several tocolytic agents, including **nifedipine,** it is not risk-free.
Pulmonary edema and CV problems occur at a frequency similar to that with β-mimetics (~1%). Maternal infection, decreased colloid osmotic pressure, and fluid overload are each predisposing risk factors. A recent decision analysis examining costs concluded that **nifedpine** and **indomethacin** offered greater value as tocolytic agents. There is no evidence to support the practice of weaning the **magnesium sulfate** infusion rate when the decision is made to stop tocolysis.
Side effects include respiratory failure, CV collapse, hypothermia, depressed cardiac function, pulmonary edema, depressed reflexes,

hypotension, drowsiness, N/V, hypocalcemia, hyperkalemia, flushing, blurred vision, sweating, muscle weakness, ECG changes, sedation, and confusion.

Fetal Considerations

Parenterally administered magnesium crosses the placenta and increases the fetal level. Though there is some controversy, there is no clear evidence of adverse effects from short-term **magnesium sulfate** therapy. Respiratory depression may occur if there is severe hypermagnesemia at delivery. Rodent studies suggest maternal seizures may be associated with fetal brain injury, an effect possibly ameliorated by **magnesium sulfate.** Some human studies also suggest a protective effect of **magnesium sulfate** against cerebral palsy in very low-birth-weight infants. **Magnesium sulfate** was given to >500 women <30w who were expected to deliver within 24h; the children were followed until a corrected age of 2y. Children exposed to magnesium had a significantly lower rate of substantial gross motor function. In another recent RCT enrolling 2241 women 24-31w, **magnesium sulfate** reduced the rate of cerebral palsy in survivors. Thus, additional large clinical trials are needed to resolve the controversy. Maternal administration does not protect against neonatal necrotizing enterocolitis. It remains controversial whether the intrapartum administration of **magnesium sulfate** reduces fetal heart variability and reactivity.

Breastfeeding Safety

Some case reports describe engorgement and galactorrhea during tocolysis with IV **magnesium sulfate.** The mechanism remains unknown. Symptoms gradually subside after discontinuation. Magnesium is normally present in human breast milk, and its concentration stable throughout the 1st year of lactation. It is unknown whether **magnesium sulfate** increases the magnesium content of breast milk. Considering the indication and dosing, limited use is unlikely to pose a clinically significant risk to the breastfeeding neonate.

Drug Interactions

The dose of barbiturates, narcotics, hypnotics (or systemic anesthetics), or other CNS depressants should be adjusted because of the additive CNS depressant effects of magnesium.
CNS depression and peripheral transmission defects produced by magnesium may be antagonized by calcium.

References

Ascarelli MH, Johnson V, May WL, et al. Am J Obstet Gynecol 1998; 179:952-6.
Atkinson MW, Belfort MA, Saade GR, Moise KJ Jr. Obstet Gynecol 1994; 83:967-70.
Atkinson MW, Guinn D, Owen J, Hauth JC. Am J Obstet Gynecol 1995; 173:1219-22.
Belfort MA, Anthony J, Saade GR. Semin Perinatol 1999; 23:65-78.
Belfort MA, Saade GR, Moise KJ Jr. Acta Obstet Gynecol Scand 1993; 72:526-30.
Belfort MA, Saade GR, Moise KJ Jr. Am J Obstet Gynecol 1992; 167:1548-53.
Cahill AG, Macones GA, Odibo AO, Stamilio DM. Obstet Gynecol 2007; 110:601-7.
Chames MC, Livingston JC, Ivester TS, et al. Am J Obstet Gynecol 2002; 186:1174-7.
Crowther CA, Hiller JE, Doyle LW. *In* The Cochrane Library, Issue 2. Oxford, UK: Update Software, 2003.
Crowther CA, Hiller JE, Doyle LW, Balsam RR. JAMA 2003; 290:2669-76.
El-Sayed YY, Riley ET, Holbrook RH Jr, et al. Obstet Gynecol 1999; 93:79-83.

Ghidini A, Espada RA, Spong CY. Acta Obstet Gynecol Scand 2001; 80:126-9.
Gordon MC, Iams JD. Clin Obstet Gynecol 1995; 38:706-12.
Grether JK, Hoogstrate J, Selvin S, Nelson KB. Am J Obstet Gynecol 1998; 178:1-6.
Grether JK, Hoogstrate J, Walsh-Greene E, Nelson KB. Am J Obstet Gynecol 2000; 183:717-25.
Gyetvai K, Hannah ME, Hodnett ED, Ohlsson A. Obstet Gynecol 1999; 94:869-77.
Hallak M, Hotra JW, Custodio D, Kruger ML. Am J Obstet Gynecol 2000; 18:793-8.
Hallak M, Martinez-Poyer J, Kruger ML, et al. Am J Obstet Gynecol 1999; 181:1122-7.
Hayes E, Moroz L, Pizzi L, Baxter J. Am J Obstet Gynecol 2007; 197:383.e1-6.
Hennessy A, Hill I. Aust NZ J Obstet Gynaecol 1999; 39:256-7.
Kimberlin DF, Hauth JC, Goldenberg RL, et al. Am J Perinatol 1998; 15:635-41.
Lewis DF, Bergstedt S, Edwards MS, et al. Am J Obstet Gynecol 1997; 177:742-5.
Livingston JC, Livingston LW, Ramsey R, et al. Obstet Gynecol 2003; 101:217-20.
Lu JF, Nightingale CH. Clin Pharmacokinet 2000; 38:305-14.
Lu J, Pfister M, Ferrari P, et al. Clin Pharmacokinet 2002; 41:1105-13.
Lucas MJ, Leveno KJ, Cunningham FG. N Engl J Med 1995; 333:201-5.
Lurie S, Rotmensch S, Feldman N, Glezerman M. Am J Perinatol 2002; 19:239-40.
Lyell DJ, Pullen K, Campbell L, et al. Obstet Gynecol 2007; 110:61-7.
Martin RW, Martin JN Jr, Pryor JA, et al. Am J Obstet Gynecol 1988; 158:1440-5.
Martin RW, Perry KG Jr, Martin JN Jr, et al. J Miss State Med Assoc 1998; 39:180-2.
Matsuda Y, Ikenoue T, Hokanishi H. Gynecol Obstet Invest 1993; 36:102-7.
Mittendorf R, Dambrosia J, Pryde PG, et al. Am J Obstet Gynecol 2002; 186:1111-8.
Nelson KB, Grether JK. Pediatrics 1995; 95:263-9.
[No authors]. Lancet 2002; 359:1877-90.
Odendaal HJ, Steyn DW, Norman K, et al. S Afr Med J 1995; 85:1071-6.
Pritchard JA, Cunningham FG, Pritchard SA. Am J Obstet Gynecol 1984; 148:951-63.
Rasch DK, Huber PA, Richardson CJ, et al. J Pediatr 1982; 100:272-6.
Repke JT, Power ML, Holzman GB, Schulkin J. J Reprod Med 2002; 47:472-6.
Ricci JM, Hariharan S, Helfgott A, et al. Am J Obstet Gynecol 1991; 165:603-10.
Roberts JM, Villar J, Arulkumaran S. BMJ 2002; 325:609-10.
Rouse DJ, Hirtz DG, Thom E, et al. N Engl J Med 2008; 359:895-905.
Saade GR, Taskin O, Belfort MA, et al. Obstet Gynecol 1994; 84:374-8.
Sibai BM. Am J Obstet Gynecol 1990; 162:1141-5.
Sibai BM, Graham JM, McCubbin JH. Am J Obstet Gynecol 1984; 150:728-33.
Szal SE, Croughan-Minihane MS, Kilpatrick SJ. Am J Obstet Gynecol 1999; 180:1475-9.

Taber EB, Tan L, Chao CR, et al. Am J Obstet Gynecol 2002; 186:1017-21.
Towers CV, Pircon RA, Heppard M. Am J Obstet Gynecol 1999; 180:1572-8.
Weiner CP, Renk K, Klugman M. Am J Obstet Gynecol 1988; 159:216-22.
Witlin AG, Sibai BM. Obstet Gynecol 1998; 92:883-9.

Summary

Pregnancy Category: A
Lactation Category: S

- **Magnesium sulfate** is superior to both **phenytoin** and **diazepam** for reducing the incidence of primary and secondary eclamptic convulsions.
- Locales where eclampsia has a major impact on maternal mortality should institute policies to ensure that this inexpensive and lifesaving treatment is available, and that care providers are trained to use it safely.
- The controversy as to whether **magnesium sulfate** is as effective as other tocolytic agents or ineffective is now irrelevant. **Magnesium sulfate** is clearly not superior to other tocolytic agents and has worse safety and cost profiles. Both **nifedipine** and **indomethacin** (48h course) have superior safety and cost profiles and probably greater efficacy. For these reasons, **magnesium sulfate** should not be used for tocolysis.
- While not an effective tocolytic agent, a short term infusion in at risk pregnancies 24-31w may reduce the rate of cerebral palsy.

Mannitol—(Osmitrol; Resectisol)

International Brand Name—Acrosmosol (Ecuador); D-Mannitol (Korea); Manitol (Indonesia); Manitol Pisa (Mexico)

Drug Class

Diuretics, osmotic

Indications

Oliguria from acute renal failure (prevention and treatment), cerebral edema, diuresis (forced)

Mechanism

Increases GFR

Dosage with Qualifiers

Oliguria prevention—50-100g IV over 2h
Oliguria treatment—50-100g IV over 2h
Cerebral edema—100g IV ×2-6h
Diuresis, forced—25-100g IV over 2h

NOTE: attempt to maintain urinary output >100ml/h.

- **Contraindications**—hypersensitivity to drug or class, anuria, progressive renal failure after initiation, no response to the initial bolus, pulmonary edema, severe dehydration, intracranial hemorrhage, progressive heart failure
- **Caution**—renal dysfunction

Maternal Considerations

Mannitol is an osmotic diuretic. It is confined to the extracellular space after IV administration and is rapidly excreted by the kidneys (80% within 3h). There are no adequate reports or well-controlled studies of **mannitol** in pregnant women. The published experience is limited to case reports of women often undergoing surgery for causes unrelated to pregnancy (intracranial hemorrhage or brain tumors) or for hypermagnesemia. It has also

been used for the treatment of posterior, reversible encephalopathy.
Side effects include seizures, heart failure, CV collapse, pulmonary edema, acute renal failure, CNS depression, coma, fluid imbalance, tachycardia, dehydration, electrolyte disorders, acidosis, blurred vision, thrombophlebitis, urticaria, fever, infusion site infection, dryness of mouth, thirst, rhinitis, skin necrosis, angina, and water intoxication.

Fetal Considerations ····· There are no adequate reports or well-controlled studies in human fetuses. **Mannitol** crosses the human placenta by diffusion. Rodent teratogenicity studies have not been performed. Studies of pregnant ewes reveal that maternal hyperosmolality influences the fetal arginine vasopressin secretion and renal function, and thus the amount of AF.

Breastfeeding Safety ····· There is no published literature in nursing women. It is unknown whether **mannitol** enters human breast milk.

Drug Interactions ····· No clinically relevant interactions identified.

References ····· Bain MD, Copas DK, Landon MJ, Stacey TE. J Physiol 1988; 399:313-9.
Bohman VR, Cotton DB. Obstet Gynecol 1990; 76:984-6.
Chang L, Looi-Lyons L, Bartosik L, Tindal S. Can J Anaesth 1999; 46:61-5.
Ervin MG, Ross MG, Youssef A, et al. Am J Obstet Gynecol 1986; 155:1341-7.
Narbone MC, Musolino R, Granata F, et al. Neurol Sci 2006; 27:187-9.
Quraishi AN, Illsley NP. Placenta 1999; 20:167-74.

Summary ····· **Pregnancy Category: C**
Lactation Category: U
- **Mannitol** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Maprotiline—(Ludiomil)

International Brand Name—Maprostad (Germany); Melodil (Israel); Mirpan (Germany); Psymion (Germany); Retinyl (Greece)

Drug Class ····· Antidepressants; Tetracyclics

Indications ····· Depression

Mechanism ····· Unknown; inhibits reuptake of NE

Dosage with Qualifiers ····· Depression—25-50mg PO bid or tid; max 225mg PO qd ×6w
- **Contraindications**—hypersensitivity to drug or class, MI, usage of MAOIs within 14d
- **Caution**—seizure disorders, arrhythmias, strokes, tachycardia

Maternal Considerations ····· There are no adequate reports or well-controlled studies of **maprotiline** in pregnant women.
Side effects include seizures, neuroleptic malignant syndrome, constipation, dry mouth, blurred vision, dizziness, orthostatic hypotension, drowsiness, urinary retention, tachycardia,

	diaphoresis, renal failure, rash, edema, dyskinesia, diarrhea, bitter taste, abdominal cramps, dysphagia, decreased libido, weakness, fatigue, insomnia, agitation, hallucinations, nightmares, disorientation, delusions, restlessness, hypomania, mania, exacerbation of psychosis, decrease in memory, and feelings of unreality.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **maprotiline** crosses the human placenta. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically. Rodent and chick studies suggest **maprotiline** is less embryo and organ toxic than **imipramine** and **amitriptyline.**
Breastfeeding Safety	There is no published experience in nursing women. It is unknown whether **maprotiline** enters human breast milk.
Drug Interactions	Close supervision and careful dosage adjustment are required when administering **maprotiline** with anticholinergic or sympathomimetic drugs because of the possibility of additive atropine-like effects. Use with electroshock therapy should be avoided because of the lack of experience in this area. Caution is advised with hyperthyroid patients or those on thyroid medication because of the potential for enhanced CV toxicity. May block the pharmacologic effects of **guanethidine**. The risk of seizures may be increased if taken with phenothiazines or when the dosage of benzodiazepines is rapidly tapered. Plasma concentrations may be increased if given with hepatic enzyme inhibitors (e.g., **cimetidine, fluxetine**) and decreased if used with hepatic enzyme inducers (e.g., barbituates, **phenytoin**).
References	Pinder RM, Brogden RN, Speight TM, Avery GS. Drugs 1977; 13:321-52. Wirz-Justice A, Lichtsteiner M. J Pharm Pharmacol 1976; 28:172-5.
Summary	**Pregnancy Category: B** **Lactation Category: U** • **Maprotiline** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Mazindol—(Mazanor; Sanorex)

International Brand Name—Diestet (Costa Rica, Dominican Republic, El Salvador, Guatemala, Honduras, Mexico, Panama, Peru); Liofindol (Mexico); Solucaps (Dominican Republic, El Salvador, Guatemala, Honduras, Mexico, Nicaragua); Teronac (Greece, Hungary, Indonesia, Israel, Netherlands, Peru, South Africa, Switzerland)

Drug Class	Anorexiants; CNS stimulants
Indications	Weight loss
Mechanism	Appetite suppression and CNS stimulation
Dosage with Qualifiers	Weight loss—1mg PO qd; dosage may be increased by max 3mg/d *NOTE: take with food or milk.*

- **Contraindications**—hypersensitivity to drug or class, arteriosclerosis, CV disease, hypertension, hyperthyroidism, glaucoma, anxiety
- **Caution**—drug abuse

Maternal Considerations

Mazindol behaves like an amphetamine. Its efficacy in obese nonpregnant women is at best modest, and tolerance develops. There is no published experience during pregnancy, nor are there any indications for its use.
Side effects include palpitations, tachycardia, hypertension, psychosis, insomnia, euphoria, dyskinesia, dysphoria, tremor, headaches, Tourette's syndrome, dry mouth, diarrhea, constipation, anorexia, and decreased libido.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **mazindol** crosses the human placenta. Rodent studies suggest an increase in rib abnormalities at multiples of the MRHD.

Breastfeeding Safety

There is no published experience in nursing women. It is unknown whether **mazindol** enters human breast milk.

Drug Interactions

May decrease the hypotensive effect of **guanethidine**.
May markedly potentiate the pressor effect of exogenous catecholamines. Extreme care should be taken to monitoring BP at frequent intervals and initiating pressor therapy with a low initial dose and careful titration.
May potentiate BP increases in those patients taking sympathomimetic medications.

References

There is no published experience in pregnancy or during lactation.

Summary

Pregnancy Category: C
Lactation Category: U
- There are no indications for **mazindol** during pregnancy or lactation.

Mebendazole—(Bendosan; Damaben; Drivermide; Fugacar; Ovex; Vermox)

International Brand Name—Amycil (Mexico); Anelmin (Israel); Anthex (South Africa); Antiox (Philippines); Bantenol (Spain); Benda (Thailand); Bestelar (Mexico); Cipex (South Africa); Combantrin-1 (New Zealand); Combantrin-1 with mebendazole (Australia); Conquer (Taiwan); D-Worm (South Africa); Gamax (Colombia); Helminzole (Mexico); Lomper (Spain); Mebex (India); Mindol (New Zealand); Noverme (Portugal); Noxworm (Thailand); Pantelmin (Austria, Colombia, Costa Rica, Dominican Republic, Ecuador, El Salvador, Guatemala, Honduras, Nicaragua, Panama, Peru, Portugal); Penalcol (Peru); Pharaxis M (Colombia); Revapol (Mexico); Soltric (Mexico); Sqworm (Australia); Surfont (Germany); Thelmox (Puerto Rico); Toloxim (Portugal); Vagaka (Thailand); Wormgo (South Africa); Wormin (South Africa, Israel, India); Zadomen (Malaysia); Zakor (Colombia)

Drug Class

Anthelmintics

Indications

Infection (pinworm, whipworm, hookworm, roundworm), capillariasis

Mechanism

Inhibition of microtubule formation; causes glucose depletion

Dosage with Qualifiers

Pinworm infection—100mg PO ×1
Whipworm infection—100mg PO bid ×3-5d

Hookworm infection—100mg PO bid ×3-5d
Roundworm infection—100mg PO bid ×3-5d
Capillariasis—200mg PO bid ×20d

- **Contraindications**—hypersensitivity to drug or class, pregnancy, children <2y
- **Caution**—pregnancy

Maternal Considerations

Treatment of reproductive-age women is strongly recommended in areas of widespread hookworm infection and its related anemia. In some endemic areas, treatment of all pregnant women after the 1st trimester effectively reduces the incidences of IUGR and perinatal death.
Side effects include angioedema, seizures, neutropenia, abdominal pain, N/V, diarrhea, fever, dizziness, headache, rash, pruritus, alopecia, and convulsions.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **mebendazole** crosses the human placenta. Congenital helminthic infection in humans is rare. No increase in risk for congenital malformation or other adverse outcomes was noted in the largest prospective study with 140 1st trimester exposures. There are no reported sequelae from 2nd or 3rd trimester exposure. Rodent studies suggest **mebendazole** is embryotoxic and teratogenic at fairly low doses.

Breastfeeding Safety

There is no published experience in nursing women. It is unknown whether **mebendazole** enters human breast milk.

Drug Interactions

No clinically relevant interactions identified.

References

Allen H, Crompton D, de Silva N, et al. Trends Parasitol 2002; 18:381.
Christensen PM, Hedegaard U, Brosen K. Ugeskr Laeger 2000; 162:6552.
de Silva NR, Sirisena JL, Gunasekera DP, et al. Lancet 1999; 353:1145-9.
Diav-Citrin O, Shechtman S, Arnon J, et al. Am J Obstet Gynecol 2003; 188:282-5.
Dupouy-Camet J, Kociecka W, Bruschi F, et al. Expert Opin Pharmacother 2002; 3:1117-30.
Fletouris D, Botsoglou N, Psomas I, Mantis A. J AOAC Int 1996; 79:1281-7.
Gyorkos TW, Larocque R, Casapia M, Gotuzzo E. Pediatr Infect Dis J 2006; 25:791-4.
Kurzel RB, Toot PJ, Lambert LV, Mihelcic AS. NZ Med J 1994; 107:439.
Larocque R, Casapia M, Gotuzzo E, et al. Trop Med Int Health 2006; 11:1485-95.
Stephenson LS. Paediatr Drugs 2001; 3:495-508.
St. Georgiev V. Expert Opin Pharmacother 2001; 2:223-39.
Stoukides C. J Hum Lact 1994; 10:269.

Summary

Pregnancy Category: C
Lactation Category: U

- **Mebendazole** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.
- Though **mebendazole** is not associated with significant increase in the rates of congenital defects, it is best avoided during the 1st trimester.
- Treatment is beneficial for women in developing countries where intestinal helminthiases are endemic.

Mecamylamine—(Inversine)

International Brand Name—Mevasine (Japan)

Drug Class	Adrenergic antagonists; Antihypertensives; Smoking/drug cessations
Indications	Hypertension, malignant hypertension, smoking cessation
Mechanism	Inhibits nicotinic-cholinergic receptors (ganglion blockade)
Dosage with Qualifiers	Hypertension—begin 2.5mg PO bid and increase by 2.5mg q2d until 25mg qd Smoking cessation—2.5mg PO bid • **Contraindications**—hypersensitivity to drug or class, hypertension, history of acute MI, coronary insufficiency, uremia, pyloric stenosis, glaucoma • **Caution**—renal or CV dysfunction, fever, infection, anesthesia, surgery, vigorous exercise, use of alcohol or other hypertensive drugs
Maternal Considerations	There is no published experience with **mecamylamine** during pregnancy. ***Side effects*** include dizziness, light-headedness, fainting, hypotension, urinary retention, stroke, CHF, seizures, dizziness, ileus, constipation, N/V, anorexia, glossitis, dry mouth, blurred vision, weakness, fatigue, tremor, and choreiform movements.
Fetal Considerations	There are no adequate reports or well-controlled studies of **mecamylamine** in human fetuses. Rodent teratogenicity studies have not been conducted.
Breastfeeding Safety	There is no published experience in nursing women. It is unknown whether **mecamylamine** enters human breast milk.
Drug Interactions	Patients receiving antibiotics or sulfonamides should not generally be treated with ganglion blockers. Action may be potentiated by anesthesia, other antihypertensive drugs, and ethanol.
References	There are no current relevant references.
Summary	**Pregnancy Category: C** **Lactation Category: U** • **Mecamylamine** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk. • There are alternative agents for which there is more experience regarding use during pregnancy and lactation.

Mechlorethamine—(Mustargen)

International Brand Name—Mustine (Belgium, Netherlands, Turkey); Mustine Hydrochloride Boots (Malaysia)

Drug Class	Antineoplastics, alkylating agent
Indications	Hodgkin's disease (stages III-IV), leukemia (chronic myelocytic and chronic lymphocytic), mycosis fungoides, polycythemia vera, lymphosarcoma
Mechanism	Alkylating agent
Dosage with Qualifiers	Malignancy—0.4mg/kg/course; numerous dosing schedules exist reflecting the disease, patient response, and concomitant therapy • **Contraindications**—hypersensitivity to drug or class, suppurative inflammation • **Caution**—unknown
Maternal Considerations	There are no adequate reports or well-controlled studies of **mechlorethamine** in pregnant women. Hodgkin's disease does not affect the normal progress of pregnancy. Termination of pregnancy is usually unnecessary. Based on limited published experience, **mechlorethamine** may be used during pregnancy with a good outcome. Women treated during childhood or adolescence may experience decreased gonadal function. ***Side effects*** include thrombosis, thrombophlebitis, anaphylaxis, N/V, depression, hemolytic anemia, skin eruption, delayed catamenia, oligomenorrhea, and amenorrhea.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **mechlorethamine** crosses the human placenta. Children of women treated for hematologic malignancies during pregnancy with a variety of cytotoxic agents, including **mechlorethamine,** have normal birth weight as well as normal learning and educational performances. There is no increase in the prevalence of acute leukemia or congenital, neurologic, and psychological abnormalities. Thus, chemotherapy at full doses administered during pregnancy even during the 1st trimester can end with a good outcome. **Mechlorethamine** is teratogenic in rodents.
Breastfeeding Safety	There is no published experience in nursing women. It is unknown whether **mechlorethamine** enters human breast milk.
Drug Interactions	No clinically relevant interactions identified.
References	Abboud J, Nasrallah T, Chahine G, Nasnas R. J Gynecol Obstet Biol Reprod 1993; 22:783-6. Aviles A, Neri N. Clin Lymphoma 2001; 2:173-7. Brice P, Pautier P, Marolleau JP, et al. Nouv Rev Fr Hematol 1994; 36:387-8. van den Berg H, Furstner F, van den Bos C, Behrendt H. Pediatr Blood Cancer 2004; 42:210-5.
Summary	**Pregnancy Category: D** **Lactation Category: U** • Clinical experience reveals that **mechlorethamine** can be administered even during the 1st trimester with a good outcome. • Long-term follow-up of children exposed *in utero* to chemotherapy is reassuring.

Meclizine—(Ancolan; Antivert; Duramesan; En-Vert; Meclicot; Meclizine; Meclozine; Medivert; Yonyun)

International Brand Name—Bonamina (Argentina); Bonamine (Canada, Germany, Japan, Philippines, Taiwan); Chiclida (Spain); Dramine (Spain); Navicalm (Portugal); Postadoxin (Germany); Postadoxine (Philippines); Postafen (Denmark, Finland, Norway, Sweden); Postafene (Belgium, Hong Kong); Sea-Legs (New Zealand); Suprimal (Netherlands)

Drug Class	Antiemetics; Antihistamines, H_1; Antivertigo agents
Indications	Motion sickness
Mechanism	Antagonizes ACh and H_1 receptors
Dosage with Qualifiers	N/V and dizziness due to motion sickness—25-50mg PO qd 1h before travel; repeat q24h • **Contraindications**—hypersensitivity to drug or class • **Caution**—GI and GU obstruction, usage of drug with CNS-depressive effect
Maternal Considerations	**Meclizine** effectively reduces N/V associated with emergency hormonal contraception (Yuzpe regimen). There are no adequate reports or well-controlled studies of **meclizine** in pregnant women. It is commonly used in several European countries for the treatment of 1st trimester N/V. ***Side effects*** include tachycardia, hallucinations, jaundice, ototoxicity, agitation, anxiety, hypotension, blurred vision, dry mouth, confusion, anorexia, N/V, diarrhea, rash, and constipation.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **meclizine** crosses the human placenta. A large clinical experience reveals little evidence that **meclizine** is a significant human teratogen. A population-based study in Sweden that included more than 16,000 1st trimester exposures actually reported improved pregnancy outcomes compared to the nonexposed population. Rodent studies conducted at 25-50× the MRHD reveal cleft lip and palate.
Breastfeeding Safety	There are no adequate reports or well-controlled studies in nursing women. It is unknown whether **meclizine** enters human breast milk.
Drug Interactions	No clinically relevant interactions identified.
References	Källén B, Mottet I. Eur J Epidemiol 2003; 18:665-9. Miklovich L, van den Berg BJ. Am J Obstet Gynecol 1976; 125:244-8. Raymond EG, Creinin MD, Barnhart KT, et al. Obstet Gynecol 2000; 95:271-7. Shapiro S, Kaufman DW, Rosenberg L, et al. Br Med J 1978; 1:483.
Summary	**Pregnancy Category: B** **Lactation Category: S** • **Meclizine** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk. • **Meclizine** appears a reasonable choice for the management of N/V of pregnancy that has been unresponsive to vitamin B_6.

Meclofenamate—(Meclomen)

International Brand Name—Ethos (Taiwan); Medomen (Singapore); Melvon (Korea); Movens (Italy)

Drug Class

Analgesics, non-narcotic; NSAIDs

Indications

Pain, dysmenorrhea, osteoarthritis, rheumatoid arthritis, ankylosing spondylitis, gout

Mechanism

Inhibits cyclooxygenase and lipoxygenase, leading to reduced prostaglandin synthesis

Dosage with Qualifiers

Pain—50mg PO q4-6h; max 400mg/d
Dysmenorrhea—100mg PO tid; max 6d usage
Osteoarthritis—50-100mg PO tid or qid
Rheumatoid arthritis—50-100mg PO tid or qid
Ankylosing spondylitis—50-100mg PO tid
Gout, acute—100mg PO tid

NOTE: take with food or milk.

- **Contraindications**—hypersensitivity to drug or class, NSAID-induced asthma
- **Caution**—nasal polyps, GI bleeding, hypertension, cardiac failure, asthma

Maternal Considerations

Meclofenamate is a nonsteroidal agent with anti-inflammatory, analgesic, and antipyretic activities. It has little effect on human platelet function. There are no adequate reports or well-controlled studies of **meclofenamate** in pregnant women. In rodents, **meclofenamate** induces luteolysis as indicated by the drop in maternal **progesterone** after administration. Luteolysis is followed by spontaneous labor. In contrast, *in vitro* studies demonstrate **meclofenamate** inhibits myometrial contractility. **Meclofenamate** is a popular analgesic for the treatment of postpartum pain after vaginal delivery.
Side effects include anaphylaxis, GI bleeding, bronchospasm, renal failure, interstitial nephritis, hepatic failure, Stevens-Johnson syndrome, agranulocytosis, abdominal pain, constipation, headache, dizziness, rash, urticaria, increased LFTs, drowsiness, edema, tinnitus, rash, lupus, and serum sickness–like symptoms.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **meclofenamate** crosses the human placenta. Similar-class agents do cross, cause fetal ductal constriction and decreased fetal urination. Because of the potential for premature closure of the fetal ductus arteriosus after maternal use of NSAIDs, chronic **mefenamic acid** treatment during pregnancy is not recommended without fetal monitoring. Fetal exposure should be minimized until completion of future studies since **meclofenamate** may affect fetal breathing movements and pulmonary vascular resistance. Rodent studies reveal that **meclofenamate,** like **aspirin** and other NSAIDs, can cause fetotoxicity and minor skeletal malformations (e.g., supernumerary ribs, delayed ossification) but no major teratogenicity.

Breastfeeding Safety

There is no published experience in nursing women. **Meclofenamate** enters human breast milk, though the kinetics remain to be elucidated.

Drug Interactions

Enhances the effect of **warfarin,** and the **warfarin** dose should be reduced to prevent excessive prolongation of the PT or INR. **Aspirin** may lower **meclofenamate** plasma levels, possible by competing for protein-binding sites. Greater fecal blood loss results from the use of both drugs.

References

Cooke RG, Knifton A. Res Vet Sci 1980; 29:251-4.
Facchinetti F, De Pietri R, Giunchi M, Genazzani AR. Clin J Pain 1991; 7(Suppl 1):S60-3.
Gooneratne AD, Hartmann PE, Barker I. J Reprod Fertil 1982; 65:157-62.

Summary

Pregnancy Category: C (1st and 2nd trimesters), **D** (3rd trimester)
Lactation Category: S (likely)
- Similar to other NSAIDs, **meclofenamate** poses minimal risk when used occasionally.

Medroxyprogesterone—(Amen; Aragest; Asconale; Clinovir; Curretab; Cycrin; Depo-Provera; Med-Pro; Provera)

International Brand Name—Aragest 5 (Israel); Clinofem (Germany); Depo-Prodasone (France); Farlutal (Belgium, China, France, Italy, Netherlands); GestaPolar (Germany); Gestapuran (Finland, Sweden); Manodepa (Thailand); Medrone (Taiwan); Meges (Indonesia); Meprate (India); MPA (China); MPA Gyn 5 (Germany); Perlutex (Denmark, Norway); Perlutex Leo (Costa Rica, Dominican Republic, El Salvador, Guatemala, Honduras, Panama); Prodafem (Austria, Switzerland); Progen (Korea); Progevera (Spain); Prothyra (Indonesia); Ralovera (Australia); Veraplex (Indonesia)

Drug Class

Antineoplastics, hormone; Contraceptives; Hormones

Indications

Amenorrhea, dysfunctional uterine bleeding, hormone replacement, contraception

Mechanism

Inhibits gonadotropin release, stimulates transformation of proliferative into secretory endometrium

Dosage with Qualifiers

Amenorrhea—5-10mg PO qd ×5 on days 16-21 of the cycle or qmo
Dysfunctional uterine bleeding—5-10mg PO qd ×5 on days 16-21 of the cycle or qmo
Hormone replacement—5-10mg PO qd ×12-14d
Contraception—150mg IM q3mo

- **Contraindications**—hypersensitivity to drug or class, thromboembolic disease, pregnancy, breast cancer, undiagnosed vaginal bleeding, thrombophlebitis, PE, retinal thrombosis, hepatic failure, missed abortion
- **Caution**—cerebrovascular disorders, lactation, hepatic dysfunction, cardiac failure

Maternal Considerations

Medroxyprogesterone is a popular and effective (0.42/1000 woman-years) contraceptive; irregular bleeding and amenorrhea are the most common side effects. It can be combined with an injectable estrogen. It is estimated that 68% of women who become pregnant after discontinuing conceive within 12mo, 83% within 15mo, and 93% within 18mo. If bone density does decline, it is reversible and unlikely to adversely influence clinical events either acutely or later. Because of the indications, it is inevitable

that numerous pregnant women are exposed to **medroxyprogesterone** since many pregnancies will not be recognized until after the 1st trimester. Progestational agents (i.e., not native **progesterone**) such as **medroxyprogesterone** were long used during early pregnancy to prevent 1st trimester spontaneous abortion. The wisdom of this practice cannot be substantiated. It is speculated that progestational agents may delay spontaneous abortion in women with defective ova. While there are no adequate reports or well-controlled studies of **medroxyprogesterone** in pregnant women, epidemiologic studies are reassuring as there is no demonstrable increase in the prevalence of ectopic pregnancy. **Medroxyprogesterone** is also commonly used as adjunctive therapy for endometrial cancer or adenomatous hyperplasia, especially in young women who wish to preserve fertility for the near term.

Side effects include thromboembolism, stroke, MI, hepatic adenoma, breast cancer, gallbladder disease, cholestatic jaundice, hypertension, stroke, amenorrhea, N/V, breast tenderness, weight gain, headache, edema, depression, rash, pruritus, libido changes, appetite changes, acne, hirsutism, galactorrhea, alopecia, and optic neuritis.

Fetal Considerations

There are no adequate reports or well-controlled studies of **medroxyprogesterone** in human fetuses. *In utero* exposure of male fetuses to progestational agents may double the risk of hypospadias. While there are insufficient data to quantify the risk for the female fetus, some progestational agents may cause mild virilization of the external genitalia. Defects outside the external genitalia are not noted in either humans or rodents. 1st trimester exposure is an indication for a detailed anatomic ultrasound between 18 and 22w.

Breastfeeding Safety

Trace amounts of **medroxyprogesterone** are excreted into human breast milk. It does not appear to either suppress lactation or affect the nursing newborn. It is typically given for contraception 3d after delivery since **progesterone** withdrawal may be one stimulus for the initiation of lactogenesis.

Drug Interactions

The literature suggests use with **aminoglutethimide** significantly reduces serum concentrations of **medroxyprogesterone,** likely by increasing clearance.

References

Baheiraei A, Ardsetani N, Ghazizadeh S. Int J Gynaecol Obstet 2001; 74:203-5.

Borgatta L, Murthy A, Chuang C, et al. Contraception 2002; 66:169.

Carbone JP, Figurska K, Buck S, Brent RL. Teratology 1990; 42:121-30.

Danli S, Qingxiang S, Guowei S. Contraception 2000; 62:15-8.

Kennedy KI, Short RV, Tully MR. Contraception 1997; 55:347-50.

[No authors]. FDA Med Bull 1993; 23:6-7.

Prahalada S, Carroad E, Hendrickx AG. Contraception 1985; 32:497-515.

Ratchanon S, Taneepanichskul S. Obstet Gynecol 2000; 96:926-8.

Ushijima K, Yahata H, Yoshikawa H, et al. J Clin Oncol 2007; 25:2798-803.

Summary

Pregnancy Category: X
Lactation Category: S

- **Medroxyprogesterone** should not be administered during pregnancy.
- 1st trimester exposure is an indication for a detailed anatomic ultrasound between 18 and 22w.

Mefenamic acid—(Coslan; Ponsfen; Ponstel)

International Brand Name—Algastel (Philippines); Algifort (Philippines); Alpain (Indonesia); Aprostal (Philippines); Atmose (Philippines); Beafemic (Malaysia); Benostan (Indonesia); Bonabol (Japan); Dolfenal (Thailand); Dysman (England); Dyspen (Malaysia, Thailand); Ecopan (Switzerland); Eurostan (Philippines); Femen (Thailand); Fenalac (Philippines); Fenamic (Israel); Fenamin (South Africa); Fenamol (Israel); Fengic (Philippines); Hamitan (Hong Kong); Hispen (Philippines); Hostan (Hong Kong); Johnstal (Taiwan); Kemostan (Indonesia); Lysalgo (Italy); Manic (Thailand); Manomic (Thailand); Masafen (Thailand); Mecid A (Philippines); Mefa (Hong Kong); Mefac (Ireland); Mefacap (Singapore); Mefacit (Poland); Mefalqic (South Africa); Mefast (Indonesia); Mefen (Malaysia); Mefic (New Zealand); Metmic (Philippines); Namic (Malaysia); Napan (Hong Kong); Parkemed (Austria, Germany); Passton (Taiwan); Pefamic (Thailand); Poncofen (Indonesia); Pondex (Indonesia); Pondnadysmen (Thailand); Ponser (Philippines, South Africa); Ponstan (Canada, Ecuador, England, Finland, Ghana, Greece, Israel, Japan, Kenya, Korea, Mauritius, Philippines, Portugal, South Africa, Switzerland, Tanzania, Turkey, Uganda, Venezuela, Zimbabwe); Ponstan (500 mg) (Colombia); Ponstan-500 (Mexico); Ponstan Forte (Israel, South Africa); Ponstil (Uruguay); Ponstyl (France, Mauritius); Pontacid (Hong Kong); Pontal (Japan, Korea); Pontyl (Singapore); Potarlon (Taiwan); Pynamic (Thailand); Ralgec (Philippines); Sefmic (Hong Kong); Selmac (Philippines); Sicadol (Chile, Paraguay); Solasic (Indonesia); Tanston (Peru); Tropistan (Indonesia); Vandifen (Philippines); Youfenam (Japan); Zerrmic (Philippines)

Drug Class	Analgesics, non-narcotic; NSAIDs
Indications	Pain, dysmenorrhea, osteoarthritis, rheumatoid arthritis, ankylosing spondylitis, gout
Mechanism	Inhibits cyclooxygenase and lipoxygenase, reducing prostaglandin synthesis
Dosage with Qualifiers	Pain—50mg PO q4-6h; max 400mg/d Dysmenorrhea—100mg PO tid; max 6d usage Osteoarthritis—50-100mg PO tid or qid Rheumatoid arthritis—50-100mg PO tid or qid Ankylosing spondylitis—50-100mg PO tid Gout, acute—100mg PO tid; alternatively 500mg PO, then 250mg PO q6h for not more than 7d *NOTE: take with food or milk.* • **Contraindications**—hypersensitivity to drug or class, NSAID-induced asthma • **Caution**—nasal polyps, GI bleeding, hypertension, cardiac failure, asthma
Maternal Considerations	**Mefenamic acid** is a nonsteroidal agent with anti-inflammatory, analgesic, and antipyretic action. There are no adequate reports or well-controlled studies of **mefenamic acid** in pregnant women. In one small, randomized trial, the prevalence of preterm labor was significantly reduced by **mefenamic acid** compared with placebo. This observation has not subsequently been tested adequately. If the effect of **mefenamic acid** is similar to other NSAIDs, it is unlikely to be effective for the stated indication. **Mefenamic acid** rapidly decreases uterine contractility in women with dysmenorrhea. ***Side effects*** include anaphylaxis, GI bleeding, bronchospasm, renal failure, interstitial nephritis, hepatic failure, Stevens-Johnson syndrome, agranulocytosis, abdominal pain, constipation, headache, dizziness, rash, urticaria, elevated LFTs, drowsiness, edema, tinnitus, rash, lupus, and serum sickness–like symptoms.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. **Mefenamic acid** crosses the human placenta, achieving an F:M ratio approximating 0.32 in the 2nd trimester. There are case reports of ductal closure reported as with other NSAIDs. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than

those used clinically. Embryotoxicity is noted in some species. Because of the potential for premature closure of the fetal ductus arteriosus after maternal use of NSAIDs, chronic **mefenamic acid** treatment during pregnancy is not recommended without fetal monitoring.

Breastfeeding Safety

The trace amounts of **mefenamic acid** excreted into breast milk pose no clinical risk to the nursing infant.

Drug Interactions

Mefenamic acid is a CYP2C9 substrate, and a number of compounds are recognized inhibitors of CYP2C9. However, drug interactions studies of **mefenamic acid** and these compounds have not been conducted.

May reduce the natriuretic effect of **furosemide** and thiazides presumably by the inhibition of renal prostaglandin synthesis. The patient should be observed closely for signs of renal failure, as well as to assure diuretic efficacy.

NSAIDs can increase plasma **lithium** levels (15%) by decreasing renal **lithium** clearance, presumably by inhibiting renal prostaglandin synthesis. Patients should be observed carefully for signs of **lithium** toxicity.

NSAIDs competitively inhibit **methotrexate** accumulation in rabbit kidney slices. Caution is advised when NSAIDs are administered with **methotrexate.**

The effects of **warfarin** and NSAIDs on GI bleeding are synergistic, such that users of both drugs together have a risk of serious GI bleeding higher than users of either drug alone.

Antacids containing magnesium hydroxide may increase the C_{max} and AUC of **mefenamic acid** by 125% and 36%, respectively.

May prolong PT. Frequent monitoring of PT is necessary when **mefenamic acid** is given to patients receiving oral anticoagulant drugs.

A false-positive reaction for urinary bile, using the diazo tablet test, may result after **mefenamic acid.** If biliuria is suspected, other diagnostic procedures, such as the Harrison spot test, should be performed.

References

Adverse Drug Reactions Advisory Committee. Med J Aust 1998; 169:270-1.

Buchanan RA, Eaton CJ, Koeff ST, Kinkel AW. Curr Ther Res Clin Exp 1968; 10:592-7.

MacKenzie IZ, Graf AK, Mitchell MD. Int J Gynaecol Obstet 1985; 23:455-8.

Mital P, Garg S, Khuteta RP, et al. J R Soc Health 1992; 112:214-6.

Smith RP, Powell JR. Am J Obstet Gynecol 1982; 143:286-92.

Summary

Pregnancy Category: C
Lactation Category: S

- **Mefenamic acid** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.
- Occasional use during pregnancy appears safe, though continuous use likely has the same adverse effects as other NSAIDs.

Mefloquine—(Lariam)

International Brand Name—Lariam (Canada, Chile, China, Hong Kong, Korea, Peru, Philippines, Taiwan, Uruguay); Laricam (Japan); Mefliam (Israel, South Africa); Mephaquin (Colombia, Hong Kong, Israel, Thailand); Mephaquine (Switzerland); Mequin (Thailand); Tropicur (Argentina)

Drug Class — Antiprotozoals

Indications — Malaria (prophylaxis and treatment)

Mechanism — Unknown; acts as schizonticide

Dosage with Qualifiers

Malaria prophylaxis—250mg PO qw beginning 1w before and continuing until 4w after possible exposure
Malaria treatment—1250mg PO ×1 followed by treatment with **primaquine**

NOTE: take with food and water.

- **Contraindications**—hypersensitivity to drug or class, depression, psychosis, serious life-threatening infections
- **Caution**—seizures, psychiatric disorder, hepatic dysfunction, cardiac conduction diseases, cardiac arrhythmia

Maternal Considerations

Malaria remains an important cause of maternal and perinatal morbidity and mortality in endemic countries. *P. falciparum* drug resistance increasingly limits the effectiveness of antimalarial therapy. **Mefloquine** is the most effective agent for the prevention of chloroquine-resistant falciparum malaria. The WHO favors **mefloquine** prophylaxis in pregnant women from 16w onward. **Mefloquine** and **quinine** are the only antimalarials generally available for the treatment of drug-resistant *P. falciparum* during pregnancy. Prospective studies show **mefloquine** (25mg/kg) in combination with **artesunate** (4mg/kg/d for 3d) is more effective than **quinine** (10mg/kg q8h) for the treatment of multidrug-resistant falciparum malaria during pregnancy. Many of the adverse effects of **mefloquine** reflect primary hepatic damage or symptomatic thyroid disturbances, which might occur either independently or as a secondary consequence of the hepatocellular injury. Routine intermittent treatment of women in endemic locales has been suggested.
Side effects include seizures, hallucinations, ECG conduction abnormalities, erythema multiforme, Stevens-Johnson syndrome, encephalopathy, dizziness, syncope, extrasystoles, myalgia, N/V, fever, headache, chills, diarrhea, pruritus, asthenia, transient emotional disturbances, and hair loss.

Fetal Considerations

Prophylactic (250mg/w) **mefloquine** during early pregnancy is not associated with an increased risk of malformations and is not an indication for pregnancy termination. Similarly, 2nd trimester exposure is not associated with adverse reactions. **Mefloquine** is associated with an increased risk of stillbirth but not abortion, IUGR, neurologic retardation, or congenital malformations. Rodent studies reveal that **mefloquine** at high doses is teratogenic and embryotoxic.

Breastfeeding Safety

There are no adequate reports or well-controlled studies in nursing women. The detectable amounts of drug identified in the milk of mothers receiving **mefloquine** are too small to be clinically relevant.

Drug Interactions

Use with related compounds (e.g., **chloroquine, quinidine, quinine**) may produce ECG abnormalities and increase the risk of convulsions. If these drugs are to be used in the initial treatment of severe malaria, **mefloquine** administration should be delayed at least 12h after the last dose.

Because of the potential for fatal prolongation of the QTc interval, **halofantrine** should not be given simultaneously with or subsequent to **mefloquine.**

Theoretically, use with other drugs known to alter cardiac conduction (e.g., antiarrhythmic or β-adrenergic blocking agents, antihistamines or H_1-blocking agents, calcium channel blockers, phenothiazines, TCAs) might also contribute to prolongation of the QTc interval. There are no data.

May reduce seizure control by lowering the plasma levels of anticonvulsants (e.g., **carbamazepine, phenobarbital, phenytoin, valproic acid**). Monitor blood levels and adjust the dose appropriately.

May attenuate the immune response to oral live typhoid vaccine. Vaccinations composed of attenuated live bacteria should be completed at least 3d before the first dose.

References

Bounyasong S. J Med Assoc Thai 2001; 84:1289-99.

Briand V, Cottrell G, Massougbodji A, Cot M. Malar J 2007; 6:160.

Croft AM, Herxheimer A. BMC Public Health 2002; 2:6.

Edstein MD, Veenendaal JR, Hyslop R. Chemotherapy 1988; 34:165-9.

McGready R, Brockman A, Cho T, et al. Trans R Soc Trop Med Hyg 2000; 94:689-93.

[No authors]. Prescrire Int 2000; 9:180-1.

Nosten F, van Vugt M, Price R, et al. Lancet 2000; 356:297-302.

Nosten F, Vincenti M, Simpson J, et al. Clin Infect Dis 1999; 28:808-15.

Orton LC, Orton AA. Cochrane Database Syst Rev 2008; (4):CD004912.

Rosenblatt JE. Mayo Clin Proc 1999; 74:1161-75.

Summary

Pregnancy Category: C

Lactation Category: S

- **Mefloquine** is the most effective agent for prevention of chloroquine-resistant falciparum malaria.
- Use of **mefloquine** in pregnant women has not been associated with birth defects, but the incidence of stillbirths may be increased. The WHO favors **mefloquine** prophylaxis in pregnant women from 16w onward.
- **Mefloquine** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Megestrol—(Magace; Megace; Niagestine)

International Brand Name—Endace (India); Maygace (Spain); Megace (Argentina, Australia, Austria, Canada, Chile, Czech Republic, Ecuador, England, Greece, Hungary, Ireland, Netherlands, Peru, Poland, Russia, Uruguay); Megace OS (Canada); Megaplex (Indonesia, Thailand); Megastrol (Paraguay); Megejohn (Taiwan); Megestat (Brazil, Germany); Mestrel (Mexico, Thailand)

Drug Class

Antineoplastics, Hormone/hormone modifier; Hormones, other gynecologic; Progestins

Indications

Breast cancer, endometrial cancer (palliative), AIDS wasting syndrome

Mechanism

Inhibition of pituitary gonadotropin release; stimulates transformation of proliferative endometrium to secretory; antineoplastic

Dosage with Qualifiers

Breast cancer—40mg PO qid
Endometrial cancer palliation—10-80mg PO qid
AIDS wasting syndrome—800mg PO qd; alternative 400mg PO bid

- **Contraindications**—hypersensitivity to drug or class, 1st trimester pregnancy
- **Caution**—recurrent or metastatic cancer, thromboembolic disease

Maternal Considerations

Megestrol is a synthetic, progestational drug. It is used as an implantable contraceptive. There are no adequate reports or well-controlled studies of **megestrol** in pregnant women, nor are there any indications for its use. Many case reports document successful pregnancy in women with endometrial cancer whose uterus was preserved by **megestrol.** As a treatment for weight loss in cancer patients, **megestrol** should be started only after other treatable causes are sought and addressed.
Side effects include weight increase, thrombophlebitis, PE, adrenal suppression, stroke, abdominal pain, amenorrhea, N/V, breast tenderness, weight gain, headache, edema, depression, rash, pruritus, libido changes, appetite changes, acne, hirsutism, alopecia, constipation, and cardiomyopathy.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **megestrol** crosses the human placenta. There are case reports of abnormalities, including hypospadias.

Breastfeeding Safety

There are no adequate reports or well-controlled studies in nursing women. Small quantities of **megestrol** are excreted into human breast milk. However, **megestrol** has no clinically relevant effect on breast milk when used for contraception.

Drug Interactions

Use with **indinavir** results in an ~36% decrease in the C_{max} and ~28% for the AUC of **indinavir.** A higher dose is indicated. Pharmacokinetics studies reveal no significant alterations for either **zidovudine** or **rifabutin.**

References

Abdel-Aleem H, Abol-Oyoun el-SM, Shaaban MM, et al. Contraception 1996; 54:281-6.
Farrar DJ, Aromin I, Uvin SC, et al. Genitourin Med 1997; 73:226.

Kowalczyk CL, Malone J Jr, Peterson EP, et al. J Reprod Med 1999; 44:57-60.
Lonnerdal B, Forsum E, Hambraeus L. Am J Clin Nutr 1980; 33:816-24.
Lowe MP, Bender D, Sood AK, et al. Fertil Steril 2002; 77:188-9.

Summary

Pregnancy Category: D (tablet), **X** (suspension)
Lactation Category: S (likely)
- There are no indications for **megestrol** use during pregnancy.
- **Megestrol** appears compatible with breastfeeding.

Melatonin

International Brand Name—Many.

Drug Class

Hormones, antioxidant

Indications

Sleep promotion (jet lag), insomnia, seasonal affective disorder

Mechanism

Secreted by the suprachiasmatic nuclei of the hypothalamus and directly influences circadian rhythms

Dosage with Qualifiers

Sleep promotion (jet lag)—5mg PO qd ×5d
Insomnia—0.3-1mg PO bid; should be given at 6:00 and 8:00 PM

NOTE: ***Melatonin*** *is not regulated by the FDA and is sold OTC.*

- **Contraindications—**hypersensitivity to drug or class
- **Caution—**CV disease

Maternal Considerations

There are no adequate reports or well-controlled studies of **melatonin** in pregnant women. **Melatonin** is a natural hormone (*N*-acetyl-5-methoxytryptamine) produced by the pineal gland with antioxidant properties. Its secretion is stimulated by the dark and inhibited by light. Secretion disturbances have been associated with depression. Rodent studies suggest that **melatonin** is involved in the initiation of parturition without having a direct effect on progesterone secretion. In humans, **melatonin** may also modulate myometrial function, as receptors are present.
Side effects include fatigue, depression, constriction of the coronary arteries, possible effects on fertility, and pruritus.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. **Melatonin** rapidly crosses the isolated human placenta equal to the freely diffusible marker antipyrine. It stimulates glutathione peroxidase in the human chorion and inhibits the vasospastic effects of oxidized lipids. It also crosses the rodent placenta, and fetal rodents respond to the maternal **melatonin** rhythm. **Melatonin** may offer some protection for ischemia/reperfusion-induced oxidative mitochondrial damage to the fetal rat brain.

Breastfeeding Safety

There are no adequate reports or well-controlled studies in nursing women. In both human and rodent breast milk, **melatonin** is undetectable in the light but increases rapidly after dark. The M:P ratio ranges from 0.35 to 0.8, and **melatonin** is believed responsible for shifting the newborn to the circadian rhythm of the mother.

Drug Interactions No clinically relevant interactions identified.

References

Goldman BD. Sci STKE 2003; 2003(192):PE29.
Illnerova H, Buresova M, Presl J. J Clin Endocrinol Metab 1993; 77:838-41.
Okatani Y, Wakatsuki A, Watanabe K, et al. J Pineal Res 2000; 29:74-80.
Parry BL, Meliska CJ, Sorenson DL, et al. Am J Psychiatry 2008; 165:1551-8.
Rowe SA, Kennaway DJ. Am J Physiol Regul Integr Comp Physiol 2002; 282:R797-804.
Schenker S, Yang Y, Perez A, et al. Clin Nutr 1998; 17:159-67.
Schlabritz-Loutsevitch N, Hellner N, Middendorf R, et al. J Clin Endocrinol Metab 2003; 88:908-13.
Wakatsuki A, Okatani Y, Shinohara K, et al. J Pineal Res 2001; 31:167-72.

Summary

Pregnancy Category: B
Lactation Category: S

- **Melatonin** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Meloxicam

International Brand Name—Aflamid (Mexico); Artrilox (Indonesia); Dormelox (Brazil); Ecax (Chile); Exel (Mexico); Flodin (Peru); Loxibest (Mexico); Loxicam (Colombia); Masflex (Mexico); Mecox (Indonesia); Melcox (Korea); Melicam (Taiwan); Melocam (Colombia); Melocox (Korea); Mel-OD (India); Melosteral (Mexico); Melox (Hong Kong, Israel, Malaysia, Singapore, Thailand); Meloxin (Indonesia); Merapiran (Argentina); Mevamox (Brazil); Mexican (Colombia); Mexpharm (Indonesia); Mobec (Germany); Mobic (Colombia, England, Hong Kong, Ireland, Israel, Korea, New Zealand, Philippines, Singapore, South Africa, Taiwan, Thailand); Mobicox (Costa Rica, Dominican Republic, El Salvador, Guatemala, Honduras, Mexico, Nicaragua, Panama); Mobiflex (Indonesia); Mopik (Taiwan); Movalis (Bulgaria, Czech Republic, Hungary, Poland); Movi-Cox (Indonesia); Movicox (Netherlands); Mowin (Peru); Muvera (India); Ostelox (Indonesia); Rafree (Malaysia); Rumonal (Colombia); Selektine (Israel)

Drug Class Analgesics, non-narcotic; NSAIDs

Indications Osteoarthritis

Mechanism Inhibits PGHS-II

Dosage with Qualifiers

Osteoarthritis—7.5-15mg PO qd; max 15mg/d

- **Contraindications**—hypersensitivity to drug or class, NSAID-induced asthma
- **Caution**—nasal polyps, GI bleeding, hypertension, cardiac failure, asthma

Maternal Considerations

Meloxicam is a nonsteroidal agent with anti-inflammatory, analgesic, and antipyretic activities. There is no published clinical experience during pregnancy. In the ewe, **meloxicam** is an inhibitor of uterine contractions. It, with **indomethacin,** is a modest inhibitor of preterm labor in rats treated with LPS. *In vitro,* **meloxicam** relaxes myometrial strips from pregnant and nonpregnant women, but is less potent than **celecoxib.**
Side effects include anaphylaxis, GI bleeding, bronchospasm, renal failure, interstitial nephritis, hepatic failure, Stevens-Johnson syndrome, agranulocytosis, abdominal pain, constipation, headache, dizziness, rash, urticaria, elevated LFTs, drowsiness, edema, tinnitus, lupus, and serum sickness–like symptoms.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. **Meloxicam** crosses the human placenta. The administration of high doses to rodents is associated with cardiac septal defects and embryotoxicity. **Meloxicam** attenuates RU486-stimulated labor in sheep. Because of the potential for premature closure of the fetal ductus arteriosus after maternal use of NSAIDs, chronic **meloxicam** treatment during pregnancy is not recommended without fetal monitoring.

Breastfeeding Safety

There is no published experience in nursing women. It is unknown whether **meloxicam** enters human breast milk. It does enter rodent milk.

Drug Interactions

NSAIDs may decrease the antihypertensive effect of ACEIs.

Use with **aspirin** (1000mg tid) in healthy volunteers tends to increase the AUC (10%) and C_{max} (24%) of **meloxicam.** The clinical significance is not known. As with other NSAIDs, concomitant use of **meloxicam** and **aspirin** is not generally recommended because of the potential for increased adverse effects. The use of low-dose **aspirin** with **meloxicam** may increase the rate of GI ulceration or other complications.

Cholestyramine for 4d increased the clearance of **meloxicam** by 50%, decreasing the t/2 from 19.2h to 12.5h, and the AUC 35%. This suggests the existence of a recirculation pathway for **meloxicam** in the GI tract.

NSAIDs reduce the natriuretic effect of **furosemide** and thiazide diuretics in some patients. This effect has been attributed to inhibition of renal prostaglandin synthesis. However, the pharmacokinetics and pharmacodynamics of both single and multiple doses of **furosemide** are unaffected by multiple doses of **meloxicam.**

Increases the mean predose **lithium** level and the AUC by 21% in healthy subjects compared controls receiving **lithium** alone. These effects have been attributed to inhibition of renal prostaglandin synthesis.

Anticoagulant activity should be monitored, particularly the first few days after initiating or changing **meloxicam** therapy, in patients receiving **warfarin** or similar agents, since these patients are at an increased risk of bleeding. The effect of **meloxicam** on the anticoagulant effect of **warfarin** was studied in healthy subjects receiving doses of **warfarin** that produced an INR between 1.2 and 1.8. In these subjects, **meloxicam** did not alter either **warfarin** pharmacokinetics or the the average anticoagulant effect of **warfarin** as determined by PT.

References

Lee PR, Kim SR, Jung BK, et al. Am J Obstet Gynecol 2003; 189:261-6.

McKeown KJ, Challis JR, Small C, et al. Biol Reprod 2000; 63:1899-904.

Slattery MM, Friel AM, Healy DG, Morrison JJ. Obstet Gynecol 2001; 98:563-9.

Yousif MH, Thulesius O. J Pharm Pharmacol 1998; 50:681-5.

Summary

Pregnancy Category: C

Lactation Category: U

- **Meloxicam** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.
- There are alternative agents for which there is more experience regarding use during pregnancy and lactation.

Melphalan—(Alkeran)

International Brand Name—Alkeran (Brazil, Canada, Chile, China, Colombia, Ecuador, Hong Kong, India, Indonesia, Japan, Korea, Mexico, Philippines, Taiwan, Thailand, Uruguay); Alkerana (Argentina)

Drug Class	Antineoplastics, alkylating agent
Indications	Multiple myeloma, ovarian cancer
Mechanism	Alkylates and cross-links DNA
Dosage with Qualifiers	Multiple myeloma—varies depending on tumor and protocol Ovarian cancer—varies depending on tumor and protocol *NOTE: the most commonly recommended dose is 10mg/d ×7-10d. Continuous maintenance therapy with 2mg/d is instituted when the WBC >4000cells/ml and the PLT >100,000cells/ml.* • **Contraindications**—hypersensitivity to drug or class, hypersensitivity to **chlorambucil,** resistance to drug • **Caution—**renal failure, leukopenia, thrombocytopenia, anemia, leukemia
Maternal Considerations	**Melphalan** is an alkylating agent. While **methotrexate** is the primary choice for uncomplicated malignant trophoblastic disease, occasional resistance to **methotrexate** requires alternative drug regimens that may include **melphalan** (e.g., **melphalan, actinomycin D,** and **methotrexate**). These regimens are more frequently associated with life-threatening hematologic toxicity compared to those regimens that include **methotrexate.** Women cured of either trophoblastic disease or ovarian cancer (usually stage 1A-C) using a drug regimen that includes **melphalan** can have successful pregnancies. **Melphalan** is also used for the treatment of primary thrombocythemia and for marrow conditioning prior to allogeneic marrow transplantation. There are no adequate reports or well-controlled studies of **melphalan** in pregnant women. There are only case reports of its use during an ongoing pregnancy. ***Side effects*** include bone marrow suppression, N/V, diarrhea, pulmonary fibrosis and interstitial pneumonitis, skin hypersensitivity, vasculitis, alopecia, hemolytic anemia, anaphylaxis, stomatitis, and sterility.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **melphalan** crosses the human placenta. Rodent studies reveal both embryotoxicity and teratogenicity. Anomalies include CNS and skeletal defects.
Breastfeeding Safety	There is no published experience in nursing women. It is unknown whether **melphalan** enters human breast milk.
Drug Interactions	Severe renal failure has been reported after a single dose of IV **melphalan** followed by standard oral doses of **cyclosporine. Cisplatin** may affect **melphalan** kinetics by inducing renal dysfunction and subsequently altering **melphalan** clearance. IV **melphalan** may also reduce the threshold for BCNU lung toxicity. The incidence of severe hemorrhagic necrotic enterocolitis has been reported to increase in pediatric patients when **nalidixic acid** and IV **melphalan** are given simultaneously.
References	Curry SL, Blessing JA, DiSaia PJ, et al. Obstet Gynecol 1989; 73:357-62.

Schilder JM, Thompson AM, DePriest PD, et al. Gynecol Oncol 2002; 87:1-7.
Wiqvist N, Lundstrom V, Eneroth P. Acta Obstet Gynecol Scand 1976; 55:275-8.

Summary

Pregnancy Category: D
Lactation Category: U

- **Melphalan** is an effective part of multidrug regimens for the treatment of GTDs.
- It should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.
- If possible, delay administration to the 2nd trimester.

Mepenzolate—(Cantil)

International Brand Name—Cantil (Indonesia); Cluyer (Argentina); Trancolon (Japan, Taiwan)

Drug Class

Anticholinergics; Gastrointestinals

Indications

Peptic ulcer disease; adjuvant

Mechanism

Antagonizes ACh receptors; decreases gastric acid and pepsin secretion

Dosage with Qualifiers

Gastric ulcer—25-50mg PO qid

- **Contraindications**—hypersensitivity to drug or class, glaucoma, pyloroduodenal stenosis, achalasia, GI hemorrhage, toxic megacolon, myasthenia gravis
- **Caution**—coronary heart disease, CHF, cardiac arrhythmia, tachycardia, hypertension

Maternal Considerations

There is no published experience with **mepenzolate** during pregnancy.
Side effects include N/V, constipation, loss of taste, bloated feeling, dry mouth, tachycardia, palpitations, increased ocular tension, cycloplegia, blurred vision, dizziness, weakness, drowsiness, headache, nervousness, anaphylaxis, and urticaria.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **mepenzolate** crosses the human placenta. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of higher doses than those used clinically.

Breastfeeding Safety

There is no published experience in nursing women. It is unknown whether **mepenzolate** enters human breast milk.

Drug Interactions

The following agents may increase the actions or side effects of anticholinergic drugs: **amantadine,** antiarrhythmic agents of class I (e.g., **quinidine**), antihistamines, antipsychotic agents (e.g., phenothiazines), benzodiazepines, MAOIs, narcotic analgesics (e.g., **meperidine**), nitrates and nitrites, sympathomimetic agents, TCAs, and other drugs having anticholinergic activity. Anticholinergics antagonize the effects of antiglaucoma agents. Anticholinergic drugs in the presence of increased intraocular pressure may be hazardous when used with agents such as corticosteroids.

May affect GI absorption of various drugs, such as slowly dissolving forms of **digoxin;** increased serum **digoxin** concentrations may result.
May antagonize the effects of drugs that alter GI motility, such as **metoclopramide.** Because antacids may interfere with the absorption of anticholinergic agents, simultaneous use of these drugs should be avoided.
The inhibiting effects of anticholinergic drugs on gastric hydrochloric acid secretion are antagonized by agents used to treat achlorhydria and those used to test gastric secretion.

References ..... There is no published experience in pregnancy or during lactation.

Summary .....

Pregnancy Category: B
Lactation Category: U

- **Mepenzolate** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.
- There are alternative agents for which there is more experience regarding use during pregnancy and lactation.

Meperidine—(Demerol; Doloneurin)

International Brand Name—Alodan ''Gerot'' (Austria); Centralgin (Switzerland); Cluyer (Argentina); Demero (Uruguay, Venezuela); Demerol HCl (Canada, Chile, Mexico, Philippines); Dolantin (Germany); Dolantina (Spain); Dolantine (Belgium); Dolargan (Hungary, Poland); Dolestine (Israel); Dolosal (Brazil); Dolsin (Czech Republic); Lydol (Bulgaria); Meperdol (Paraguay); Neomochin (Japan); Opistan (Japan); Pethidine (England, India, Korea); Pethidine Roche (South Africa); Pethidine Tablet (New Zealand); Petidin (Denmark, Finland, Norway, Sweden)

Drug Class ..... Analgesics, narcotic; Anesthetics, adjunct

Indications ..... Pain, preoperative sedation, obstetric analgesia

Mechanism ..... Binds opioid receptors in the CNS

Dosage with Qualifiers .....

Pain—50-150mg PO/SC/IM q3-4h; IM preferred over SC/IV
Preoperative sedation—50-100mg SC/IM ×1, 30-60min before surgery
Obstetric analgesia—50-100mg SC/IM/IV q3-4h; approximately 75mg parenteral **meperidine** = 10mg parenteral **morphine**

*NOTE: available in liquid, tablet, and parenteral forms; may be combined with **promethazine;** administer slowly and adjust dose based on CrCl.*

- **Contraindications**—hypersensitivity to drug or class, MAOI <14d
- **Caution**—respiratory, hepatic, or renal dysfunction; seizure disorder; head injury; hypothyroidism; atrial flutter; convulsions

Maternal Considerations .....

Meperidine is a synthetic narcotic qualitatively similar to **morphine.** It is metabolized to another active form, normeperidine. Historically, **meperidine** was perhaps the most commonly used parenteral opioid during labor for pain relief. Well-designed studies demonstrate that the incidence of cesarean delivery in nulliparous women with epidural analgesia is similar to IV **meperidine** but, with superior analgesia, less maternal sedation and no need for neonatal **naloxone** as with **meperidine.** When used for early labor analgesia, **meperidine** increases the prevalence of neonatal acidemia. It does not improve outcome

when given for dystocia. **Meperidine** does not have *in vitro* a significant effect on the spontaneous contractions of gravid human myometrium. Postoperatively, PCEA with **meperidine** offers high-quality pain relief with few side effects.
Side effects include respiratory arrest and depression, cardiac arrest, tachydysrhythmias, dependency, abuse, vomiting, sweating, shock, agitation, disorientation, euphoria, dysphoria, weakness, dry mouth, flushing, visual disturbances, constipation, biliary tract spasm, palpitation, hypotension, syncope, pruritus, skin rashes, and pain at the site of injection.

Fetal Considerations

Meperidine crosses the human placenta. It significantly decreases the number of FHR accelerations intrapartum, and is associated with insufficient fetomaternal gas exchange and fetal acidemia. **Meperidine** achieves its highest concentration in fetal tissues 2-3h after administration, correlating with the clinical observation that the maximal risk of neonatal depression occurs 2-3h after maternal injection. Respiratory depression requiring resuscitation at delivery is a risk. The interval before neonatal respiration becomes sustained increases if **meperidine** is given more than 1h before delivery. The greater the drug-to-delivery interval, the higher the fetal concentration of normeperidine, and the lower the newborn's performance on the Brazelton Neonatal Behavioral Assessment Scale. Spontaneous behavior and cognitive performance in exposed rhesus monkeys at 3-12mo of age is altered by **meperidine.**

Breastfeeding Safety

Meperidine is excreted into human breast milk, with peak levels occurring about 2h after administration. While a single dose of **meperidine** has little impact on the nursing infant, repeated administration negatively affects the newborn. Nursing infants repeatedly exposed to **morphine** are more alert and oriented than those exposed repeatedly to **meperidine.** This makes **morphine** the preferred narcotic for lactating mothers.

Drug Interactions

Use with caution and consider starting with a lower dose in patients who are concurrently receiving other CNS depressants, including sedatives or hypnotics, general anesthetics, phenothiazines, other tranquilizers, and ethanol. Drug-drug interactions may result in respiratory depression, hypotension, profound sedation, or coma if these drugs are taken in combination with the usual doses of **meperidine.**
Employ caution giving an agonist-antagonist analgesics (e.g., **buprenorphine, butorphanol, nalbuphine, pentazocine**) to a patient who has had or is receiving a pure opioid agonist analgesic such as **meperidine.** Mixed agonist-antagonist analgesics may reduce the analgesic effect of **medperidine** and/or precipitate withdrawal symptoms.
Acyclovir may increase the plasma concentrations of **meperidine** and its metabolite, normeperidine.
Cimetidine both reduces the clearance and volume of distribution of **meperidine** and the formation of normeperidine in healthy subjects.
Phenytoin may enhance the hepatic metabolism of **meperidine,** and thus reduce its t/2 and bioavailability in healthy subjects.
Ritonavir increases the plasma concentrations of normeperidine and should be avoided.
May enhance the neuromuscular blocking action of skeletal muscle relaxants and produce an increased degree of respiratory depression.

References

Belfrage P, Boreus LO, Hartvig P, et al. Acta Obstet Gynecol Scand 1981; 60:43-9.

Chestnut DH. Reg Anesth 1997; 22:495-9.
Clark A, Carr D, Loyd G, et al. Am J Obstet Gynecol 1998; 179:1527-33.
Gambling DR, Sharma SK, Ramin SM, et al. Anesthesiology 1998; 89:1336-44.
Golub MS, Donald JM. Biol Neonate 1995; 67:140-8.
Head BB, Owen J, Vincent RD Jr, et al. Obstet Gynecol 2002; 99:452-7.
Herbst A, Wolner-Hanssen P, Ingemarsson I. Obstet Gynecol 1997; 90:125-30.
Kariniemi V, Rosti J. J Perinat Med 1986; 14:131-5.
Kuhnert BR, Kuhnert PM, Philipson EH, Syracuse CD. Am J Obstet Gynecol 1985; 151:410-5.
Kuhnert BR, Linn PL, Kennard MJ, Kuhnert PM. Anesth Analg 1985; 64:335-42.
Lurie S, Feinstein M, Heifetz C, Mamet Y. Int J Gynaecol Obstet 1999; 65:125-7.
Ngan Kee WD, Lam KK, Chen PP, Gin T. Anesth Analg 1997; 85:380-4.
Ngan Kee WD, Lam KK, Chen PP, Gin T. Anesthesiology 1996; 85:289-94.
Nguyen Thi TV, Orliaguet G, Ngu TH, Bonnet F. Reg Anesth 1994; 19:386-9.
Paech MJ, Moore JS, Evans SF. Anesthesiology 1994; 80:1268-76.
Peiker G, Muller B, Ihn W, Noschel H. Zentralbl Gynakol 1980; 102:537-41.
Ramin SM, Gambling DR, Lucas MJ, et al. Obstet Gynecol 1995; 86:783-9.
Sharma SK, Alexander JM, Messick G, et al. Anesthesiology 2002; 96:546-51.
Sharma SK, Sidawi JE, Ramin SM, et al. Anesthesiology 1997; 87:487-94.
Sheiner E, Shoham-Vardi I, Sheiner EK, et al. Arch Gynecol Obstet 2000; 263:95-8.
Solt I, Ganadry S, Weiner Z. Isr Med Assoc J 2002; 4:178-80.
Sosa CG, Balaguer E, Alonso JG, et al. Am J Obstet Gynecol 2004; 191:1212-8.
Sosa CG, Buekens P, Hughes JM, et al. Eur J Obstet Gynecol Reprod Biol 2006; 129:135-9.
Spigset O, Hagg S. Paediatr Drugs 2000; 2:223-38.
Thorp JA, Hu DH, Albin RM, et al. Am J Obstet Gynecol 1993; 169:851-8.
Vincent RD Jr, Chestnut DH. Am Fam Physician 1998; 58:1785-92.
Wittels B, Glosten B, Faure EA, et al. Anesth Analg 1997; 85:600-6.
Yoo KY, Lee J, Kim HS, Jeong SW. Anesth Analg 2001; 92:1006-9.

Summary

Pregnancy Category: B
Lactation Category: S (likely)

- There is a long clinical experience with **meperidine** during pregnancy and lactation that is reassuring overall.
- Repeated use during labor leads to the accumulation of **meperidine** and normeperidine in fetal tissues, reaching a maximum about 3h after administration.
- Neonatal depression may occur 2-3h after maternal administration.
- **Morphine** is preferred when postpartum analgesia is required in breastfeeding women.

Mephentermine—(This drug is not distributed in the US.)

International Brand Name—Mephentermin (Bulgaria); Mephentine (India); Wyamine (Czech Republic, Greece)

Drug Class	Adrenergic agonists; Pressors
Indications	Hypotension
Mechanism	Stimulates the release of NE/epinephrine
Dosage with Qualifiers	Hypotension shock—1mg/ml IV solution in D_5W; may also be given as a stock solution of 30mg/ml IV ×1 Hypotension spinal anesthesia—15mg IV push ×1; may be repeated in 30min; maintenance of BP accomplished by a continuous infusion of a 0.1% solution of **mephentermine** in D_5W (1mg/ml solution) • **Contraindications**—hypersensitivity to drug or class, hypotension induced by **chlorpromazine,** MAOI <14d • **Caution**—general anesthesia, CV diseases, hypertension, hyperthyroidism
Maternal Considerations	**Mephentermine** is a synthetic sympathomimetic used for treatment of hypotension. It increases stroke volume and thus increases both systolic and diastolic BP. There is also a variable degree of peripheral vasoconstriction. **Mephentermine** increases HR by the release of epinephrine. There are no adequate reports or well-controlled studies of **mephentermine** in pregnant women. It has been used during pregnancy to restore or support uteroplacental blood flow after spinal or epidural analgesia. Though a recent RCT concluded **ephedrine** and **mephentermine** had similar efficacy, it has largely been abandoned in favor of **ephedrine.** ***Side effects*** include nervousness, anxiety, arrhythmias, transient extrasystoles, AV block, and hypertension.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **mephentermine** crosses the human placenta. Rodent teratogenicity studies have not been performed. Studies in animals and humans reveal fetal hypoxia after **mephentermine** presumably secondary to uterine artery constriction and decreased uterine blood flow. Transient fetal hypertension (mean arterial BP >20% of control) is also reported.
Breastfeeding Safety	There is no published experience in nursing women. It is unknown whether **mephentermine** enters human breast milk.
Drug Interactions	Cyclopropane and **halothane** anesthetics increase cardiac automatic irritability and therefore seem to sensitize the myocardium to the action of catecholamine. Hence, use during cyclopropane and **halothane** anesthesia is generally considered contraindicated because of the risk of producing ventricular tachycardia or VF. The same type of cardiac arrhythmias may result from catecholamines in patients with profound hypoxia or hypercarbia.
References	Chestnut DH, Ostman LG, Weiner CP, et al. Anesthesiology 1988; 68:363-6. James FM 3rd, Greiss FC Jr, Kemp RA. Anesthesiology 1970; 33:25-34.

Kansal A, Mohta M, Sethi AK, et al. Anaesthesia 2005; 60:28-34.
Lauckner W, Schwarz R, Retzke U. Zentralbl Gynakol 1978; 100:217-21.
Ralston DH, Shnider SM, DeLorimier AA. Anesthesiology 1974; 40:354-70.
Senties L, Arellano G, Casellas A, et al. Am J Obstet Gynecol 1970; 107:892-7.

Summary

Pregnancy Category: C
Lactation Category: U

- **Mephentermine** is an alternative to **ephedrine** for the management or prevention of hypotensive episodes following spinal and epidural analgesia.

Mephenytoin—(This drug is not distributed in the US.)

International Brand Name—None identified.

Drug Class

Anticonvulsants; Hydantoins

Indications

Seizure disorder

Mechanism

Modulates neuronal voltage-dependent sodium and calcium channels

Dosage with Qualifiers

Seizure disorder—begin with 50-100mg qd and increase 50-100mg qw until desired effect; max 800mg/d in divided doses

- **Contraindications**—hypersensitivity to drug or class
- **Caution**—unknown

Maternal Considerations

Seizure control should be sought prior to pregnancy. **Mephenytoin** should be used only after safer anticonvulsants are given an adequate trial and failed. There are no adequate reports or well-controlled studies of **mephenytoin** in pregnant women. Drug clearance increases between preconception and the 2nd and 3rd trimesters. Thus, many pregnant women require higher doses to maintain therapeutic levels. **Mephenytoin** is no longer available in the US or the UK. It is still studied largely because of its interesting hydroxylation polymorphism.
Side effects include leukopenia, thrombocytopenia, agranulocytosis, pancytopenia, neutropenia, neuroleptic malignant syndrome, exfoliative dermatitis, Stevens-Johnson syndrome, pulmonary fibrosis, drowsiness, N/V, insomnia, dizziness, alopecia, weight gain, edema, photophobia, conjunctivitis, ataxia, diplopia, nystagmus, dysarthria, fatigue, irritability, choreiform movements, depression, tremor, nervousness, gum hyperplasia, and SLE.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **mephenytoin** crosses the human placenta. The great majority of mothers on anticonvulsant medication deliver normal infants. Rodent studies suggest that the other hydantoins may not have the same behavioral and teratogenic effects as **phenytoin.**

Breastfeeding Safety	There is no published experience in nursing women. It is unknown whether **mephenytoin** enters human breast milk.
Drug Interactions	See **Phenytoin.**
References	Minck DR, Acuff-Smith KD, Vorhees CV. Teratology 1991; 43:279-93. Wells PG, Kupfer A, Lawson JA, Harbison RD. J Pharmacol Exp Ther 1982; 221:228-34.
Summary	**Pregnancy Category: C** **Lactation Category: U** • **Mephenytoin** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk. • **Mephenytoin** should be used only after safer anticonvulsants are given an adequate trial and fail.

Mephobarbital

International Brand Name—Prominal (Australia, England, Spain)

Drug Class	Anticonvulsants; Barbiturates; Hypnotics; Sedatives
Indications	Seizure disorder (grand mal and petit mal epilepsy), anxiety
Mechanism	Alters sensory cortex, cerebellar, and motor activities; induces sedation, hypnosis, and anesthesia
Dosage with Qualifiers	Seizure disorder—400-600mg PO qd Anxiety—50mg PO tid or qid • **Contraindications**—hypersensitivity to drug or class, porphyria, psychological dependence on barbiturates • **Caution**—rickets, osteomalacia, vitamin K or C deficiencies, hepatic dysfunction
Maternal Considerations	Seizure control should be sought prior to pregnancy. There are no adequate reports or well-controlled studies of **mephobarbital** in pregnant women. Clearance is altered by pregnancy and may require frequent adjustment through the puerperium. **Mephobarbital** must be increased in 85% of pregnancies to maintain therapeutic levels. Barbiturates are hepatic enzyme inducers and alter the clearance of many other drugs. ***Side effects*** include drowsiness, sedation, hypnosis, marked excitement, depression, confusion, respiratory depression, erythema multiforme, Stevens-Johnson syndrome, angioedema, megaloblastic anemia, TTP, urticaria, blood dyscrasias, thrombophlebitis, necrosis, dependence, hepatitis, and swelling.
Fetal Considerations	There are no adequate reports or well-controlled studies of **mephobarbital** in human fetuses. Barbiturates rapidly cross the human placenta, reaching F:M ratios approaching unity. Retrospective case-control studies suggested a connection between the maternal consumption of barbiturates and a higher than expected incidence of fetal abnormalities. The great majority of women on anticonvulsant medication deliver normal infants. Rodent teratogenicity studies have not apparently been conducted with **mephobarbital.**

Breastfeeding Safety

There is no published experience in nursing women. It is unknown whether **mephobarbital** enters human breast milk. Small amounts of other barbiturates are excreted.

Drug Interactions

Most reports of clinically significant drug interactions with the barbiturates have involved **phenobarbital.** However, the application of this experience to other barbiturates appears valid and warrants serial blood level determinations of the relevant drugs when there are multiple therapies.

May lower the plasma levels of **dicumarol** (name previously used: **bishydroxycoumarin**), thus causing a decrease in the PT.

Barbiturates induce hepatic microsomal enzymes resulting in increased metabolism and decreased anticoagulant response to oral anticoagulants (e.g., acenocoumarol, **dicumarol,** phenprocoumon, **warfarin**). Patients stabilized on anticoagulant therapy may require dose adjustments should a barbiturate be added or withdrawn from their regimen.

May enhance the metabolism of exogenous corticosteroids, probably through the induction of hepatic microsomal enzymes. Patients stabilized on corticosteroid therapy may require dosage adjustments if barbiturates are added or withdrawn.

May interfere with the absorption of oral **griseofulvin,** decreasing the blood level.

May shorten the t/2 of **doxycycline,** probably through the induction of hepatic microsomal enzymes that metabolize the antibiotic, for as long as 2w after barbiturate therapy is discontinued. The clinical response to **doxycycline** should be monitored closely.

Because the effect of barbiturates on the metabolism of **phenytoin** is not predictable, **phenytoin** and barbiturate blood levels should be measured more frequently if these drugs are given concurrently. **Valproate** and **valproic acid** appear to decrease barbiturate metabolism; therefore, barbiturate blood levels should be monitored and appropriate adjustments made as indicated.

Use with other CNS depressants, including other sedatives or hypnotics, antihistamines, tranquilizers, or ethanol, may produce additive depressant effects.

MAOIs prolong the effects of barbiturates probably because metabolism of the barbiturate is inhibited.

Pretreatment or concurrent use may decrease the effect of **estradiol** by increasing its metabolism. There have been reports of women treated with **phenobarbital** who become pregnant while taking oral contraceptives.

References

Lander CM, Eadie MJ. Epilepsia 1991; 32:257-66.

Summary

Pregnancy Category: D
Lactation Category: U

- **Mephobarbital** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.
- There are alternative agents for which there is more experience during pregnancy and lactation.

Meprobamate—(Amosene; Atacin; Disatral; Equanil; Mepriam; Meproban-400; Meprospan; Miltown; Neuramate; Oasil-Simes; Probate; Procalmadiol; Sinanin; Trancot; Tranmep)

International Brand Name—Andaxin (Hungary); Ansiowas (Spain); Apo-Meprobamate (Canada); Atraxin (Japan); Distoncur (Argentina); Epikur (Austria); Harmonin (Japan); Meprin (Argentina); Mepro (Israel); Meprodil (Switzerland); Miltaun (Austria, Germany); Oasil (Belgium); Pertranquil (Austria, Belgium); Placidon (Argentina); Praol (Greece); Procalmidol (Belgium); Quanil (Italy); Restenil (Sweden); Sycropaz (Argentina); Visanon (Germany)

Drug Class	Anxiolytics
Indications	Anxiety
Mechanism	Unknown; has effects on multiple CNS sites, including thalamus and limbic system
Dosage with Qualifiers	Anxiety—400mg PO bid; max 2400mg/d • **Contraindications**—hypersensitivity to drug or class, alcohol consumption • **Caution**—job requiring driving or operating machinery
Maternal Considerations	There are no adequate reports or well-controlled studies of **meprobamate** in pregnant women. **Meprobamate** decreases clearance of alcohol in rodents during pregnancy. ***Side effects*** include dependence, ataxia, slurred speech, vertigo, anxiety, anorexia, insomnia, vomiting, tremors, muscle twitching, confusional states, hallucinosis, convulsive seizures, paresthesias, impairment of visual accommodation, euphoria, overstimulation, paradoxic excitement, palpitation, tachycardia, arrhythmia, transient ECG changes, syncope, hypotension, maculopapular rash, leukopenia, acute nonthrombocytopenic purpura, petechiae, ecchymoses, eosinophilia, peripheral edema, adenopathy, fever, anaphylaxis, exfoliative dermatitis, stomatitis, Stevens-Johnson syndrome, agranulocytosis, aplastic anemia, thrombocytopenic purpura, coma, shock, and vasomotor and respiratory collapse.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. **Meprobamate** crosses the human placenta. Several studies suggest an increased prevalence of malformations associated with the 1st trimester use of minor tranquilizers such as **meprobamate, chlordiazepoxide,** and **diazepam.** However, there was no clear evidence of either teratogenicity or fetotoxicity following attempted maternal suicide with very large doses. Monotherapy and the lowest effective quantity given in divided doses to minimize the peaks might minimize the risks. While rodent studies reveal that **meprobamate** reduces the learning ability of mature rodent offspring, this effect is not seen in humans.
Breastfeeding Safety	The small amount of **meprobamate** entering breast milk and ingested by the nursing newborn (~4% of the weight-adjusted maternal dose) does not pose a clinically significant risk.
Drug Interactions	No clinically significant interactions identified.
References	Belafsky HA, Breslow S, Hirsch LM, et al. Obstet Gynecol 1969; 34:378-86. Hartz SC, Heinonen OP, Shapiro S, et al. N Engl J Med 1975; 292:726-8.

Leonard BE. Arch Toxicol Suppl 1982; 5:48-58.
Nordeng H, Zahlsen K, Spigset O. Ther Drug Monit 2001; 23:298-300.
Rawat AK. Adv Exp Med Biol 1980; 132:561-8.
Rosenberg JM. N Y State J Med 1975; 75:1334-5.
Timmermann G, Acs N, Banhidy F, Czeizel AE. Toxicol Ind Health 2008; 24:97-107.

Summary

Pregnancy Category: D
Lactation Category: S

- **Meprobamate** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.
- It is rarely required during pregnancy and should be avoided at least during the 1st trimester.

Mercaptopurine—(Purinethol)

International Brand Name—Classen (Japan); Empurine (Philippines, Thailand); Ismipur (Italy); Leukerin (Japan); Mercaptopurina (Spain); Puri-Nethol (Austria, Belgium, Brazil, Bulgaria, China, Czech Republic, Denmark, Ecuador, England, Finland, Germany, Hong Kong, India, Indonesia, Ireland, Korea, Malaysia, Norway, Paraguay, Sweden, Switzerland, Taiwan, Thailand, Uruguay); Purinethol (Argentina, Australia, Canada, Chile, France, Greece, Italy, Mexico, Netherlands, Philippines, Poland, Russia)

Drug Class

Antineoplastics, antimetabolite; Immunomodulators

Indications

Leukemia (acute lymphocytic and acute myelogenous), Crohn's disease, ulcerative colitis

Mechanism

Unknown; multiple biochemical effects leading to cell death

Dosage with Qualifiers

Acute lymphocytic leukemia—numerous dosing schedules depending on disease, response, and concomitant therapy
AML—numerous dosing schedules depending on disease, response, and concomitant therapy
Crohn's disease—75-125mg PO qd; max 1.5mg/kg/d
Ulcerative colitis—begin with 50mg PO qd; typical dose 75-125mg PO qd; max 1.5mg/kg/d

NOTE: monitor CBC qw ×4 then qmo and LFTs q3mo after induction or during maintenance of remission; discontinue temporarily with evidence of an abnormally large decrease in WBC or platelet count, or Hb concentration.

- **Contraindications**—hypersensitivity to drug or class, renal dysfunction
- **Caution**—bone marrow suppression

Maternal Considerations

Mercaptopurine and **azathioprine** are the most commonly used immunomodulatory agents most commonly encountered during pregnancy in women with inflammatory bowel disease. Both drugs require caution. In addition to the listed indications, **mercaptopurine** is used as an adjunct to prevent organ rejection after transplantation. There are no adequate reports or well-controlled studies of **mercaptopurine** in pregnant women. Inflammatory bowel disease can be challenging. Women with quiescent disease are likely to have an uncomplicated pregnancy, whereas those with active disease are more likely to suffer spontaneous abortion, stillbirth, IUGR, and exacerbation of disease. In women considering pregnancy, an active episode should be treated aggressively and remission accomplished before

pregnancy is attempted. A woman who unexpectedly conceives while her disease is active should be treated aggressively, as remission provides the greatest hope for a favorable outcome. The treatment of AML typically involves a complex drug regimen that includes **mercaptopurine.** Multiple case reports suggest the use of **mercaptopurine** can produce a complete and sustained remission culminating in the delivery of a normally developed infant.

Side effects include leukopenia, thrombocytopenia, anemia, hepatotoxicity, urate nephropathy, nephrolithiasis, diarrhea, fever, N/V, anorexia, jaundice, abdominal pain, edema, and bleeding.

Fetal Considerations

There are no adequate reports or well-controlled studies of **mercaptopurine** in human fetuses. It likely crosses the human placenta as transient but severe neonatal bone marrow hypoplasia is reported. The impact of **mercaptopurine** use during the 1st trimester on development is controversial. Retrospective studies conclude there is no increased prevalence of anomalies. However, a more recent population-based cohort study concluded the risk of malformation is increased more than 6-fold. In a second recent report, the incidence of fetal loss was higher in women with inflammatory bowel disease previously treated with **mercaptopurine** compared to those who had not been so treated. Whether this was related to their older age at conception, longer duration of disease, initially more severe disease, or use of **mercaptopurine** could not be determined. Although it was suggested **mercaptopurine** increases the risk of spontaneous abortion, it proved a poor abortifacient in one prospective trial. Exposure during the 2nd and 3rd trimesters does affect the fetal immune system, and birth weight may be reduced. Toxic effects on the neonatal pancreas, liver, and lymphocytes are reported. Rodent studies reveal teratogenicity perhaps mediated by DNA modification or drug-induced changes in mineral metabolism (zinc). Malformations include cleft palate, micrognathia and agnathia, microglossia, short limbs, and gut herniation. Zinc supplementation reduces the risk of an adverse effect.

Breastfeeding Safety

There is no published experience in nursing women. It is unknown whether **mercaptopurine** enters human breast milk. Until such data become available, it is perhaps best to avoid immunosuppressive medications while breastfeeding.

Drug Interactions

Reduce the dose of **mercaptopurine** ⅓ to ¼ when **allopurinol** and **mercaptopurine** are used together to avoid severe toxicity.

There is usually complete cross-resistance between **mercaptopurine** and **thioguanine.**

Dose may need to be reduced if combined with other drugs whose primary or secondary toxicity is myelosuppression.

Enhanced marrow suppression has been noted in some patients also receiving **trimethoprim-sulfamethoxazole.**

Inhibition of the anticoagulant effect of **warfarin** has been reported when given with **mercaptopurine**.

There is *in vitro* evidence that aminosalicylate derivatives (e.g., **mesalamine, olsalazine, sulphasalazine**) inhibit the TPMT enzyme. They should be used cautiously in patients receiving **mercaptopurine.**

References

Amemiya K, Keen CL, Hurley LS. Teratology 1986; 34:321-34.
Davis AR, Miller L, Tamimi H, Gown A. Obstet Gynecol 1999; 93:904-9.
Francella A, Dyan A, Bodian C, et al. Gastroenterology 2003; 124:9-17.

Goldstein LH, Dolinsky G, Greenberg R, et al. Birth Defects Res A Clin Mol Teratol 2007; 79:696-701.
Little BB. Semin Perinatol 1997; 21:143-8.
Malganinos G, Gikas A, Delicha E, et al. Rev Med Chir Soc Nat Sasi 2007; 111:613-9.
Modigliani R. Eur J Gastroenterol Hepatol 1997; 9:854-7.
Nielsen OH, Vainer B, Rask-Madsen J. Aliment Pharmacol Ther 2001; 15:1699-708.
Nørgård B, Pedersen L, Christensen LA, Sørensen HT. Am J Gastroenterol 2007; 102:1406-13.
Norgard B, Pedersen L, Fonager K, et al. Aliment Pharmacol Ther 2003; 17:827-34.
Rajapakse R, Korelitz BI. Curr Treat Options Gastroenterol 2001; 4:245-51.
Ramsey-Goldman R, Schilling E. Rheum Dis Clin North Am 1997; 23:149-67.
Platzek T, Schwabe R, Rahm U, Bochert G. Chem Biol Interact 1994; 93:59-71.
Shah RM, Burdett DN. Can J Physiol Pharmacol 1979; 57:53-8.
Zlatanic J, Korelitz BI, Rajapakse R, et al. J Clin Gastroenterol 2003; 36:303-9.

Summary

Pregnancy Category: D
Lactation Category: U

- **Mercaptopurine** is one of the most commonly used drugs for the treatment of inflammatory bowel disease.
- Women with ulcerative colitis should be advised to conceive when their disease is quiescent.
- **Mercaptopurine** should be used during pregnancy only if the benefit justifies the potential perinatal risk. It is contraindicated during lactation.
- Zinc supplementation may reduce the risk of an adverse perinatal effect.

Meropenem—(Merrem IV)

International Brand Name—Mepem (Taiwan); Meronem (Colombia, Czech Republic, Denmark, England, Finland, Germany, Greece, Hong Kong, Hungary, Indonesia, Israel, Netherlands, Peru, Philippines, Spain, Sweden, Switzerland, Thailand); Meropen (Japan, Korea); Merrem (Canada, Mexico)

Drug Class

Antibiotics; Carbapenems

Indications

Bacterial infections (gram-positive aerobes: *S. pneumoniae, S. viridians;* gram-negative aerobes: *E. coli, H. influenzae* [β-lactamase and non–β-lactamase-producing], *Klebsiella pneumoniae, N. meningitidis, Pseudomonas aeruginosa;* anaerobes: *B. fragilis, B. thetaiotaomicron, Peptostreptococcus* species), appendicitis, peritonitis, bacterial meningitis

Mechanism

Bactericidal—inhibits bactericidal cell wall synthesis

Dosage with Qualifiers

Bacterial infections—*appendicitis:* 1g IV q8h; *peritonitis:* 1g IV q8h; *bacterial meningitis:* 2g IV q8h

NOTE: renal dosing.

- **Contraindications**—hypersensitivity to drug or class, penicillin allergy
- **Caution**—seizure disorder, renal dysfunction

Maternal Considerations

There are no adequate reports or well-controlled studies of **meropenem** in pregnant women. One multicenter study concluded **meropenem** is an effective and safe alternative to **clindamycin-gentamicin** for the treatment of women with acute obstetric infections. There is a case report of its successful use to treat pyogenic sacroiliitis in pregnancy.

Side effects include seizures, *C. difficile* colitis, back pain, abdominal pain, chest pain, sepsis, shock, fever, abdominal enlargement, hepatic failure, CHF, tachycardia, hypertension, MI, PE, bradycardia, hypotension, syncope, anemia, peripheral edema, hypoxia, insomnia, agitation, delirium, confusion, dizziness, seizure, renal failure, dysuria, dyspnea, injection site reaction, rash, pruritus, and constipation.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. **Meropenem** crosses the isolated perfused human placenta cotyledon. The mean F:M ratio is 0.04. Maternal and fetal mean **meropenem** peak concentrations are 54.3 ± 3.3 mcg/ml and 2.2 ± 0.18 mcg/ml, respectively, and mean trough concentrations are 12.7 ± 1.3 mcg/ml and 0.41 ± 0.10 mcg/ml, respectively. This makes it a poor candidate for fetal treatment. Rodent and monkey studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically.

Breastfeeding Safety

There is no published experience in nursing women. It is unknown whether **meropenem** enters human breast milk.

Drug Interactions

Probenecid inhibits the renal excretion of **meropenem** by competing for active tubular secretion. As a result, the elimination t/2 is increased by at least ⅓ and systemic exposure by ½. Therefore, use of **probenecid** with **meropenem** is not recommended.

May reduce serum levels of **valproic acid**.

References

Chimura T, Banzai M, Yamakawa M, et al. Jpn J Antibiot 2001; 54:491-6.

Chimura T, Murayama K, Oda T, et al. Jpn J Antibiot 2001; 54:1-7.

Hemsell DL, Martens MG, Faro S, et al. Clin Infect Dis 1997; 24(Suppl 2):S222-30.

Hnat M, Bawdon RE. Infect Dis Obstet Gynecol 2005; 13:223-7.

Summary

Pregnancy Category: B

Lactation Category: U

- **Meropenem** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.
- There are alternative agents for which there is more experience regarding use during pregnancy and lactation.

Mesalamine—(Asacol; Pentasa; Rowasa)

International Brand Name—5-ASA 400 (Argentina, Paraguay); Asacol (Belgium, Canada, Denmark, England, Finland, Greece, Israel, Italy, Mexico, Netherlands, New Zealand, Norway, Portugal, Singapore, South Africa, Sweden, Switzerland, Taiwan); Asacolitin (Germany); Asacolon (Colombia); Asalit (Brazil); Claversal (Austria, Belgium, Czech Republic, Germany, Italy, Portugal); Colitofalk (Belgium); Fivasa (France); Ipocol (England); Kenzomyl (Mexico); Mesacol (India, South Africa); Mesalin (Korea); Mesasal (Australia, Canada, Denmark, Norway); Mesren MR (England); Pentasa (Australia, Belgium, Canada, China, Denmark, England, France, Hong Kong, Malaysia, Netherlands, Norway, Philippines, Switzerland, Taiwan); Pentasa Enema (New Zealand); Pentasa SR (Korea); Pentasa Tab (New Zealand); Salofalk (Austria, Canada, Colombia, Germany, Hong Kong, Hungary, Indonesia, Ireland, Italy, Korea, Malaysia, Netherlands, Peru, Philippines, Switzerland, Thailand)

Drug Class ..... Gastrointestinals; Salicylates

Indications ..... Ulcerative colitis, Crohn's disease

Mechanism ..... Unknown

Dosage with Qualifiers .....

Ulcerative colitis—1000mg PO qid ×8w; alternatively, 4g PR qh ×3-6w
Crohn's disease—1000mg PO qid ×8w

- **Contraindications**—hypersensitivity to drug or class, hypersensitivity to salicylates
- **Caution**—renal or hepatic dysfunction, pyloric stenosis, bowel movement suppressants

Maternal Considerations .....

Inflammatory bowel disease can be challenging. Women with quiescent disease are likely to have an uncomplicated pregnancy, whereas those with active disease are more likely to suffer spontaneous abortion, stillbirth, IUGR, and exacerbation of disease. This is truer for patients with Crohn's disease than those with ulcerative colitis. In women considering pregnancy, an active episode should be treated aggressively and remission accomplished before pregnancy is attempted. A woman who unexpectedly conceives while her disease is active should be treated aggressively, as remission provides the greatest hope for a favorable outcome. **Mesalamine** is a by-product of 5-aminosalicylic acid bound to sulfapyridine. Most patients with adverse effects from **sulfasalazine** will tolerate **mesalamine. Mesalamine** is at least equivalent or superior to **sulfasalazine,** and superior to placebo, with a dose-response benefit, in inducing remission of acute inflammatory bowel disease. It is also comparable to **sulfasalazine** and superior to placebo for long-term maintenance of remission.
Side effects include bloody diarrhea, fever, headache, rash, anaphylaxis, thrombocytopenia, leukopenia, anemia, agranulocytosis, interstitial nephritis, peptic ulcer, nephropathy, myocarditis, hepatitis, peripheral neuropathy, Stevens-Johnson syndrome, headache, abdominal pain, dyspepsia, N/V, flatulence, constipation, asthenia, diarrhea, back pain, arthralgia, rhinitis, dry mouth, elevated LFTs, elevated BUN/Cr, dysmenorrhea, hair loss, and flu-like symptoms.

Fetal Considerations .....

There are no adequate reports or well-controlled studies in human fetuses. While it is unknown whether **mesalamine** crosses the human placenta, only trace amounts of the active metabolite, 5-aminosalicylic acid, can be found in the fetus. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically. Perhaps the greatest threat to a normal conception is active disease.

Inflammatory bowel disease is associated with increased prematurity and decreased birth weight (−330g, adjusted 95% CI: −509 to −150g, p <.001); the birth weight is even lower if **mesalamine** or steroids are required.

Breastfeeding Safety

There are no adequate reports or well-controlled studies in nursing women. While it is unknown whether **mesalamine** enters human breast milk, only trace amounts of its active metabolite, 5-aminosalicylic acid, are excreted.

Drug Interactions

No clinically relevant interactions identified.

References

Ambrosius Christensen L, Rasmussen SN, Hansen SH, et al. Acta Obstet Gynecol Scand 1987; 66:433-5.
Bell CM, Habal FM. Am J Gastroenterol 1997; 92:2201-2.
Christensen LA, Rasmussen SN, Hansen SH. Acta Obstet Gynecol Scand 1994; 73:399-402.
Diav-Citrin O, Park YH, Veerasuntharam G, et al. Gastroenterology 1998; 114:23-8.
Jenss H, Weber P, Hartmann F. Am J Gastroenterol 1990; 85:331.
Ludvigsson JF, Ludvigsson J. Acta Paediatr 2002; 91:145-51.
Marteau P, Tennenbaum R, Elefant E, et al. Aliment Pharmacol Ther 1998; 12:1101-8.
Mulder CJ, Tytgat GN, Weterman IT, et al. Gastroenterology 1988; 95:1449-53.
Saubermann LJ, Wolf JL. Inflamm Bowel Dis 1999; 5:148-9.
Schroeder KW. Scand J Gastroenterol Suppl 2002; 236:42-7.
Stein RB, Hanauer SB. Drug Saf 2000; 23:429-48.

Summary

Pregnancy Category: B
Lactation Category: S

- **Mesalamine** is a first-line agent for the treatment of inflammatory bowel disease during pregnancy.
- **Mesalamine** does not appear to pose a major teratogenic risk when used at recommended doses.

Mesoridazine—(Serentil)

International Brand Name—Mesorin (Korea)

Drug Class

Antipsychotics; Phenothiazines

Indications

Anxiety, alcoholism

Mechanism

Unknown; dopamine D_2 antagonist

Dosage with Qualifiers

Anxiety—30-150mg PO qd; max 150mg/d
Alcoholism—begin 25mg PO bid; max 200mg/d

- **Contraindications**—hypersensitivity to drug or class, cardiac arrhythmia, CNS depression, coma, prolonged QT interval, arrhythmia, hypotension, glaucoma, paralytic ileus, GI obstruction, bone marrow depression
- **Caution**—renal or hepatic dysfunction, CV disease, Parkinson's disease, seizure disorder, CNS depression

Maternal Considerations

Because of its proarrhythmic effect, **mesoridazine** is indicated for the management of schizophrenic patients who first fail to

respond adequately to other antipsychotic drugs. There are no adequate reports or well-controlled studies of **mesoridazine** in pregnant women.
Side effects include thrombocytopenia, leukopenia, aplastic anemia, agranulocytosis, neuroleptic malignant syndrome, dystonia, fever, laryngeal edema, angioneurotic edema, asthma, QT interval prolongation, torsades de pointes, arrhythmia, N/V, jaundice, biliary stasis, blurred vision, rash, tachycardia, tardive dyskinesia, phototoxicity, miosis, anorexia, and sudden death.

Fetal Considerations ..... There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **mesoridazine** crosses the human placenta. Rodent teratogenicity studies have not been performed.

Breastfeeding Safety ..... There is no published experience in nursing women. It is unknown whether **mesoridazine** enters human breast milk.

Drug Interactions ..... Drugs that prolong the QTc interval would likely be additive and are thus contraindicated.

References ..... There is no published experience in pregnancy or during lactation.

Summary .....

Pregnancy Category: C
Lactation Category: U
- **Mesoridazine** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.
- There are alternative agents for which there is more experience regarding use during pregnancy and lactation.

Mestranol—(Genora; Micronor; Nelova; Norethin; Norinyl; Ortho-Novum)

International Brand Name—Anamai (Thailand); Combiginor (Uruguay); Norace (Mexico); Norinyl-1 (England, Hong Kong, Ireland, Mexico, South Africa); Norinyl-1 28 (Australia, New Zealand, South Africa); Norinyl-28 (Mexico); Ortho-Novin (Israel); Ortho-Novum 1 50 (Austria, Canada, Germany, Israel, Netherlands, Switzerland)

Drug Class ..... Contraceptives; Estrogens; Hormones

Indications ..... Contraception, dysmenorrhea, dysfunctional uterine bleeding, endometriosis, polycystic ovary syndrome

Mechanism ..... Inhibits gonadotropin release, leading to anovulation and changes in the proprieties of cervical mucus and endometrium

Dosage with Qualifiers .....

Contraception—1 tab PO qd
Dysmenorrhea—1 tab PO qd
Dysfunctional uterine bleeding—1 tab PO qd
Endometriosis—1 tab PO qd
Polycystic ovary syndrome—1 tab PO qd

NOTE: combined with ***norethindrone.***

- **Contraindications**—hypersensitivity to drug or class, pregnancy, hepatic carcinoma, smoker >35y of age,

undiagnosed vaginal bleeding, breast cancer, endometrial cancer, CAD, stroke, history of hepatic dysfunction, or a history of cholestatic jaundice with other OCPs or pregnancy
- **Caution**—hepatic dysfunction, diabetes, hyperlipidemia, depression, breastfeeding, migraine

Maternal Considerations

Mestranol is the 3-methyl ether of **ethinyl estradiol.** An inactive prodrug, it was the estrogen used in many of the first oral contraceptives, and is the estrogen in several currently popular oral contraceptives. **Mestranol** is demethylated in the liver with a conversion efficiency of 70% (50mcg of **mestranol** is pharmacokinetically bioequivalent to 35mcg of **ethinyl estradiol**). The use of oral contraceptives containing **mestranol** is causally related to an increased incidence of benign liver adenomas and a decreased incidence of benign breast disease. These adenomas are not necessarily worsened by pregnancy. There is sufficient evidence in experimental animals to conclude **mestranol** is a potential carcinogen. Other estrogens are implicated as human carcinogens. It is now well recognized that there are differences in the physiologic responses to native and synthetic estrogens. There is no indication for **mestranol** during pregnancy and lactation. ***Side effects*** include thromboembolism, MI, stroke, hypertension, cholestatic jaundice, hepatic adenoma, N/V, abdominal pain, bloating, changes in menstrual flow, amenorrhea, breast tenderness, edema, migraine, weight changes, cervical secretions changes, emotional lability, headache, breakthrough bleeding, vaginal candidiasis, acne, rash, and glucose intolerance.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. The observation that maternal administration of **mestranol** inhibits **testosterone** synthesis in the rodent fetal testes suggests it crosses the rodent placenta. Limited rodent studies are otherwise reassuring, revealing no evidence of teratogenicity after early pregnancy exposure.

Breastfeeding Safety

There are no adequate reports or well-controlled studies in nursing women. **Mestranol** enters human breast milk, though the kinetics remain to be detailed. Lactation and infant weight gain are reduced when **mestranol** is given during the immediate postpartum period. As a result, it is generally considered incompatible with breastfeeding until the milk reflex is well established.

Drug Interactions

See **Ethinyl estradiol.**

References

Christensen SE, Andersen VR, Vilstrup H. Acta Obstet Gynecol Scand 1981; 60:519.
Varma SK, Bloch E. Acta Endocrinol 1987; 116:193-9.
Vido I, Cepicky P. Cesk Gynekol 1989; 54:654-61.
Wallace ME, Badr FM, Badr RS. J Med Genet 1979; 16:206-9.

Summary

Pregnancy Category: X
Lactation Category: NS
- **Mestranol** is an effective contraceptive when combined with a progestational agent.
- There are no indications for its use during pregnancy.

Metaproterenol—(Alupent; Arm-A-Med; Dey-Dose; Metaprel; Prometa)

International Brand Name—Alotec (Japan); Alupent (Austria, Bulgaria, Canada, Denmark, England, Finland, Germany, Greece, India, Indonesia, Ireland, Italy, Korea, Netherlands, Peru, Russia, Spain, Taiwan, Venezuela); Astmopent (Poland); Nonasma (Taiwan)

Drug Class	Adrenergic agonists; β_2-Agonists; Bronchodilators
Indications	Asthma
Mechanism	β_2-Adrenergic agonist
Dosage with Qualifiers	Asthma—2-3 puffs INH q3-4h; max 12 puffs/d; or 0.2-0.3ml 5% sol NEB q4h; or 20mg PO tid or qid *NOTE: available for inhalation, and for PO use as a tablet or syrup.* • **Contraindications**—hypersensitivity to drug or class, arrhythmia, tachycardia, hyperthyroidism, seizure disorder • **Caution**—hypertension, hypokalemia, heart disease, diabetes, cirrhosis, concomitant use of cardiac glycosides
Maternal Considerations	**Metaproterenol** is a bronchodilator popular during pregnancy for the treatment of asthma. Similar to other β-mimetic agents, **metaproterenol** increases pulse, lowers BP, and alters the ECG pattern. There are no adequate reports or well-controlled studies of **metaproterenol** in pregnant women. It has been used as a tocolytic agent (a.k.a. fenoterol, partusisten), but there is no evidence it provides any unique advantage. *In vitro,* β_2-adrenergic agonists are equally potent in inhibiting myometrial contractility as **nitroglycerin.** There are only case reports of its use during pregnancy in asthmatic women requiring ICU admission. **Metaproterenol**-saline solution irrigation is used for bronchoalveolar lavage to facilitate restoration of bronchial function. ***Side effects*** include tachycardia, nervousness, cardiac arrest, tremor, headache, palpitation, N/V, dizziness, asthma exacerbation, insomnia, and diarrhea.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. While it is unknown whether **metaproterenol** crosses the human placenta, other β-mimetic agents do. In rabbits, **metaproterenol** is a teratogen given at doses more than 50× the MRHD; there is no adverse effect on other rodents. Studies in animals and humans reveal no evidence that β_2-adrenergic agonists pose a CV risk for the fetus and neonate. It may be that β_2-adrenoreceptor ontogenesis is completed near term.
Breastfeeding Safety	There is no published experience in nursing women. It is unknown whether **metaproterenol** enters human breast milk.
Drug Interactions	Other β-adrenergic bronchodilators should not be used as they may have additive effects. β-Adrenergic agonists should be used cautiously in patients receiving MAOIs or TCAs, since the action of β-adrenergic agonists on the vascular system may be potentiated.
References	David M, Hamann C, Chen FC, et al. J Perinat Med 2000; 28:232-42.

Ivanov S. Akush Ginekol 1997; 36:9-10.
Kast A, Hermer M. J Perinat Med 1993; 2:97-106.
Schreier L, Cutler RM, Saigal V. Am J Obstet Gynecol 1989; 160:80-1.

Summary

Pregnancy Category: C
Lactation Category: U

- **Metaproterenol** is an effective bronchodilator for women with bronchial asthma and reversible bronchospasm.
- **Metaproterenol** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Metaraminol—(Aramine)

International Brand Name—Aramin (Brazil); Aramine (Belgium, Malaysia, Netherlands, Norway, Thailand); Fadamine (Argentina); Levicor (Greece, Italy)

Drug Class

Adrenergic agonists; α- and β-agonists

Indications

Shock

Mechanism

Mixed α- and β_1-adrenergic agonist

Dosage with Qualifiers

Shock—0.5-5mg IV

- **Contraindications**—hypersensitivity to drug or class, general anesthesia with **halothane** or cyclopropane
- **Caution**—CV disease, thyroid disease, diabetes, history of malaria

Maternal Considerations

Metaraminol is a potent sympathomimetic that increases both systolic and diastolic BP. There are no adequate reports or well-controlled studies of **metaraminol** in pregnant women. **Metaraminol** has been used to maintain arterial pressure during spinal anesthesia before cesarean delivery, and for CV support in women with septic shock. *In vitro,* **metaraminol** is a more potent constrictor of the uterine arteries than **ephedrine.** The effect is more pronounced in uterine compared to femoral arteries. For that reason, many prefer **ephedrine** prior to spinal anesthesia. However, a recent RCT suggests **metaraminol** given as a continuous infusion provides a superior clinical result compared to a continuous infusion of **ephedrine.** Confirmation of this study would be helpful.
Side effects include cardiac arrest, pulmonary edema, hypertension, seizures, arrhythmia, cerebral hemorrhage, anxiety, restlessness, dizziness, headache, N/V, flushing, pallor, and sweating.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **metaraminol** crosses the human placenta. Rodent teratogenicity studies have not been performed. Fetal bradycardia or late decelerations are well-recognized complications of untreated spinal/epidural analgesia–induced hypotension. They are a product of hypotension secondary to peripheral sympathetic blockade. In studies of spinal anesthesia, **metaraminol**-treated pregnancies may have a lower incidence of neonatal acidosis compared to **ephedrine.**

Breastfeeding Safety

There is no published experience in nursing women. It is unknown whether **metaraminol** enters human breast milk.

	However, considering the dose and route, it is unlikely the breastfed neonate would ingest clinically relevant amounts.
Drug Interactions	Use with caution in digitalized patients, as the combination may cause ectopic arrhythmias. MAOIs or TCAs may potentiate the action of sympathomimetic amines. The initial dose should be small when initiating pressor therapy, and given with caution.
References	Cavanagh D, McLeod AG. Am J Obstet Gynecol 1966; 96:913-8. James FM 3rd, Greiss FC Jr, Kemp RA. Anesthesiology 1970; 33:25-34. Ngan Kee WD, Khaw KS, Lee BB, et al. Anesth Analg 2001; 93:703-8. Ngan Kee WD, Khaw KS, Lee BB, et al. Br J Anaesth 2001; 87:772-4. Ngan Kee WD, Lau TK, Khaw KS, Lee BB. Anesthesiology 2001; 95:307-13. Speroff L. Am J Obstet Gynecol 1966; 95:139-51. Tong C, Eisenach JC. Anesthesiology 1992; 76:792-8.
Summary	**Pregnancy Category: C** **Lactation Category: S** (likely) • **Metaraminol** effectively maintains arterial pressure during spinal/epidural analgesia.

Metaxalone—(Skelaxin)

International Brand Name—None identified.

Drug Class	Muscle relaxants
Indications	Muscle spasm
Mechanism	Unknown
Dosage with Qualifiers	Muscle spasm—800mg PO tid or qid on an empty stomach • **Contraindications**—hypersensitivity to drug or class, hemolytic anemia • **Caution—**renal or hepatic dysfunction
Maternal Considerations	There is no published experience with **metaxalone** during pregnancy. ***Side effects*** include hemolytic anemia, leukopenia, hepatotoxicity, dizziness, drowsiness, light-headedness, paradoxical stimulation, abdominal pain, N/V, headache, and nervousness.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **metaxalone** crosses the human placenta. Rodent teratogenicity studies have not been performed. Post-marketing surveys do not suggest any increase in adverse fetal outcomes.
Breastfeeding Safety	There is no published experience in nursing women. It is unknown whether **metaxalone** enters human breast milk.
Drug Interactions	May enhance the effects of ethanol, barbiturates, and other CNS depressants.

References	There is no published experience in pregnancy or during lactation.
Summary	**Pregnancy Category: C** **Lactation Category: U** • **Metaxalone** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk. • There are alternative agents for which there is more experience regarding use during pregnancy and lactation.

Metformin—(Glucophage; Glucophage XR)

International Brand Name—Apophage (Israel); Benofomin (Indonesia); Dabex (Mexico); Denkaform (Philippines); Deson (Thailand); Dextin (South Africa); Diabetase (Germany); Diabetase S (Germany); Diabetformin (Peru); Diabetmin (Hong Kong, Malaysia); Diabetmin Retard (Hong Kong); Diabetol (Paraguay); Diabex (Australia, Indonesia); Diafat (Philippines); Diaformin (Australia, China, Hong Kong, Taiwan); Diaformina (Uruguay); Diaformina LP (Uruguay); Diametin (Philippines); Diamin (Singapore); Diformin (Finland, Korea); Diformin Retard (Finland); Dimefor (Brazil, Costa Rica, Dominican Republic, El Salvador, Guatemala, Honduras, Mexico, Nicaragua, Panama, Peru); Dybis (Korea); Eraphage (Indonesia); Espa-Formin (Germany); Euform Retard (Philippines); Formin (India); Fornidd (Philippines); Glafornil (Chile); Glibudon (Taiwan); Gliformin (Colombia, Indonesia); Glucaminol (Colombia); Glucofage (Ecuador, Venezuela); Glucofago (Peru); Glucoform (Philippines); Glucoformin (Brazil); Glucohexal (Australia); Glucoless (Thailand); Glucomet (Hong Kong, Thailand); Glucomin (Israel); Glucomine (Taiwan); Gluconil (Korea); Glucophage (Argentina, Austria, Belgium, Canada, Colombia, Czech Republic, Denmark, England, Finland, France, Greece, Hong Kong, India, Indonesia, Ireland, Italy, Malaysia, Norway, Peru, Philippines, Portugal, Russia, Spain, Sweden, Switzerland, Taiwan, Turkey); Glucophage Forte (Costa Rica, Czech Republic, Dominican Republic, El Salvador, Guatemala, Honduras, Mexico, Netherlands, Nicaragua, Panama, Philippines, South Africa); Glucophage-Mite (Germany); Glucophage Retard (Germany, Israel, Poland); Glucophage SR (England, Ireland); Glucotika (Indonesia); Gludepatic (Indonesia); Glufor (Indonesia, Israel); Gluformin (Thailand); Glumeformin (Korea); Glumet (Hong Kong, Philippines); Glumin (Indonesia); Glupa (Korea); Glustress (Thailand); Glyciphage (India); Glycomet (Singapore); Glycon (Canada); Glycoran (Singapore); Glyformin (Taiwan); Hipoglucin (Peru); I-Max (Philippines); Islotin (Argentina); Juformin (Germany); Maformin (Thailand); Meglucon (Germany); Melbin (Japan); Mescorit (Germany); Metfogamma (Germany); Metforal (Italy, Singapore); Metomin (New Zealand); Miformin (Thailand); Neoform (Philippines); Orabet (Austria, Denmark, England, Ireland); Reglus-500 (Indonesia); Siamformet (Thailand); Siofor (Bulgaria, Germany, Hungary); Thiabet (Germany); Vimetrol (Philippines); Walaphage (India)

Drug Class	Biguanides; Hypoglycemics
Indications	Diabetes mellitus type 2, PCOS
Mechanism	Increases insulin sensitivity, decreases hepatic glucose production and intestinal glucose absorption; decrease serum insulin and androgen levels
Dosage with Qualifiers	Diabetes mellitus—begin 850mg PO qd or 500mg PO bid; usual dose 850mg PO bid; max 2550mg/d. Alternatively, XR format; 500mg PO qd with evening meal, increase 500mg qw up to 2000mg qd. PCOS—500mg PO tid *NOTE: renal dosing; hold for iodinated contrast study.* • **Contraindications**—hypersensitivity to drug or class, renal or hepatic dysfunction, metabolic acidosis, CHF, acute MI, concurrent use of iodinated contrast • **Caution**—pulmonary disease, hepatic dysfunction
Maternal Considerations	**Metformin** is an insulin-sensitizing agent effective in women with PCOS who have significant insulin resistance. PCOS is one of the most common endocrinopathies with approximately 5% of women being affected. Seventy percent of those women taking only **metformin** and who ovulate conceive in less than 6mo. **Metformin** also improves the outcome of *in vitro* fertilization in women with **clomiphene**-resistant PCOS. There are no adequate

reports or well-controlled studies of **metformin** in pregnant women. **Metformin** therapy in women with PCOS is associated with a decreased rate of spontaneous abortions and an approximately 10-fold reduction in the incidence of gestational diabetes in case control studies. **Metformin** and **glyburide** are proposed as alternatives to **insulin** in controlling gestational diabetes. Their use remains exciting but investigational.
Side effects include flatulence, diarrhea, N/V, asthenia, indigestion, abdominal discomfort, headache, megaloblastic anemia, anorexia, altered taste, and rash.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses, though there is at least one RCT underway. **Metformin** crosses the isolated, perfused human placental cotyledon. The maternal-fetal transport rates for **metformin** and antipyrine were 10.61 ± 2.85% and 30.98 ± 5.62%, respectively. The clearance index, calculated as the ratio between the permeabilities of **metformin** and antipyrine, was 0.34 ± 0.05. It does not block placental glucose uptake and transport in the isolated perfused cotyledon model. In limited clinical study, **metformin** was not teratogenic, and did not adversely affect birth weight, height, weight, or motor and social development at 3 and 6mo of life. Newborns of women who had their serum glucose levels controlled by **metformin** do not develop hypoglycemic episodes more frequently than newborns delivered of women treated by **insulin** alone. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically. There is evidence of poor placental transport in the rat.

Breastfeeding Safety

Only 0.28% of the weight-normalized maternal dose of **metformin** enters human breast milk. In rodents, the **metformin** concentration in milk approaches that of the maternal plasma. This is well below the 10% level usually expected for the concentration to have a clinical impact.

Drug Interactions

A single-dose, pharmacokinetics **metformin-furosemide** study in healthy subjects revealed the parameters of both compounds were affected by co-administration. **Furosemide** increased the **metformin** plasma C_{max} by 22% and AUC by 15%, without any significant change in **metformin** renal clearance. When administered with **metformin,** the C_{max} and AUC of **furosemide** were 31% and 12% lower, and the terminal t/2 decreased by 32% without significant change in **furosemide** renal clearance.
Nifedipine increases plasma **metformin** C_{max} and AUC by 20% and 9%, respectively, and increases the amount excreted in the urine. **Nifedipine** appears to enhance the absorption of **metformin.**
Cationic drugs (e.g., **amiloride, digoxin, morphine, procainamide, quinidine, quinine, ranitidine, triamterene, trimethoprim, vancomycin**) eliminated by renal tubular secretion have the potential to interact with **metformin** by competing for common renal tubular transport systems. Such has been shown between **metformin** and **cimetidine** in healthy volunteers, with a 60% increase in peak **metformin** plasma and whole blood concentrations and a 40% increase in plasma and whole blood **metformin** AUC. Careful patient monitoring and dose adjustment of **metformin** and/or the interfering drug is recommended.
Certain drugs produce hyperglycemia and may lead to loss of glycemic control. These drugs include the thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products,

estrogens, oral contraceptives, **phenytoin,** nicotinic acid, sympathomimetics, calcium channel–blocking drugs, and **isoniazid.** When such drugs are administered to a patient receiving **metformin,** the patient should be closely observed for loss of blood glucose control.

References

Briggs GG, Ambrose PJ, Nageotte MP, et al. Obstet Gynecol 2005; 105:1437-41.
Coetzee EJ, Jackson WP. Diabetes Res Clin Pract 1986; 1:281-7.
Coetzee EJ, Jackson WP. S Afr Med J 1984; 65:635-7.
Elliott BD, Langer O, Schuessling F. Am J Obstet Gynecol 1997; 176:527-30.
Glueck CJ, Phillips H, Cameron D, et al. Fertil Steril 2001; 75:46-52.
Glueck CJ, Wang P, Goldenberg N, Sieve-Smith L. Hum Reprod 2002; 17:2858-64.
Glueck CJ, Wang P, Kobayashi S, et al. Fertil Steril 2002; 77:520-5.
Hale TW, Kristensen JH, Hackett LP, et al. Diabetologia 2002; 45:1509-14.
Heard MJ, Pierce A, Carson SA, Buster JE. Fertil Steril 2002; 77:669-73.
Kovo M, Haroutiunian S, Feldman N, et al. Eur J Obstet Gynecol Reprod Biol 2008; 136:29-33.
Legro RS. Minerva Ginecol 2002; 54:97-114.
Phipps WR. Obstet Gynecol Clin North Am 2001; 28:165-82.
Seli E, Duleba AJ. Curr Opin Obstet Gynecol 2002; 14:245-54.
Stadtmauer LA, Toma SK, Riehl RM, Talbert LM. Reprod Biomed Online 2002; 5:112-6.

Summary

Pregnancy Category: B
Lactation Category: S

- **Metformin** therapy throughout pregnancy in women with PCOS reduces the high rate of 1st trimester spontaneous abortion and gestational diabetes.
- It may be a useful adjunct when **glyburide** alone fails to achieve euglycemia.
- Further studies are necessary to determine whether **metformin** and other hypoglycemic agents will be safe and effective in women with gestational diabetes.

Methacholine—(Provocholine)

International Brand Name—Provocholine (Canada)

Drug Class

Cholinergics; Diagnostics, nonradioactive

Indications

Diagnosis of bronchial airway hyperreactivity

Mechanism

Stimulates cholinergic receptors

Dosage with Qualifiers

Diagnosis of bronchial airway hyperreactivity—5 breaths (NEB); measure FEV_1 at baseline and after 5 breaths
NOTE: diagnostic purpose only. **Methacholine** inhalation challenge should be performed only under the supervision of a physician trained in and thoroughly familiar with all aspects of the technique.

- **Contraindications**—hypersensitivity to drug or class, asthma, concurrent usage of β-blocker, $FEV_1 < 70\%$
- **Caution**—CV disease, epilepsy, thyroid disease

Maternal Considerations	**Methacholine** is the β-methyl homolog of ACh and differs primarily in its greater duration and selectivity. It is more slowly hydrolyzed by acetylcholinesterase and is almost totally resistant to nonspecific cholinesterase or pseudocholinesterase inactivation. There are no adequate reports or well-controlled studies of **methacholine** in pregnant women. Pregnancy is associated with an improvement in airway responsiveness in asthmatic women. ***Side effects*** include respiratory distress, headache, lightheadedness, chest tightness, dyspnea, cough, throat irritation, wheezing, and pruritus.
Fetal Considerations	There are no adequate reports or well-controlled studies of **methacholine** in human fetuses. Rodent teratogenicity studies have not been conducted. Based on its physiologic actions, it is unlikely limited exposure to **methacholine** during a diagnostic procedure would pose a significant risk to the fetus.
Breastfeeding Safety	There is no published experience in nursing women. It is unknown whether **methacholine** enters human breast milk. However, considering the dose and route, it is unlikely the breastfed neonate would ingest clinically relevant amounts.
Drug Interactions	No clinically significant interactions identified.
References	Juniper EF, Daniel EE, Roberts RS, et al. Am Rev Respir Dis 1989; 140:924-31.
Summary	**Pregnancy Category: C** **Lactation Category: S** (likely) • **Methacholine** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Methadone—(Dolophine; Dolophine HCL; Methadone HCl; Methadose; Tussol; Westadone)

International Brand Name—Amidona (Chile); Biodone (New Zealand); Biodone Extra Forte (New Zealand); Biodone Forte (New Zealand); Depridol (Hungary); Dolmed (Finland); Eptadone (Italy); Gobbidona (Argentina); L-Polamidon (Germany); Mephenon (Belgium); Metadol (Canada, Peru); Metadon (Brazil, Denmark, Sweden, Uruguay); Metasedin (Spain); Methaddict (Germany); Methadose (Colombia); Methaforte Mix (New Zealand); Pallidone (New Zealand); Physeptone (Australia, England, Hong Kong, Ireland, South Africa); Symoron (Netherlands)

Drug Class	Analgesics, narcotic
Indications	Pain, opiate addiction
Mechanism	Partial opiate receptor agonist
Dosage with Qualifiers	Pain—2.5-10mg PO q3-4h Opiate addiction—15-20mg PO qd; max 120mg qd Opiate addiction maintenance therapy—20-120mg PO qd *NOTE: equianalgesic: PO = 2× IV dose.* • **Contraindications**—hypersensitivity to drug or class • **Caution**—renal or hepatic dysfunction; hypothyroidism; Addison's disease; acute abdominal pain; concomitant use of **rifampin, pentazocine, desipramine,** or MAOIs

■ Maternal Considerations

Methadone is a synthetic narcotic analgesic with many actions quantitatively similar to **morphine** except its intense euphoria. **Methadone** is a first-line agent for the treatment of heroin addiction. The goal of maintenance is to relieve the narcotic craving, suppress withdrawal, and block the euphoric effects associated with **heroin.** The majority of patients require 80-120mg/d or more. Treatment continues for an indefinite period of time. Illicit drug use during pregnancy is a major perinatal health issue worldwide. Some 200,000 addicted infants are born each year in the US. Because most drug-addicted women use a variety of illicit agents, the impact of **methadone** alone is difficult to ascertain. That said, **methadone** exposure during the entire gestational period is associated with better drug-treatment outcomes (less illicit drug use) but no greater prevalence of severe neonatal abstinence syndrome than women who begin methadone in the 2nd or 3rd trimester. **Methadone** is nonsedating. A major problem with opiate-addicted women is postoperative pain management. **Methadone**-maintained women have similar analgesic needs and responses during labor, but require 70% more opiate analgesic after cesarean delivery. It is generally recommended that **methadone** treatment be continued while short-acting narcotics are given as necessary (preferably on a fixed schedule) to relieve the pain. The elimination rate of **methadone** is higher and the t/2 lower during pregnancy, perhaps because of a decrease in the fraction absorbed. **Methadone** is not recommended for obstetric analgesia because its long duration of action increases the probability of neonatal respiratory depression. Patients maintained on this drug react to life problems and stresses with the same symptoms of anxiety as do others. Do not confuse such symptoms with those of withdrawal and try to treat anxiety by increasing the dose of **methadone.** The action of **methadone** in maintenance treatment is limited to the control of narcotic withdrawal symptoms and is ineffective for relief of general anxiety. Maintenance patients on a stable dose of **methadone** who experience physical trauma, postoperative pain, or other acute pain will not derive analgesia from their ongoing dose of **methadone.** Instead, they should be administered analgesics, including opioids, in doses that would otherwise be indicated for non–methadone-treated patients with similar painful conditions. Due to the opioid tolerance induced by **methadone,** somewhat higher and/or more frequent doses will often be required than would be the case for nontolerant patients when opioids are required.

Side effects include euphoria, dysphoria, weakness, insomnia, agitation, visual disturbances, headache, disorientation, seizures, shock, cardiac arrest, respiratory depression or arrest, dizziness, sedation, N/V, sweating, dry mouth, flushing, urinary retention, rash, and thrombocytopenia.

■ Fetal Considerations

Methadone crosses the human placenta; however, transfer in the fetal-to-maternal direction is 10-15% greater than in the maternal-to-fetal direction, suggesting involvement of P-glycoprotein. Daily maternal maintenance treatment reduces fetal breathing and total fetal activity. Trough mean plasma **methadone** concentrations decline as gestation progresses from 0.12mg/L in the 1st trimester to 0.07mg/L in the 3rd trimester. The weight-adjusted clearance rates gradually increase from a mean of 0.17 to 0.21L/hr/kg during pregnancy, although patterns differed substantially among women. Women (and rodents) who continue **heroin** use throughout pregnancy have a greater likelihood of preterm birth and IUGR. Infants whose mothers are on **methadone** maintenance have higher mean birth weights and head circumferences than those of untreated addicted women.

It is not associated with respiratory depression. However, the withdrawal is more intense in the **methadone**-treated group compared to **heroin**-exposed babies without **methadone** treatment (convulsions 47.1% vs. 27.1%). Maternal **methadone** dosage is related to the duration of neonatal hospitalization, neonatal abstinence score, and treatment for withdrawal. Interestingly, neonates who undergo withdrawal have almost undetectable concentrations of **methadone** in their umbilical cord blood. Heroin supplementation does not alter this dose-response relationship. In one study of selected pregnancies, lowering the maternal **methadone** dose was associated with both a decreased incidence and severity of neonatal withdrawal. Other case-control study conclude that the maternal **methadone** level does not correlate with neonatal withdrawal. If true, the maternal benefits of effective **methadone** dosing would not be offset by neonatal harm. **Methadone** does not appear detrimental for fetal brain development. Some reports suggest an increased incidence of SIDS in neonates delivered of mothers who use **methadone** during pregnancy. This association may be more circumstantial.

Breastfeeding Safety

Only small quantities of **methadone** are excreted into human breast milk. It is estimated the average newborn would ingest only 0.05mg **methadone** per day, an amount too small to reliably prevent neonatal withdrawal. The risk of an adverse event with either breastfeeding or weaning is low. Newborns of narcotics abusers are at risk for withdrawal despite being breastfed by their **methadone**-using mother. Pregnant women on methadone maintenance therapy are to be encouraged to nurse if they are HIV-negative.

Drug Interactions

Users may experience withdrawal symptoms when given an antagonist or partial antagonist (e.g., **buprenorphine, butorphanol, nalbuphine, naloxone, naltrexone, pentazocine**).
Use of **abacavir, amprenavir, efavirenz, nelfinavir, nevirapine, ritonavir,** or the **lopinavir-ritonavir** combination increases the clearance and decreases the plasma levels of **methadone.**
Methadone decreases both the AUC and peak levels of **didanosine** and **stavudine,** with a more significant decrease for **didanosine.**
Increases the AUC of **zidovudine,** which could result in toxic effects.
In vitro studies suggest hepatic *N*-demethylation by CYP3A4, CYP2B6, CYP2C19, and to a lesser extent CYP2C9 and CYP2D6. Use with inducers of these enzymes may result in a more rapid metabolism and decreased efficacy, whereas use with inhibitors may reduce metabolism and potentiate **methadone's** effects.
Rifampin markedly reduces **methadone** levels and and increases the prevalence of withdrawal symptoms.
Phenytoin (250mg bid initially for 1d, followed by 300mg qd for 3-4d) causes a 50% reduction in **methadone** exposure and a concurrent increase in withdrawal symptoms. Upon discontinuation of **phenytoin,** the incidence of withdrawal symptoms declines and the **methadone** level increases to that prior to **phenytoin.**
Methadone-treated patients using strong inhibitors of CYP3A4, such as azole antifungal agents (e.g., **ketoconazole**), should be carefully monitored and the dose reduced if warranted. Some SSRIs (e.g., **fluvoxamine, sertraline**) may increase **methadone** levels with a resultant increase in opiate effects and/or toxicity.
Repeat doses of **voriconazole** (400mg q12h for 1d, then 200mg q12h for 4d) increases the C_{max} and AUC of (*R*-)**methadone** by 31% and 47%, respectively, in subjects receiving **methadone**

maintenance (30-100mg qd). The C_{max} and AUC of (*S*-)**methadone** increases by 65% and 103%, respectively. Increased concentrations of **methadone** have been associated with toxicity, including QT prolongation. Frequent monitoring for adverse events and toxicity related to **methadone** is recommended during co-administration.

Meperidine may trigger severe reactions in patients concurrently receiving or who have received MAOIs within 14d. While similar reactions have not been reported with **methadone,** a sensitivity test should be performed during which repeated small, incremental doses of **methadone** are administered over the course of several hours.

May increase blood levels of **desipramine.**

Extreme caution is necessary when any drug known to potentially prolong the QT interval is prescribed in conjunction with **methadone.** Pharmacokinetic/pharmacodynamic interactions may occur with concomitant use of **methadone** and arrhythmogenic agents such as class I and III antiarrhythmics, some neuroleptics and TCAs, and calcium channel blockers.

Caution should also be exercised when prescribing **methadone** with drugs capable of inducing electrolyte disturbances (hypomagnesemia, hypokalemia) that may prolong the QT interval. These drugs include diuretics, laxatives, and, in rare cases, mineralocorticoid hormones.

Can have additive effects when used in conjunction with ethanol, other opioids or CNS depressants, or illicit drugs that cause CNS depression. Deaths have been reported when **methadone** was abused in conjunction with benzodiazepines.

References

Begg EJ, Malpas TJ, Hackett LP, Ilett KF. Br J Clin Pharmacol 2001; 52:681-5.

Berghella V, Lim PJ, Hill MK, et al. Am J Obstet Gynecol 2003; 189:312-7.

Dashe JS, Sheffield JS, Olscher DA, et al. Obstet Gynecol 2002; 100:1244-9.

Geraghty B, Graham EA, Logan B, Weiss EL. J Hum Lact 1997; 13:227-30.

Gressens P, Mesples B, Sahir N, et al. Semin Neonatol 2001; 6:185-94.

Hulse GK, O'Neill G. Aust N Z J Obstet Gynaecol 2001; 41:329-32.

Jarvis MA, Wu-Pong S, Kniseley JS, Schnoll SH. J Addict Dis 1999; 18:51-61.

Joseph H, Stancliff S, Langrod J. Mt Sinai J Med 2000; 67:347-64.

Kunko PM, Smith JA, Wallace MJ, et al. J Pharmacol Exp Ther 1996; 277:1344-51.

Kuschel CA, Austerberry L, Cornwell M, et al. Arch Dis Child Fetal Neonatal Ed 2004; 89:F390-3.

Langlois NE, Ellis PS, Little D, Hulewicz B. Am J Forensic Med Pathol 2002; 23:162-6.

Lim S, Prasad MR, Samuels P, et al. Am J Obstet Gynecol 2008; Oct 29 Epub.

McCarthy JJ, Leamon MH, Stenson G, Biles LA. J Subst Abuse Treat 2008; 35:202-6.

McCarthy JJ, Posey BL. J Hum Lact 2000; 16:115-20.

Meyer M, Wagner K, Benvenuto A, et al. Obstet Gynecol 2007; 110:261-6.

Nekhayeva IA, Nanovskaya TN, Deshmukh SV, et al. Biochem Pharmacol 2005; 69:187-97.

Pierson PS, Howard P, Kleber HD. JAMA 1972; 220:1733-4.

Sarman I. Lakartidningen 2000; 97:2182-4, 2187-8, 2190.

Scimeca MM, Savage SR, Portenoy R, Lowinson J. Mt Sinai J Med 2000; 67:412-22.
Sinha C, Ohadike P, Carrick P, et al. Int J Gynaecol Obstet 2001; 74:241-6.
Swift RM, Dudley M, DePetrillo P, et al. J Subst Abuse 1989; 1:453-60.
Wolff K, Boys A, Rostami-Hodjegan A, et al. Eur J Clin Pharmacol 2005; 61:763-8.
Woulides TA, Roberts AB, Pryor JE, et al. Neurotoxicol Teratol 2004; 26:23-34.
Ziegler M, Poustka F, von Loewenich V, Englert E. Nervenarzt 2000; 71:730-6.

Summary

Pregnancy Category: B
Lactation Category: S

- **Methadone** maintenance is not a curative treatment for heroin addiction and should be undertaken only in specialized centers.
- **Methadone** maintenance reduces and/or eliminates the use of heroin, reduces the death rates and criminality associated with heroin use, and allows patients to improve their health and social productivity.
- Enrollment in a **methadone** maintenance program has the potential to reduce the transmission of infectious diseases associated with heroin injection.

Methamphetamine—(Desoxyn; Methampex)

International Brand Name—Cidrin (Chile)

Drug Class

Amphetamines; Anorexiants; CNS stimulants

Indications

ADD, weight loss, narcolepsy

Mechanism

Appetite suppression and CNS stimulation

Dosage with Qualifiers

ADD—20-25mg PO qd
Weight loss—5-10mg PO tid; treatment should not exceed few weeks
Narcolepsy—5-60mg/d in divided doses

- **Contraindications**—hypersensitivity to drug or class, glaucoma, arteriosclerosis, CV disease, severe hypertension, hyperthyroidism, agitation, drug abuse
- **Caution**—hypertension

Maternal Considerations

Methamphetamine is a CNS stimulant that has no medical indications during pregnancy. The illicit use of **methamphetamine,** also called *crystal meth* or *speed,* is a major health care problem in some locales. It may be injected, smoked, snorted, or ingested orally. Prolonged use leads to dependence. Five-10% of adolescents have tried **methamphetamine** and its use is associated with risky sexual behaviors. The use of a variant, Ecstasy (3,4-methylenedioxymethamphetamine) is also becoming more common during pregnancy. Maternal death occurs with usage. Ecstasy users during pregnancy tend to be young and single, report psychological morbidity, and have a higher rate of unplanned pregnancies and a higher likelihood of using other

potentially harmful substances (smoking, heavy alcohol intake, and polydrug usage).
Side effects include tachycardia, palpitation, dizziness, dysphoria, overstimulation, euphoria, insomnia, tremor, restlessness, headache, diarrhea, constipation, dry mouth, unpleasant taste, urticaria, decreased libido, stroke, cardiac arrhythmia, stomach cramps, shaking, anxiety, paranoia, hallucinations, structural changes to the brain, and suppression of growth.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. **Methamphetamine** crosses the human placenta and produces significant and long-lasting maternal and fetal CV effects, including a decrease in fetal PaO_2 after maternal administration. The latter reflects decreased uteroplacental perfusion, whereas the observed changes in fetal BP and fetal pH are a direct result of **methamphetamine.** Children of abusers are at risk for IUGR and preterm birth. Antenatal **methamphetamine** exposure is associated with postnatal developmental disorders associated with neuronal damage, enduring cognitive deficits, and greater risks of neglect and abuse postnatally. Children exposed to **methamphetamine** antenatally have smaller subcortical volumes and associated neurocognitive deficits compared with a control group. These changes are also associated with abnormalities of brain energy metabolism. The neuronal damage may be mediated by free radical formation, affect the serotoninergic and MAO systems, and differ by fetal gender. Rodent studies reveal embryotoxicity and an increased incidence of microcephaly, NTDs, incomplete rotation of the body axis, and a tortuous spinal cord. Increased frequencies of clefting, cardiac anomalies, and IUGR are reported in humans. Reliable and sensitive screening procedures are available using meconium or hair to identify antenatal exposure to illicit drugs.

Breastfeeding Safety

There is no published experience in nursing women. It is unknown whether **methamphetamine** enters human breast milk.

Drug Interactions

May alter **insulin** requirements in association with decreased dietary intake.
May decrease the hypotensive effect of **guanethidine**.
MAOIs are contraindicated.
Use of TCAs and indirect-acting sympathomimetic amines such as the amphetamines should be closely supervised and dosage carefully adjusted.
Phenothiazines are reported to antagonize the CNS stimulant action of amphetamines.

References

Anglin MD, Burke C, Perrochet B, et al. J Psychoactive Drugs 2000; 32:137-41.
Catanzarite VA, Stein DA. West J Med 1995; 162:454-7.
Chang L, Smith LM, LoPresti C, et al. Psychiatry Res 2004; 132:95-106.
De Vito MJ, Wagner GC. Psychopharmacology (Berl) 1989; 97:432-5.
Garcia-Bournissen F, Rokach B, Karaskov T, Koren G. Arch Dis Child Fetal Neonatal Ed 2007; 92:F351-5.
Ho E, Karimi-Tabesh L, Koren G. Neurotoxicol Teratol 2001; 23:561-7.
Moriya F, Chan KM, Noguchi TT, Wu PY. J Anal Toxicol 1994; 18:41-5.
Perez JA Jr, Arsura EL, Strategos S. J Emerg Med 1999; 17:469-71.
Plessinger MA. Obstet Gynecol Clin North Am 1998; 25:119-38.

Smith LM, Chang L, Yonekura ML, et al. Neurology 2001; 57:255-60.
Stek AM, Baker RS, Fisher BK, et al. Am J Obstet Gynecol 1995; 173:1592-8.
Stek AM, Fisher BK, Baker RS, et al. Am J Obstet Gynecol 1993; 169:888-97.
Stewart JL, Meeker JE. J Anal Toxicol 1997; 21:515-7.
Yamamoto Y, Yamamoto K, Hayase T, et al. Reprod Toxicol 1998; 12:133-7.
Zapata LM, Hillis SD, Marchbanks PA, et al. J Sch Health 2008; 78:641-8.

Summary

Pregnancy Category: C
Lactation Category: U

- **Methamphetamine** is the most common illicitly abused amphetamine; it can be inhaled, injected IV, or smoked. More and more pregnant women report use of 3,4-methylene-dioxymethamphetamine (Ecstasy) during pregnancy.
- **Methamphetamine** increases the risk of adverse outcome and congenital malformations.

Methantheline—(Banthine)

International Brand Name—Vagantin (Germany)

Drug Class

Anticholinergics; Gastrointestinals

Indications

Peptic ulcer, adjunctive treatment

Mechanism

Cholinergic antagonist; reduces GI motility and gastric acid secretion

Dosage with Qualifiers

Peptic ulcer—50-100mg PO qid; may decrease dose to 25-50mg for maintenance therapy

- **Contraindications**—hypersensitivity to drug or class, glaucoma, achalasia, paralytic ileus, bowel obstruction, pyloric stenosis, ulcerative colitis, toxic megacolon, myasthenia gravis
- **Caution**—autonomic neuropathy, hepatic or renal disease, CAD, CHF, tachyarrhythmias, hypertension, hiatal hernia, hyperthyroidism

Maternal Considerations

There is one old report of the use of **methantheline** to treat N/V of pregnancy.
Side effects include drowsiness, blurred vision, dry mouth, decreased sweating, mydriasis, cycloplegia, increased ocular tension, tachycardia, palpitations, loss of the sense of taste, headache, nervousness, mental confusion, weakness, dizziness, insomnia, N/V, constipation, bloated feeling, suppression of lactation, and urticaria.

Fetal Considerations

There are no published studies in human fetuses. It is unknown whether **methantheline** crosses the human placenta. Rodent teratogenicity studies have not been performed.

Breastfeeding Safety

There is no published experience in nursing women. It is unknown whether **methantheline** enters human breast milk.

Drug Interactions

Anticholinergics may delay absorption of other medication. Use with belladonna alkaloids, synthetic or semisynthetic anticholinergic agents, narcotic analgesics (e.g., **meperidine**), class 1 antiarrhythmic drugs (e.g., **disopyramide, procainamide, quinidine**), antihistamines, phenothiazines, TCAs, or other psychoactive drugs may lead to excessive cholinergic blockade. May potentiate the sedative effect of phenothiazines. Increased intraocular pressure may result from concurrent administration of anticholinergics and corticosteroids. Use with slow-dissolving tablets of **digoxin** may cause increased serum **digoxin** levels. This interaction can be avoided by using only those **digoxin** tablets that rapidly dissolve by USP standards.

References

Weber JE, Fetchko AM, Corcoran AW, Carroll JH. Am J Obstet Gynecol 1953; 66:602-6.

Summary

Pregnancy Category: C
Lactation Category: U

- **Methantheline** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.
- There are alternative agents for which there is more experience during pregnancy and lactation.

Methazolamide—(MZM; Neptazane)

International Brand Name—Glaumetax (Argentina); Mezomin (Korea)

Drug Class

Carbonic anhydrase inhibitors

Indications

Glaucoma

Mechanism

Carbonic anhydrase inhibitor

Dosage with Qualifiers

Glaucoma—50-100mg bid or tid; may be used concomitantly with miotic and osmotic agents

- **Contraindications**—hypersensitivity to drug or class, hyponatremia, hypokalemia, depressed respiratory function, cirrhosis, hyperchloride acidosis, adrenocortical insufficiency
- **Caution**—cirrhosis, hepatic dysfunction, pulmonary obstruction, emphysema

Maternal Considerations

There is no published experience with **methazolamide** during pregnancy. It is well absorbed orally.
Side effects include aplastic anemia, Stevens-Johnson syndrome, toxic epidermal necrolysis, fulminant hepatitis, paresthesias, hearing dysfunction, tinnitus, fatigue, malaise, loss of appetite, taste alteration, N/V, diarrhea, drowsiness, confusion, metabolic acidosis, electrolyte imbalance, dyspepsia, and polyuria.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **methazolamide** crosses the human placenta. **Methazolamide** causes skeletal abnormalities in rodents when given at high multiples of the MRHD.

Breastfeeding Safety

There is no published experience in nursing women. It is unknown whether **methazolamide** enters human breast milk.

Drug Interactions

Steroid use may lead to hypokalemia.
Anorexia, tachypnea, lethargy, coma, and death have been reported with the combined use of high-dose **aspirin** and carbonic anhydrase inhibitors.

References

There is no published experience in pregnancy or during lactation.

Summary

Pregnancy Category: C
Lactation Category: U
- **Methazolamide** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Methenamine—(Hexydal; Lemandine; Mandameth; Mandelamine; Metanamin; Methenamine)

International Brand Name—Haiprex (Denmark); Hipeksal (Finland); Hippramine (Puerto Rico, South Africa); Hippuran (Sweden); Hip-Rex (Canada); Hiprex (Austria, Belgium, Costa Rica, Dominican Republic, El Salvador, England, Finland, Guatemala, Honduras, Ireland, Israel, New Zealand, Norway, Oman, Panama, Philippines, Sweden, United Arab Emirates); Urotractan (Germany)

Drug Class

Antibiotics; Urologics

Indications

Bacterial infections (gram-positive aerobes: *S. pneumoniae, S. viridans;* gram-negative aerobes: *E. coli, Klebsiella, Enterobacter, P. mirabilis, Morganella morganii*); urinary tract infection

Mechanism

Bactericidal; hydrolyzed to ammonia and bactericidal formaldehyde

Dosage with Qualifiers

Bacterial infections, urinary—1g PO qid

NOTE: ineffective for some infections with P. vulgaris and urea-splitting strains of Pseudomonas aeruginosa and A. aerogenes.

- **Contraindications**—hypersensitivity to drug or class, renal insufficiency, hypovolemia, sulfonamide usage
- **Caution**—unknown

Maternal Considerations

There are no adequate reports or well-controlled studies of **methenamine** in pregnant women. **Methenamine** is used for chronic suppressive treatment of bacteriuria during pregnancy. Approximately 80% of the oral dose is excreted into the urine within 24h. Pathogens resistant to other antibacterial agents may respond to **methenamine** because of the nonspecific effect of formaldehyde formed in the acid urine.
Side effects include edema, lipoid pneumonitis, N/V, cramps, bladder irritation, proteinuria, dysuria, urinary urgency, headache, hematuria, stomatitis, and anorexia.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. **Methenamine** crosses the human placenta. The concentration of **methenamine** in umbilical cord plasma is low, approximating that in maternal plasma after 4h. Low concentrations of **methenamine** are also found in amniotic fluid. Rodent teratogenicity studies have not been conducted.

Breastfeeding Safety

Methenamine enters human breast milk at a concentration similar to maternal plasma. It is generally considered compatible with breastfeeding.

Drug Interactions — Should not be administered with **sulfamethizole** since formaldehyde and **sulfamethizole** form an insoluble precipitate in acid urine.

References — Allgen LG, Holmberg G, Persson B, Sorbo B. Acta Obstet Gynecol Scand 1979; 58:287-93.

Summary —

Pregnancy Category: C
Lactation Category: S
- **Methenamine** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Methicillin—(Staphcillin)

International Brand Name—None identified.

Drug Class — Antibiotics; Penicillins

Indications — Bacterial infections (penicillinase-resistant staphylococci)

Mechanism — Bactericidal—inhibits cell wall synthesis

Dosage with Qualifiers — Bacterial infections—1-2g IM/IV q4-6h

- **Contraindications**—hypersensitivity to drug or class
- **Caution**—renal or hepatic dysfunction

Maternal Considerations — The role of **methicillin** in therapy has been largely replaced by flucloxacillin and **dicloxacillin.** However, the phrase "**methicillin**-resistant *Staphylococcus aureus*" continues to be used to describe *S. aureus* strains resistant to all penicillins. Pregnant women often have mixed vaginal flora of both MSSA and MRSA. Strains of MRSA are a major cause of nosocomial infection. Chorioamnionitis with MRSA is a rare complication of pregnancy. There are no adequate reports or well-controlled studies of **methicillin** in pregnant women. Epidemiological studies suggest colonization rates in pregnancy reflect the local populace. ***Side effects*** include anaphylactic reaction (angioneurotic edema, laryngospasm, bronchospasm, hypotension, vascular collapse, death), serum sickness–like symptoms (fever, malaise, urticaria, myalgia, arthralgia, abdominal pain), N/V, diarrhea, stomatitis, hairy tongue, interstitial nephritis, agranulocytosis, neutropenia, and bone marrow depression.

Fetal Considerations — There are no adequate reports or well-controlled studies in human fetuses. **Methicillin** crosses the human placenta, achieving an M:F ratio approximating unity. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically. Routine surveillance reveals a rising incidence of MRSA infections in NICUs. Maternal-neonatal transmission of MRSA is documented.

Breastfeeding Safety — There are no adequate reports or well-controlled studies in nursing women. **Methicillin** enters human breast milk, though the kinetics remain to be elucidated. There is only limited published experience in women with mastitis; most cases are secondary to **methicillin**-sensitive staphylococci. Mastitis secondary to MRSA is reported, as is toxic shock syndrome. **Methicillin** is generally considered compatible for breastfeeding based on this clinical experience.

Drug Interactions

May reduce the efficacy of oral contraceptives.
Disulfiram and **probenecid** may increase penicillin levels.
Methicillin may increase the effect of oral anticoagulants.
Monitor PT closely.

References

Andre P, Thebaud B, Guibert M, et al. Am J Perinatol 2000; 17:423-7.
Beigi R, Hanrahan J. Infect Dis Obstet Gynecol 2007; 708-16.
Fujiwara Y, Endo S. Kansenshogaku Zasshi 2001; 75:898-903.
Gaufberg VV, Moroz AZ, Gurtovoi BL. Antibiotiki 1975; 20:445-51.
Geisler JP, Horlander KM, Hiett AK. Clin Exp Obstet Gynecol 1998; 25:119-20.
Kulakov VI, Zak IR, Kulikova NN, Smekuna FA. Antibiotiki 1981; 26:110-3.
Mitsuda T, Arai K, Fujita S, Yokota S. Eur J Pediatr 1996; 155:194-9.
Morel AS, Wu F, Della-Latta P, et al. Am J Infect Control 2002; 30:170-3.
Nau H. Dev Pharmacol Ther 1987; 10:174-98.
Novak FR, Almeida JA, Warnken MB, et al. Mem Inst Oswaldo Cruz 2000; 95:29-33.
Pacifici GM, Nottoli R. Clin Pharmacokinet 1995; 28:235-69.
Ziv G, Soback S, Bor A. J Vet Pharmacol Ther 1983; 6:41-7.
Ziv G, Storper M. J Vet Pharmacol Ther 1985; 8:276-83.
Zueva VS, Dmitrenko OA, Gladkova KK, Zueva EA. Zh Mikrobiol Epidemiol Immunobiol 1994; 2:20-3.

Summary

Pregnancy Category: B
Lactation Category: S

- **Methicillin** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.
- MRSA must be considered when chorioamnionitis or refractory endometritis is encountered.

Methimazole—(Antitroide-GW; Favistan; Mercaptizol; Mercazole; Tapazole)

International Brand Name—Based (Taiwan); Danantizol (Argentina); Metimazol (Finland); Strumazol (Belgium, Netherlands); Tapazol (Brazil, Venezuela); Tapazole (Canada, Philippines); Thacapzol (Sweden); Thiamazol (Austria, Germany, Russia); Thycapzol (Denmark); Thyrozol (Bulgaria, Germany, Russia); Tirodril (Germany); Unimazole (Greece)

Drug Class

Antithyroid agents; Hormones

Indications

Hyperthyroidism secondary to thyroid-stimulating immunoglobulin

Mechanism

Inhibits thyroid hormone synthesis

Dosage with Qualifiers

Hyperthyroidism—begin 5-20mg PO q8h, then 5-15mg PO qd

NOTE: take with food.

- **Contraindications**—hypersensitivity to drug or class, lactation
- **Caution**—pregnancy, agranulocytosis, bone marrow suppression

Maternal Considerations

Several clinical aspects of hyperthyroidism have received special attention in the recent past. Hyperthyroidism associated with *hyperemesis gravidarium* was originally believed secondary to

inappropriate secretion of β-hCG. More recently, a mutation in the thyrotropin-releasing hormone receptor was discovered. It does not require treatment. The most common cause of maternal hyperthyroidism during pregnancy is Graves' disease. The mainstay of treatment is an antithyroid drug, either **propylthiouracil** or **methimazole**. During a 12w study of Graves' hyperthyroidism, a single daily dose of 15mg **methimazole** was much more effective in the induction of euthyroidism than a single daily dose of 150mg **propylthiouracil.** Thyroid function tests should be obtained during gestation in women suffering from hyperthyroidism and the dose of **methimazole** adjusted accordingly to keep T_3 and T_4 within the upper normal range for these women. The lowest effective dose is recommended. Women previously treated with either a radioactive cocktail or thyroidectomy may still be producing thyroid-stimulating immunoglobulin even though they are themselves euthyroid. If the level is elevated, the fetus is at risk and should be referred to a fetal center for evaluation (see **Propylthiouracil**).
Side effects include agranulocytosis, leukopenia, thrombocytopenia, nephritis, hypoprothrombinemia, anemia, and periarteritis.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. **Methimazole** crosses the human placenta and is an alternative to **propylthiouracil** for the treatment of fetal hyperthyroidism secondary to thyroid-stimulating immunoglobulin. The fetal response is often different than the maternal, and some recommend it be tested directly.
Methimazole can induce fetal goiter and even cretinism in a dose-dependent fashion. Recent studies of exposed children followed until 3-11y reveal no deleterious effects on either thyroid function or physical and intellectual development with doses up to 20mg daily. However, rare instances of aplasia cutis (manifest as scalp defects), esophageal atresia with tracheoesophageal fistula, and choanal atresia with absent/hypoplastic nipples (**methimazole** syndrome) are reported, suggesting **methimazole** may be a weak human teratogen. More recent studies have been unable to confirm a significant teratogenic difference between **methimazole** and **propylthiouracil.**

Breastfeeding Safety

Methimazole is excreted in human breast milk, but the quantities are small (2-3%) and neonatal thyroid function unaltered. Several recent studies observed no deleterious effects on neonatal thyroid function or on physical and intellectual development of breastfed infants whose mothers were treated with up to 20mg daily.

Drug Interactions

The activity of anticoagulants may be potentiated by anti–vitamin K activity secondary to **methimazole.**
Hyperthyroidism may cause increased clearance of β-blockers with a high extraction ratio. A dose reduction of β-adrenergic blockers may be necessary when a hyperthyroid patient becomes euthyroid.
Serum **digoxin** levels may rise when hyperthyroid patients on a stable **digoxin** regimen become euthyroid, necessitating a reduction in the dosage of **digoxin.**
Theophylline clearance may decrease when hyperthyroid patients on a stable **theophylline** regimen become euthyroid; a reduced dose of **theophylline** may be needed.

References

Azizi F, Khamseh ME, Bahreynian M, Hedayati M. J Endocrinol Invest 2002; 25:586-9.
Azizi F, Khoshniat M, Bahrainian M, Hedayati M. J Clin Endocrinol Metab 2000; 85:3233-8.

Banbers P, Valdez R, Rodriguez H, et al. Am J Med Genet A 2008; 146A:2390-5.
Becks GP, Burrow GN. Med Clin North Am 1991; 75:121-50.
Clark SM, Saade GR, Snodgrass WR, Hankins GD. Ther Drug Monit 2006; 28:477-83.
Cooper DS. Am J Obstet Gynecol 1987; 157:234-5.
De Santis M, Carducci B, Cavaliere AF, et al. Drug Saf 2001; 24:889-901.
Di Gianantonio E, Schaefer C, Mastroiacovo PP, et al. Teratology 2001; 64:262-6.
He CT, Hsieh AT, Pei D, et al. Clin Endocrinol (Oxf) 2004; 60:676-81.
Johansen K, Andersen AN, Kampmann JP, et al. Eur J Clin Pharmacol 1982; 23:339-41.
Mestman JH. Curr Opin Obstet Gynecol 1999; 11:167-75.
Mortimer RH, Cannell GR, Addison RS, et al. J Clin Endocrinol Metab 1997; 82:3099-102.
Shepard TH, Brent RL, Friedman JM, et al. Teratology 2002; 65:153-61.

Summary

Pregnancy Category: D
Lactation Category: S

- **Methimazole** may be a weak human teratogen and should be avoided during embryogenesis.
- **Methimazole** is an effective alternative to **propylthiouracil** for the management of maternal Graves' disease or fetal hyperthyroidism secondary to maternal thyroid-stimulating immunoglobulin if **propylthiouracil** is contraindicated.

Methocarbamol—(Bolaxin; Carbacot; Forbaxin; Methocarb; Miolaxin; Robaxin; Skedesin; Traumacut; Tresortil)

International Brand Name—Carbametin (Japan); Carbamol (Korea); Carmol (Korea); Carxin (Japan); Laxan (Thailand); Lumirelax (France); Manobaxine (Thailand); Merbamol (Korea); Myocin (Thailand); Myolax (Taiwan); New-Rexan (Korea); Ortoton (Germany); Robaxin (Canada, Hong Kong, Japan, Korea, South Africa, Taiwan); Robaxin-750 (Canada, England); Robinax (India); Sinaxar (Colombia); Trolar (Greece)

Drug Class

Muscle relaxants

Indications

Muscle spasm

Mechanism

Unknown (centrally acting muscle relaxant)

Dosage with Qualifiers

Muscle spasm—1-1.5g PO qid

- **Contraindications**—hypersensitivity to drug or class, renal dysfunction, seizures
- **Caution—**unknown

Maternal Considerations

There is no published experience during pregnancy.
Methocarbamol has no direct effect on the contractile mechanism of striated muscle, the motor end plate or the nerve fiber.
Side effects include seizures, anaphylaxis, light-headedness, dizziness, urticaria, N/V, rash, conjunctivitis, blurred vision, headache, fever, bradycardia, hypotension, and thrombophlebitis.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **methocarbamol** crosses the human placenta. Rodent teratogen studies have not been performed.

Breastfeeding Safety	There is no published experience with **methocarbamol** in nursing women. The manufacturer indicates minimal amounts are found in the milk, though no details are provided.
Drug Interactions	May inhibit the effect of **pyridostigmine** and should be used with caution in patients with myasthenia gravis receiving anticholinesterase agents.
References	There is no published experience in pregnancy or during lactation.
Summary	**Pregnancy Category: C** **Lactation Category: U** • **Methocarbamol** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk. • There are alternative agents for which there is more experience regarding use during pregnancy and lactation.

Methohexital—(Brevital)

International Brand Name—Brevimytal (Germany); Brevital (South Africa); Brieta (Austria, Belgium, Bulgaria, Canada, Czech Republic, Denmark, England, France, Hungary, Netherlands, Norway, Russia, Sweden, Switzerland, Taiwan); Brietal (Austria, Bulgaria, Denmark, England, Hungary, Netherlands, Norway, Poland, Russia, Sweden, Switzerland, Taiwan); Brietal Sodium (Australia)

Drug Class	Anesthetics, general; Barbiturates
Indications	Anesthesia, induction/maintenance
Mechanism	Alters sensory cortex, cerebellar, and motor activities
Dosage with Qualifiers	Anesthesia, induction/maintenance—1-2mg/kg IV, followed by 0.25-1mg/kg IV as needed • **Contraindications—**hypersensitivity to drug or class, porphyria • **Caution—**severe CV disease, hypotension, hepatic or renal dysfunction
Maternal Considerations	**Methohexital** is an ultra-short-acting barbiturate. Compared with **thiamylal** and **thiopental, methohexital** is at least twice as potent on a weight basis and lasts only half as long. Cumulative effects are fewer and recovery is more rapid than with thiobarbiturates. When used for cesarean delivery, analgesic requirements during the 1st postoperative hour are increased compared to **propofol.** It appears similar to **propofol** when used for 1st trimester suction abortion in terms of efficacy, acceptability, cost, and side effects when used as the single anesthetic agent for inducing general anesthesia. ***Side effects*** include arrhythmias, tachycardia, bradycardia, CV collapse, hypotension, dyspnea, respiratory depression, excitatory phenomena, and thrombophlebitis.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. **Methohexital** rapidly crosses the placenta. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically (6-7× the MRHD).
Breastfeeding Safety	There is no published experience in nursing women. It is unknown whether **methohexital** enters human breast milk.

Considering its rapid clearance, it is unlikely a clinically significant amount would enter the breast milk when used for the noted indications.

Drug Interactions

Barbiturates may influence the metabolism of other concomitantly used drugs, such as **phenytoin, halothane,** anticoagulants, corticosteroids, ethanol, and propylene glycol–containing solutions.

References

Herman NL, Li AT, Van Decar TK, et al. J Clin Anesth 2000; 12:25-30.
Lichtenberg ES, Hill LJ, Howe M, et al. Contraception 2003; 68:211-7.
Miranda AF, Kyi W, Sivalingam N. Med J Malaysia 1992; 47:280-6.

Summary

Pregnancy Category: B
Lactation Category: S (likely)

- **Methohexital** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.
- It is one of several adjuncts available for anesthesia during pregnancy.

Methotrexate—(Abitrexate; Emtexate; Folex; Mexate; Rheumatrex; Tremetex)

International Brand Name—Abitrexate (Austria, Israel, Taiwan, Thailand); Biotrexate (India); Canceren (Korea); Emthexat (Sweden); Emthexate (Belgium, Denmark, Greece, Korea, Malaysia, Netherlands, New Zealand, Norway, Philippines, Portugal, Spain, Switzerland, Taiwan, Thailand, Turkey); Farmitrexat (Germany, Indonesia); Farmotrex (Denmark); Ifamet (Mexico); Lantarel (Germany); Ledertrexate (Belgium, Finland, France, Mexico, Netherlands, Portugal); Maxtrex (England, Philippines); Metex (Germany); Methotrexate (Australia, Hong Kong, Indonesia, Israel, Japan, Malaysia, Peru, Philippines, South Africa, Taiwan, Thailand); Methotrexat Ebewe (Colombia); Methotrexato (Argentina, Chile); Meticil (Peru); Metotrexin (Brazil); Metrex (Paraguay); Mexate (Ecuador, Philippines); MTX (Korea); Neotrexate (India); Novatrex (France); Pterin (Philippines); Reumatrex (Peru); Texate (Mexico); Texate-T (Mexico); Texorate (Indonesia); Trexan (Bulgaria, Finland, Hungary, Poland, Russia, Taiwan, Turkey); Trixilem (Mexico, Thailand); Xaken (Mexico); Zexate (Philippines, Venezuela)

Drug Class

Antineoplastics, antimetabolite; Antirheumatics; Abortificants

Indications

Ectopic pregnancy, trophoblastic disease, rheumatoid arthritis, psoriasis, mycosis fungoides, chemotherapy

Mechanism

Inhibits dihydrofolate reductase and lymphocyte proliferation; immunosuppressant

Dosage with Qualifiers

Ectopic pregnancy—50mg/m^2 IM ×1; may be repeated in 1w if hCG rising
Trophoblastic disease—15-30mg PO/IM qd ×5d; repeat ×3-5 at >1w intervals; administer with **folic acid** 1mg PO qd or **leukovorin** 5mg qw
Rheumatoid arthritis—7.5-25mg PO/IM/SC qw; alternatively 2.5-7.5mg PO q12h 3×/w; max 30mg/w
Psoriasis—10-25mg PO/IM/SC qw; alternatively 2.5-7.5mg PO q12h 3×/w; max 30mg/w
Mycosis fungoides—5-50mg PO/IV qw; alternatively 15-37.5mg PO 2×/w
Chemotherapy—numerous dosing schedules depending on disease, response, and concomitant therapy

NOTE: renal dosing.

- **Contraindications**—hypersensitivity to drug or class, alcohol consumption, hepatic failure, infection, pleural effusion, immunodeficiency syndrome
- **Caution**—renal or hepatic dysfunction, bone marrow depression, ulcerative colitis, peptic ulcer

■ Maternal Considerations

Methotrexate is an antimetabolite with multiple uses in reproductive-age women, including the treatment of ectopic pregnancy, neoplastic disease, autoimmune disorders, and inflammatory conditions. **Methotrexate** originated in the 1940s when Dr. Sidney Farber at Children's Hospital Boston was testing the effects of **folic acid** on acute childhood leukemia. Inspired, he asked Lederle Laboratories to synthesize **methotrexate.** Dr. Farber then administered it to a small group of very ill children. The remarkable clinical improvement he observed began the era of modern cancer chemotherapy.

Ectopic pregnancy: Ectopic pregnancy is a major cause of maternal morbidity and mortality. Its treatment remains primarily surgical, but medical treatment is routine in some locales. Criteria include serum β-hCG titer <5000IU/L, at most free fluid confined to the pelvis, and pregnancy diameter <3.5cm. Surgery is preferred after tubal rupture, or with a high potential for rupture, hypotension, and anemia, or a pregnancy >3.5cm diameter. Some report that **methotrexate** is safe and effective for the treatment of a hemodynamically stable ectopic characterized by an adnexal mass up to 5cm, or a β-hCG titer >5000IU/L. Larger trials are needed for confirmation. Treatment often leads to an increase in mass size and should not be considered a sign of failure. Severe abdominal/pelvic pain may follow, and the surgeon must determine whether the pain is secondary to medical treatment or failure of the **methotrexate** and rupture of the ectopic. Persistent ectopic pregnancy is usually diagnosed when there is abdominal pain, intra-abdominal hemorrhage, or plateau β-hCG titers. In those situations, **methotrexate** can be administered a 2nd time. Ten to 20% of treated women ultimately require surgery. **Methotrexate** does not alter subsequent ovarian reserve. Though the greatest experience is with a tubal ectopic, there are case reports supporting its use in cervical, corneal, interstitial, and uterine incision scar ectopic pregnancies. Oral **methotrexate** ($60mg/m^2$) may also be successful, though the body of clinical experience is small. Local injection of **methotrexate** reduces the frequency of persistent ectopic pregnancy after linear salpingostomy.

GTD: **Methotrexate** is a first choice for uncomplicated malignant trophoblastic disease. Resistance to **methotrexate** is encountered requiring the use of alternative drug regimens (see **melphalan**). Prognostic factors useful for treatment decisions divide women into low-, medium-, and high-risk groups. Low-risk patients are treated by a single agent, preferably **methotrexate.** Medium- to high-risk populations require multidrug regimens that frequently include **methotrexate.** Women should avoid pregnancy until their β-hCG titer is normal for 1y.

Medical abortion: **Methotrexate** has been used to induce a medical abortion of an intrauterine pregnancy. It is more effective combined with **misoprostol** than alone. As it is not 100% effective, women must be followed clinically until there is complete normalization of β-hCG titers from their serum.

Side effects include thrombocytopenia, leukopenia, anemia (severe or aplastic), hepatic and renal dysfunction, immunosuppression, opportunistic infection, leukoencephalopathy, seizures, neurotoxicity, arachnoiditis, myelopathy, Stevens-Johnson syndrome, pulmonary fibrosis, erythema multiforme, elevated

LFTs, N/V, exfoliative dermatitis, fever, dizziness, diarrhea, pruritus, alopecia, and photosensitivity.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **methotrexate** crosses the human placenta. **Methotrexate** is rapidly taken up by the trophoblast in a fashion that does not interfere with folate uptake, and then extruded. It seems reasonable to conclude that 1st trimester exposure results in an increased risk of internal and external malformations (craniofacial, axial skeletal, cardiopulmonary, GI and dermatologic abnormalities) and developmental delay, though most pregnancies exposed to low doses are successful. The teratogenic effect is enhanced by the addition of **misoprostil.** Others report no association between later pregnancy exposure and congenital abnormalities.

Breastfeeding Safety

There are no adequate reports or well-controlled studies in nursing women. It is unknown whether **methotrexate** enters human breast milk. Despite the lack of information, **methotrexate** is generally considered contraindicated in nursing mothers.

Drug Interactions

Use of some NSAIDs with high-dose **methotrexate** has been reported to elevate and prolong serum **methotrexate** levels, resulting in deaths from severe hematologic and GI toxicity. They are contraindicated. Caution is indicated whenever NSAIDs and salicylates are administered with lower doses of **methotrexate.** Despite the potential interactions, studies of **methotrexate** in patients with rheumatoid arthritis have usually included concurrent use of constant-dosage regimens of NSAIDs, without apparent problems. However, the doses used in rheumatoid arthritis (7.5-15mg/w) are somewhat lower than those used in psoriasis and larger doses could lead to unexpected toxicity.
Toxicity may be increased by the displacement of **methotrexate** by certain drugs, such as **phenylbutazone, phenytoin,** salicylates, and sulfonamides. Renal tubular transport is also diminished by **probenecid.**
Oral antibiotics (e.g., **chloramphenicol, tetracycline,** nonabsorbable broad-spectrum antibiotics) may decrease intestinal absorption of **methotrexate** or interfere with the enterohepatic circulation by inhibiting bowel flora and suppressing metabolism of the drug by bacteria.
Penicillins may reduce the renal clearance of **methotrexate** and increase serum concentrations with resultant hematologic and GI toxicity.
May decrease the clearance of **theophylline; theophylline** levels should be monitored closely.
Vitamin preparations containing **folic acid** or its derivatives may decrease the response to **methotrexate.**
Folate deficiency states may increase toxicity.
Trimethoprim-sulfamethoxazole has been reported rarely to increase bone marrow suppression probably by an additive antifolate effect.

References

Barnhart K, Coutifaris C, Esposito M. Expert Opin Pharmacother 2001; 2:409-17.
Chew S, Anandakumar C. Singapore Med J 2001; 42:537-9.
Creinin MD, Darney PD. Contraception 1993; 48:339-48.
Del Campo M, Kosaki K, Bennett FC, Jones KL. Teratology 1999; 60:10-2.
el-Lamie IK, Shehata NA, Kamel HA. J Reprod Med 2002; 47:144-50.

Flam F, Karlstrom PO, Carlsson B, Garoff L. Eur J Obstet Gynecol Reprod Biol 1999; 83:127-9.
Gamzu R, Almog B, Levin Y, et al. Hum Reprod 2002; 17:2585-7.
Gerulath AH, Ehlen TG, Bessette P, et al. J Obstet Gynaecol Can 2002; 24:434-46.
Gracia CR, Brown HA, Barnhart KT. Fertil Steril 2001; 76:1191-5.
Johns DG, Rutherford LD, Leighton PC, Vogel CL. Am J Obstet Gynecol 1972; 112:978-80.
Kaya H, Babar Y, Ozmen S, et al. J Am Assoc Gynecol Laparosc 2002; 9:464-7.
Kozlowski RD, Steinbrunner JV, MacKenzie AH, et al. Am J Med 1990; 88:589-9.
Lewden B, Vial T, Elefant E, et al; French Network of Regional Pharmacovigilance Centers. J Rheumatol 2004; 31:2360-5.
Lipscomb GH, McCord ML, Stovall TG, et al. N Engl J Med 1999; 341:1974-8.
Lipscomb GH, Meyer NL, Flynn DE, et al. Am J Obstet Gynecol 2002; 186:1192-5.
Margolis K. Aust N Z J Obstet Gynaecol 2000; 40:347-9.
Mussalli GM, Shah J, Berck DJ, et al. J Perinatol 2000; 20:331-4.
Newlands ES, Bagshawe KD, Begent RH, et al. Br J Obstet Gynaecol 1991; 98:550-7.
Newlands ES, Bower M, Holden L, et al. Int J Gynaecol Obstet 1998; 60:S65-70.
Nguyen C, Duhl AJ, Escallon CS, Blakemore KJ. Obstet Gynecol 2002; 99:599-602.
Nijman RG, Mantingh A, Aarnoudse JG. BJOG 2002; 109:587-8.
Oriol B, Barrio A, Pacheco A, et al. Fertil Steril 2008; 90:1579-82.
Ostensen M, Hartmann H, Salvesen K. J Rheumatol 2000; 27:1872-5.
Ostensen M, Ramsey-Goldman R. Drug Saf 1998; 19:389-410.
Riggs JC, Jahshan A, Schiavello HJ. J Reprod Med 2000; 45:595-8.
Sheiner E, Yanai I, Yohai D, Katz M. Harefuah 1999; 137:537-40.
Shufaro Y, Nadjari M. Fertil Steril 2001; 75:1217.
Sweiry JH, Yudilevich DL. Biochim Biophys Acta 1985; 821: 497-501.

Summary

Pregnancy Category: X
Lactation Category: NS (possibly)

- **Methotrexate** is contraindicated during ongoing pregnancy and lactation because of its teratogenic potential.
- **Methotrexate** is effective for the medical treatment of ectopic pregnancy in selected women. A high serum β-hCG is the single most important factor predictive of single-dose **methotrexate** treatment failure.
- **Methotrexate** is the drug of choice for low-risk malignant trophoblastic disease.

Methotrimeprazine—(Nosinan, Nozinan, Levoprome)

International Brand Name—Neurocil (Europe), Nozinan (Canada, Europe)

Drug Class

Analgesics, non-narcotic

Indications

Preanesthetic medication, acute pain, obstetric pain, postoperative analgesia

Mechanism

Suppresses sensory impulses, reduces motor activity, sedates and tranquilizes, raises the pain threshold, and produces amnesia

Dosage with Qualifiers

Preanesthetic medication—2-20mg IM q45min-3h
Pain, acute—10-20mg IM q4-6h
Obstetric analgesia—15-20mg IM q4-6h prn
Postoperative analgesia—2.5-7.5mg IM q4-6h

- **Contraindications**—hypersensitivity to drug or class; antihypertensive medication; MAOIs <14d; CNS depression; severe cardiac, renal, or hepatic dysfunction; MI; hypotension
- **Caution**—infertility

Maternal Considerations

Methotrimeprazine is an aliphatic phenothiazine neuroleptic drug that produces sedation and tranquilization (also called levomepromazine). There are no adequate reports or well-controlled studies of **methotrimeprazine** in pregnant women. ***Side effects*** include orthostatic hypotension, disorientation, dizziness, weakness, jaundice, biliary stasis, abdominal discomfort, N/V, nasal congestion, chills, uterine atony, dry mouth, amenorrhea, agranulocytosis, pancytopenia, leukopenia, eosinophilia, thrombocytopenia, constipation, cardiac arrest, tachycardia, dyskinesia, dystonia, parkinsonism, opisthotonos, hyperreflexia, photosensitivity, itching, erythema, urticaria, pigmentation, rash, exfoliative dermatitis, lenticular and corneal deposits, pigmentary retinopathy, edema, and asthma.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **methotrimeprazine** crosses the human placenta. Rodent teratogenicity studies have not been performed.

Breastfeeding Safety

There is no published experience in nursing women. It is unknown whether **methotrimeprazine** enters human breast milk.

Drug Interactions

Dosages of concomitantly administered opioids should be reduced by approximately half, because **methotrimeprazine** amplifies the therapeutic actions and side effects of opioids.
Use with **tramadol** enhances the risk of seizures.
Additive sedative effects and confusional states may emerge if **methotrimeprazine** is given with benzodiazepines or barbiturates. This may be avoided by using the lowest dose possible with the substances in question.
Exert particular caution in combining **methotrimeprazine** with other anticholinergic drugs (TCAs and antiparkinsonian agents). Particularly the elderly may develop delirium, high fever, severe obstipation, even ileus and glaucoma.
Caffeine and/or stimulants of the **ephedrine**/amphetamine type may counteract the specific actions of **methotrimeprazine.** Use of these substances should be avoided.
Coffee and black tea should be avoided because they decrease the absorption of **methotrimeprazine** considerably. The same is true

for antacids; these should be given 1-2h before or after oral administration of **methotrimeprazine.**

References ..... There are no current relevant references.

Summary .....

Pregnancy Category: C
Lactation Category: U

- **Methotrimeprazine** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.
- There are alternative agents for which there is more experience regarding use during pregnancy and lactation.

Methoxamine—(Vasoxyl)

International Brand Name—Vasoxine (Austria, England, Israel)

Drug Class ..... Adrenergic agonists; Dermatologics

Indications ..... Hypotension

Mechanism ..... α-Adrenergic agonist

Dosage with Qualifiers .....

Hypotension—3-5mg IV; alternatively 10-15mg IM before or at the time of spinal anesthesia

- **Contraindications**—hypersensitivity to drug or class, hypertension
- **Caution**—concomitant use of TCAs or oxytocic agents or MAOIs <14d, heart block, hyperthyroidism, bradycardia, myocardial disease, arteriosclerosis

Maternal Considerations .....

Neuraxial analgesia is frequently accompanied by hypotension. If untreated, there are many well-described maternal and fetal effects. Perioperative hypotension may be controlled by **methoxamine** should **ephedrine** fail. There are no adequate reports or well-controlled studies of **methoxamine** in pregnant women. It decreases uterine blood flow in pregnant ewes and monkeys at doses similar to human. In rats, **methoxamine** increases uterine contractility in a dose-dependent fashion. It is unclear whether the same occurs in humans. **Methoxamine** was used in one study to alter afterload as part of an evaluation of women thought recovered from peripartal cardiomyopathy.
If used to correct hypotension during labor and delivery, oxytocic drugs such as **ergonovine, ergotamine, methylergonovine,** and **vasopressin** may cause severe hypertension.
Side effects include uterine hypertonus, fetal bradycardia, hypertension, N/V, headache, anxiety, sweating, piloerection, and urinary urgency.

Fetal Considerations .....

There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **methoxamine** crosses the human placenta. It decreases uterine blood flow and, consequently, causes fetal bradycardia and acidemia when given to pregnant ewes and monkeys at doses similar to human doses. Doppler studies reveal a brief increase in uterine artery pulsatility index after **methoxamine** for epidural-related hypotension, whereas **ephedrine** has no effect. This short-lived effect is small compared to the effect of the hypotension.

Breastfeeding Safety ..... There is no published experience in nursing women. It is unknown whether **methoxamine** enters human breast milk.

Drug Interactions ..... See **Phenylephrine.**

References .....

Estan L, Morales-Olivas FJ, Rubio E, Esplugues J. Gynecol Obstet Invest 1985; 19:53-6.
Lampert MB, Weinert L, Hibbard J, et al. Am J Obstet Gynecol 1997; 176:189-95.
Morgan P. Can J Anaesth 1994; 41:404-13.
Palop V, Tarazona E, Martinez-Mir I, et al. Gynecol Obstet Invest 1992; 34:1-5.
Tamura T, Kobashigawa T, Morishige Y, et al. Masui 1998; 47:1212-6.
Wright PM, Iftikhar M, Fitzpatrick KT, et al. Anesth Analg 1992; 75:56-63.

Summary .....

Pregnancy Category: C
Lactation Category: U

- **Methoxamine** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.
- **Ephedrine** remains the first drug of choice for hypotension associated with neuraxial anesthesia.

Methoxsalen—(Deltasoralen; Houva-Caps; 8-MOP; Oxsoralen)

International Brand Name—Delsoralen (Indonesia); Dermox (Mexico); Geroxalen (Denmark, Hungary, Netherlands, Norway); Macsoralen (India); Meladinina (Costa Rica, Dominican Republic, El Salvador, Guatemala, Honduras, Mexico, Nicaragua, Panama, Paraguay); Meladinine (Bulgaria, France, Germany, Netherlands, Switzerland, Thailand); Melaoline (Greece); Metoxaleno Fides (Uruguay); Mopsalem (Colombia); Mopsoralen (Belgium); 8-MOP Ultra (Argentina); Oxsoralen (Austria, Brazil, Canada, Czech Republic, Hong Kong, Japan, Netherlands, Philippines, Poland, South Africa, Switzerland); Oxsoralen Ultra (Canada, Hong Kong, Malaysia, Taiwan); Oxsoralen-Ultra (Israel); Oxsoralon (Belgium, Spain); Sorialen (Taiwan); Ultra-MOP (Canada); UltraMOP Lotion (Canada)

Drug Class ..... Photosensitizers; Psoralens

Indications ..... Psoriasis, severe

Mechanism ..... Unknown; photosensitizes to UV radiation probably by DNA damage, decreasing cell proliferation

Dosage with Qualifiers .....

Psoriasis, severe—20mg PO with food 4h before UVA light exposure; treat only on alternate days

NOTE: each patient should first be evaluated to determine the minimum phototoxic dose and phototoxic peak time after drug administration; available in cream.

- **Contraindications**—hypersensitivity to drug or class, invasive squamous cell carcinomas, melanoma
- **Caution**—SLE, porphyria cutanea tarda, erythropoietic protoporphyria, variegate porphyria, xeroderma pigmentosum, albinism

Maternal Considerations ..... There are no adequate reports or well-controlled studies of **methoxsalen** in pregnant women.
Side effects include ocular damage, skin aging, skin cancer, skin burn, nervousness, insomnia, depression, N/V, pruritus, erythema,

edema, dizziness, headache, malaise, hypopigmentation, vesiculation, rash, herpes simplex, miliaria, urticaria, folliculitis, GI disturbances, cutaneous tenderness, leg cramps, hypotension, and extension of psoriasis.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **methoxsalen** crosses the human placenta. Rodent teratogenicity studies have not been performed. In one limited study, there was no increase in the risk of specific defects after exposure to **methoxsalen,** but it may be embryotoxic.

Breastfeeding Safety

There is no published experience in nursing women. It is unknown whether **methoxsalen** enters human breast milk.

Drug Interactions

Care should be exercised when treating patients who are receiving other agents (either topically or systemically) with known photosensitizing activities, such as **anthralin,** coal tar or coal tar derivatives, **griseofulvin,** phenothiazines, **nalidixic acid,** halogenated salicylanilides (bacteriostatic soaps), sulfonamides, tetracyclines, thiazides, and certain organic staining dyes such as **methylene blue,** toluidine blue, rose bengal, and methyl orange.

References

Diawara MM, Kulkosky PJ. Pediatr Pathol Mol Med 2003; 22:247-58.
Nietsche UB. Int J Dermatol 1978; 17:149-57.
Stern RS, Lange R. Arch Dermatol 1991; 127:347-50.

Summary

Pregnancy Category: C
Lactation Category: U

- **Methoxsalen** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Methscopolamine—(Pamine)

International Brand Name—None identified.

Drug Class

Anticholinergics; Gastrointestinals

Indications

Peptic ulcer, adjunctive treatment

Mechanism

Acetylcholine antagonist; inhibits GI propulsive motility and decreases gastric acid secretion

Dosage with Qualifiers

Peptic ulcer—2.5mg PO qac, qhs

- **Contraindications**—hypersensitivity to drug or class, ulcerative colitis, glaucoma, GI obstruction, paralytic ileus, acute hemorrhage, toxic megacolon, myasthenia gravis
- **Caution**—high temperature, hyperthyroidism, CAD, CHF, tachyarrhythmias, tachycardia, hypertension

Maternal Considerations

There are no adequate reports or well-controlled studies of **methscopolamine** in pregnant women. It can also be used for stomach or intestinal spasms, to reduce salivation, and to treat motion sickness. **Methscopolamine** is also commonly used as a drying agent in cold and allergy medications (Extendryl, AlleRx, Rescon). (See **Scopolamine.**)

	Side effects include tachycardia, palpitations, N/V, constipation, decreased sweating, urticaria, blurred vision, headaches, nervousness, mental confusion, drowsiness, and dizziness.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **methscopolamine** crosses the human placenta. Rodent teratogenicity studies have not been performed. (See **Scopolamine.**)
Breastfeeding Safety	There is no published experience in nursing women. It is unknown whether **methscopolamine** enters human breast milk. (See **Scopolamine.**)
Drug Interactions	Use with antipsychotics, TCAs, and other drugs with anticholinergic effects will produce additive anticholinergic effects. Antacids may interfere with absorption.
References	See **Scopolamine.**
Summary	**Pregnancy Category: C** **Lactation Category: U** • **Methscopolamine** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk. • There are superior agents for which there is more experience regarding use during pregnancy and lactation.

Methsuximide—(Celontin)

International Brand Name—Celontin (Canada); Petinutin (Austria, Czech Republic, Switzerland)

Drug Class	Anticonvulsants; Succinimides
Indications	Seizures (petit mal)
Mechanism	Depresses the motor cortex and elevates the CNS threshold to convulsive stimuli
Dosage with Qualifiers	Seizures (petit mal)—300mg PO qd; increase 300mg qw until desired effect; max 1.2g qd • **Contraindications**—hypersensitivity to drug or class • **Caution**—blood dyscrasias, hepatic dysfunction
Maternal Considerations	**Methsuximide** is indicated for the control of absence (petit mal) seizures refractory to other drugs. There is no published experience during pregnancy. ***Side effects*** include N/V, anorexia, diarrhea, weight loss, abdominal pain, constipation, eosinophilia, leukopenia, monocytosis, pancytopenia, irritability, nervousness, headache, blurred vision, photophobia, hiccups, insomnia, drowsiness, ataxia, dizziness, urticaria, Stevens-Johnson syndrome, hyperemia, proteinuria, and periorbital edema.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **methsuximide** crosses the human placenta. Rodent teratogenicity studies have not been conducted. Many anticonvulsants are associated with an increased risk of malformation. The limited experience with **methsuximide** precludes comment. As for most anticonvulsant drugs, using

monotherapy and the lowest effective quantity given in divided doses to minimize the peaks can minimize the risks.

Breastfeeding Safety	There is no published experience in nursing women. It is unknown whether **methsuximide** enters human breast milk.
Drug Interactions	May interact with concurrently administered antiepileptic drugs (e.g., increases the plasma concentrations of **phenytoin** and **phenobarbital**); periodic serum level determinations of these drugs may be necessary.
References	There is no published experience in pregnancy or during lactation.
Summary	**Pregnancy Category: C** **Lactation Category: U** • **Methsuximide** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk. • There are alternative agents for which there is more experience regarding use during pregnancy and lactation.

Methyclothiazide—(Aquatensen; Enduron; Thiazidil; Urimor)

International Brand Name—Enduron (Malaysia); Enduron-M (Australia)

Drug Class	Diuretics; Thiazides
Indications	Hypertension (chronic), edema
Mechanism	Inhibits resorption of sodium and chloride
Dosage with Qualifiers	Chronic hypertension—2.5-5mg PO qd; if no control 8-12w, add a 2nd agent Edema (peripheral)—2.5-10mg PO qd; max 10mg PO qd *NOTE: may be combined with reserpine.* • **Contraindications—**hypersensitivity, electrolyte imbalances, anuria • **Caution**—hypersensitivity to sulfonamides
Maternal Considerations	There are no adequate reports or well-controlled studies of **methyclothiazide** in pregnant women. Thiazides and other diuretics are inappropriate treatment for physiologic edema of pregnancy. They are not indicated for the treatment of preeclampsia. (See **Chlorothiazide.**) ***Side effects*** include renal failure, hyponatremia, hypochloremia, hypomagnesemia, glucose intolerance, hyperlipidemia, and photosensitivity.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **methyclothiazide** crosses the human placenta. Other thiazide diuretics do cross. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically. (See **Chlorothiazide.**)
Breastfeeding Safety	There are no adequate reports or well-controlled studies in nursing women. It is unknown whether **methyclothiazide** enters

	human breast milk. Other thiazide diuretics are excreted into milk. (See **Chlorothiazide.**)
Drug Interactions	Hypokalemia can sensitize the heart to the toxic effects of **digoxin** (e.g., increased ventricular irritability). Hypokalemia may develop during concomitant use of steroids or ACTH. May decrease arterial responsiveness to NE. This diminution is not sufficient to preclude effectiveness of the pressor agent for therapeutic use. May increase the responsiveness to **tubocurarine.** Reduces **lithium** renal clearance, increasing the risk of **lithium** toxicity. May add to or potentiate ganglionic or peripheral adrenergic blocking drugs.
References	No current relevant references were identified. (See **Chlorothiazide.**)
Summary	**Pregnancy Category: B** **Lactation Category: S** (likely) • **Thiazide** diuretics are contraindicated during pregnancy except for women with CHF (see **Chlorothiazide**).

Methylcellulose—(None identified)

International Brand Name—None identified.

Drug Class	Laxatives
Indications	Constipation
Mechanism	Increases stool bulk
Dosage with Qualifiers	Constipation—1 tbsp PO qd to tid • **Contraindications**—hypersensitivity to drug or class, appendicitis, fecal impaction, acute abdomen • **Caution**—unknown
Maternal Considerations	There are no adequate reports or well-controlled studies of **methylcellulose** in pregnant women. **Methylcellulose** is frequently used in the gel preparations for local application of prostaglandin or relaxin. Like cellulose, it is neither digestible, toxic, nor allergenic. Systemic absorption is likely low. ***Side effects*** include nausea, diarrhea, and abdominal cramps.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. Based on molecular size, it is unlikely **methylcellulose** crosses the human placenta. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically. **Methylcellulose** did not influence behavior, appearance, or growth postnatally.
Breastfeeding Safety	There are no adequate reports or well-controlled studies in nursing women. It is unknown whether **methylcellulose** enters human breast milk. Animal studies reveal no evidence that **methylcellulose** adversely affects lactation.

Drug Interactions ..... No clinically relevant interactions identified.

References ..... Buttino LT Jr, Garite TJ. J Reprod Med 1990; 35:155-8.
Elliott JP, Clewell WH, Radin TG. J Reprod Med 1992; 37:713-6.
Hoshi N, Ueno K, Igarashi T, et al. J Toxicol Sci 1985; 10(Suppl 2):203-34.

Summary .....

Pregnancy Category: B
Lactation Category: S

- **Methylcellulose** is a suitable vehicle for suspending pharmacologic materials during pregnancy.

Methyldopa—(Aldomet; Alfametildopa; Dimal; Elanpres; Highprepin; Hypermet; Medomet; Methyldopum; Modepres; Prodop; Scandopa)

International Brand Name—Aldomet (Argentina, Australia, Belgium, Brazil, Bulgaria, Denmark, Ecuador, England, Finland, France, Greece, Hong Kong, Hungary, Ireland, Italy, Mexico, Netherlands, Norway, Paraguay, Philippines, Portugal, Russia, Spain, Sweden, Switzerland, Taiwan, Thailand, Turkey, Uruguay, Venezuela); Aldomet-Forte (Hong Kong); Aldometil (Austria); Aldomet M (Malaysia); Aldomet-M (Hong Kong); Aldomin (Israel); Aldomine (Portugal); Alphadopa (India); Apo-Methyldopa (Canada); Becanta (Japan); Densul (Japan); Dopagyt (India); Dopamet (Czech Republic, Denmark, England, Finland, Indonesia, Ireland, Israel, Malaysia, Norway, Switzerland); Dopasian (Thailand); Dopatens (Greece); Dopegyt (Bulgaria, Czech Republic, Hong Kong, Hungary, Israel, Malaysia, Poland, Puerto Rico, Thailand); Equibar (France); Grospisk (Japan); H.G. Metil Dopa (Ecuador); Hydopa (Australia); Hypolag (Puerto Rico, South Africa); Hy-po-tone (South Africa); Medopa (Indonesia, Japan, Thailand); Medopal (Mexico); Medopren (Italy); Meldopa (Philippines); Methoplain (Japan); Metpata (Thailand); Novomedopa (Canada); Nudopa (Australia); Pharmet (South Africa); Polinal (Japan); Presilan (Peru); Presinol (Austria, Bulgaria, Germany); Presinol 500 (Austria, Germany); Prodopa (New Zealand); Pulsoton (Mexico); Sembrina (Finland, Netherlands, South Africa); Siamdopa (Thailand); Sinepress (South Africa); Tensodopa (Peru); Tildopan (Japan)

Drug Class ..... Adrenergic antagonists, central; Antihypertensives

Indications ..... Hypertension

Mechanism ..... Central α_2-adrenergic agonist

Dosage with Qualifiers .....

Hypertension—250-500mg PO bid; begin 250mg PO bid and adjust q2d; max 3g/d; alternative 250-500mg IV q6h×4, then PO

NOTE: obtain a CBC, Coombs' test, and LFTs before beginning.

- **Contraindications**—hypersensitivity to drug or class, acute hepatitis, cirrhosis
- **Caution**—usage of other antihypertensives or levodopa, renal dysfunction, MAOI <14d, positive Coombs' test, hemolytic anemia

Maternal Considerations .....

One to 6% of young women have chronic hypertension. **Methyldopa** is perhaps the best-studied antihypertensive agent during pregnancy. It remains a first-line agent for the treatment of moderate to mild hypertension. **Methyldopa** requires 48-72h to exert its effect. The delay can be reduced to <12h if the patient is loaded either parenterally or orally. Hypertension predating pregnancy should be differentiated from preeclampsia. While treatment is indicated for women with a systolic BP >170mmHg and/or a diastolic BP >109mmHg, there is no consensus whether lesser degrees of hypertension require treatment during pregnancy. In women with mild to moderate chronic hypertension, antihypertensive therapy improves the

maternal but apparently not the fetal outcome. In such patients, **methyldopa** prolongs pregnancy by some 10d compared to placebo, but does not decrease the prevalence of superimposed preeclampsia. **Methyldopa** is less effective than **metoprolol,** but as effective as **nifedipine, labetalol,** and **ketanserin,** in decreasing both systolic and diastolic BP in women with chronic hypertension. On average, **methyldopa** decreases the maternal MAP 10.0mmHg and the mean heart rate by 6.0 bpm. The hypotensive effect is associated with a decrease in sFH-1 and an increase in PIGF. The uterine artery pulsatility index is generally unchanged. One small cohort study of early antihypertensive treatment with **methyldopa** in normotensive pregnant women with type 1 diabetes and microalbuminuria observed a significant reduction in preterm birth <34w. This finding needs prospective confirmation. Neither short- nor long-term use of **methyldopa** is associated with adverse maternal effects. Rare, sporadic cases of reactive hepatitis are reported in women treated with **methyldopa** during pregnancy. In chronically hypertensive women, **methyldopa** increases prolactin, thyrotropin, and T_3 in a dose-dependent fashion, indicating decreased dopaminergic inhibition of pituitary hormone release. In contrast, **methyldopa** decreases plasma T_4 levels.
Side effects include hemolytic anemia, myocarditis, thrombocytopenia, leukopenia, bradycardia, pancreatitis, headache, sedation, angina, weakness, CHF, N/V, pancreatitis, reactive hepatitis, diarrhea, bone marrow suppression, black tongue, pericarditis, myocarditis, arthralgia, myalgia, jaundice, amenorrhea, breast enlargement, decreased libido, and hepatic dysfunction.

Fetal Considerations

Most antihypertensive agents cross the placental barrier. **Methyldopa** is the only drug accepted for use during the 1st trimester of pregnancy. Neither short- nor long-term effects on the fetus or the neonate are reported after long-term **methyldopa** use. **Methyldopa** does not significantly alter fetal cardiac activity or produce any fetal hemodynamic changes as measured by Doppler flow studies. In contrast, **methyldopa** decreases placental vascular resistance in mild preeclampsia and in chronic hypertension. The available data are inadequate to conclude whether **methyldopa** adversely affects the fetal or neonatal HR and pattern. Until such data are available, FHR changes cannot be reliably attributed to drug effect, but rather may be due to progression of the underlying maternal or placental disease. Longitudinal studies revealed no developmental disturbances at 3y in children exposed *in utero*. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically.

Breastfeeding Safety

Methyldopa enters human breast milk, but the M:P ratio is low. Breastfed neonates delivered of women who are using **methyldopa** are normotensive.

Drug Interactions

May potentiate other antihypertensive drugs.
May require reduced doses of anesthetics; resulting hypotension is usually controllable by vasopressors.
May increase the risk of **lithium** toxicity.
Co-administration with **ferrous sulfate** or **ferrous gluconate** is not recommended.

References

Beardmore KS, Morris JM, Gallery ED. Hypertens Preg 2002; 21:85-95.
Borghi C, Esposti DD, Cassani A, et al. J Hypertens 2002; 20(Suppl 2):S52-6.
De Andrade J. Arq Bras Cardiol 1990; 55:137-9.

Hauser GJ, Almog S, Tirosh M, Spirer Z. Helv Paediatr Acta 1985; 40:83-6.
Henderson-Smart DJ, Horvath JS, Phippard A, et al. Clin Exp Pharmacol Physiol 1984; 11:351-4.
Hung JH, Yen MY, Pan YP, Hsu LP. Ultrasound Obstet Gynecol 2000; 15:513-9.
Jayawardana J, Lekamge N. Ceylon Med J 1994; 39:87-90.
Kalil A, Muttukrishna S, Harrington K, Jauniaux E. PloS ONE 2008; 3:e2766.
Khedun SM, Maharaj B, Moodley J. Paediatr Drugs 2000; 2:419-36.
Kirsten R, Nelson K, Kirsten D, Heintz B. Clin Pharmacokinet 1998; 35:9-36.
Magee LA. Best Pract Res Clin Obstet Gynaecol 2001; 15:827-45.
Montan S, Anandakumar C, Arulkumaran S, et al. Am J Obstet Gynecol 1993; 168:152-6.
Nielsen LR, Müller C, Damm P, Mathiesen ER. Diabet Med 2006; 23:426-31.
Oumachigui A, Verghese M, Balachander J. Indian Heart J 1992; 44:39-41.
Plouin PF, Breart G, Maillard F, et al. Br J Obstet Gynaecol 1988; 95:868-76.
Rath W. Z Geburtshilfe Neonatol 1997; 201:240-6.
Rey E. Obstet Gynecol 1992; 80:783-7.
Sibai BM. Obstet Gynecol 1991; 78:451-61.
Sibai BM, Mabie WC, Shamsa F, et al. Am J Obstet Gynecol 1990; 162:960-6; discussion 966-7.
Smith GN, Piercy WN. Am J Obstet Gynecol 1995; 172:222-4.
Sulyok E, Bodis J, Hartman G, Ertl T. Acta Paediatr Hung 1991; 31:53-65.
Voto LS, Zin C, Neira J, et al. J Cardiovasc Pharmacol 1987; 10(Suppl 3):S101-3.
Waterman EJ, Magee LA, Lim KI, et al. Hypertens Pregnancy 2004; 23:155-69.
Weitz C, Khouzami V, Maxwell K, Johnson JW. Int J Gynaecol Obstet 1987; 25:35-40.
White WB, Andreoli JW, Cohn RD. Clin Pharmacol Ther 1985; 37:387-90.
Wide-Swensson D, Montan S, Arulkumaran S, et al. Am J Obstet Gynecol 1993; 169:1581-5.

Summary

Pregnancy Category: B
Lactation Category: S

- **Methyldopa** is an agent of choice for the treatment of hypertension during pregnancy.
- There is no evidence of adverse effects on the progeny when observed long-term after exposure to **methyldopa.**

Methylene blue—(Methylthioninium Chloride; Urolene Blue)

International Brand Name—None identified.

Drug Class ..... Antidotes

Indications ..... Methemoglobinemia

Mechanism ..... Converts ferrous iron to ferric iron, producing methemoglobin

Dosage with Qualifiers

Methemoglobinemia—1-2mg/kg IV over 5min

NOTE: usually not recommended for cyanide poisoning.

- **Contraindications**—hypersensitivity to drug or class, renal insufficiency, intraspinal or intrathecal injection, SC injection
- **Caution**—G6PD deficiency, prolonged use

Maternal Considerations

Methylene blue causes smooth muscle contraction of many vessels, including the uterine arteries, by inhibiting guanylate cyclase. In the past, **methylene blue** was injected intra-amniotically to facilitate the diagnosis of PPROM and to demonstrate that independent sacs were sampled during amniocentesis of a multiple gestation. Based on concerns of vasoconstriction and case reports of methemoglobinemia in susceptible women, **methylene blue** has been largely replaced by **indigo carmine** for amniocentesis.
Side effects include abdominal or precordial pain, dizziness, headache, methemoglobin, necrotic abscess, fecal discoloration, urine discoloration, hypertension, chest pain, N/V, fever, skin coloration, bladder irritation, diaphoresis, and mental confusion.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. **Methylene blue** crosses the human placenta after intra-amniotic injection and is excreted in the maternal urine. Preterm neonates with G6PD deficiency exposed *in utero* may experience severe hemolysis and hyperbilirubinemia requiring exchange transfusion. A specific syndrome is described that includes hemolytic anemia, hyperbilirubinemia, and methemoglobinemia. Photosensitization is reported in very-low-birth-weight neonates exposed prenatally. **Methylene blue** use for 2nd trimester amniocentesis in twin gestation is associated with a dose-dependent increased risk of fetal intestinal atresia and/or death. In rodents, **methylene blue** given late in gestation induces preterm delivery and IUGR.

Breastfeeding Safety

There are no adequate reports or well-controlled studies in nursing women. It is unknown whether **methylene blue** enters human breast milk. It is excreted into the milk of cows and goats.

Drug Interactions

No clinically relevant interactions identified.

References

Cragan JD. Teratology 1999; 60:42-8.
Crooks J. Arch Dis Child 1982; 57:872-3.
Gauthier TW. J Matern Fetal Med 2000; 9:252-4.
Izumi H, Makino Y, Shirakawa K, Garfield RE. Am J Obstet Gynecol 1995; 172:1477-84.
Kidd SA, Lancaster PA, Anderson JC, et al. Prenat Diagn 1996; 16:39-47.
Lopes P, Aubron F, Le Neel JC, et al. Presse Med 1991; 20:1568-9.
Mhaskar R, Mhaskar AM. Int J Gynaecol Obstet 2002; 77:41-2.
Nicolini U, Monni G. Lancet 1990; 336:1258-9.
Porat R, Gilbert S, Magilner D. Pediatrics 1996; 97:717-21.
Sirisena J, Lanerolle SD. Ceylon Med J 2000; 45:44-5.
Thompson LP, Weiner CP. Am J Physiol 1993; 264:H1139-45.
van der Pol JG, Wolf H, Boer K, et al. Br J Obstet Gynaecol 1992; 99:141-3.
Weiner C, Liu KZ, Thompson L, et al. Am J Physiol 1991; 261:H1275-83.

Summary

Pregnancy Category: C
Lactation Category: U

- **Methylene blue** is contraindicated for obstetric procedures because of its fetal risks.

Methylergonovine—(Methergine)

International Brand Name—Basofortina (Paraguay); Demergin (Greece); Elpan-S (Japan); Eumegotrim (Philippines); Gometin (Korea); Ingagen-M (India); Mergot (Philippines); Mergotrex (Philippines); Methergin (Colombia, Czech Republic, Ecuador, England, Greece, Hong Kong, Ireland, Israel, Mexico, Peru, Poland, Portugal, Slovenia, South Africa, Thailand); Metrine (Thailand); Mitrotan (Bulgaria, Greece); Nathergen (Thailand); Usamema (Philippines); Utergin (India)

Drug Class ..... Ergot alkaloids; Oxytocics; Uterine stimulants

Indications ..... Postpartum bleeding

Mechanism ..... 5-HT agonist; acts directly on myometrium to increase tone, rate, and amplitude of contractions

Dosage with Qualifiers .....

Postpartum bleeding—*emergent:* 0.2mg IM q2-4h; max 5 doses; *nonemergent:* 0.2-0.4mg PO q6-12h; max duration 7d

- **Contraindications**—hypersensitivity to drug or class, hypertension, toxemia, pregnancy
- **Caution**—sepsis

Maternal Considerations .....

Postpartum hemorrhage remains a leading cause of maternal death and morbidity. **Oxytocin, methylergonovine,** and several prostaglandin agents are the pharmacologic agents most frequently used to prevent or treat postpartum hemorrhage. There is a long clinical experience with **methylergonovine.** It is effective and inexpensive. Unfortunately, its shelf life is compromised in tropical climates, where **misoprostol** may be preferable. **Methylergonovine** is typically administered in the immediate postpartum period when **oxytocin** alone fails to control myometrial atony. However, it is not effective prophylaxis for atony after delivery, and its administration with delivery of the anterior shoulder may actually increase the risk of a retained placenta. One RCT concluded **oxytocin** after delivery of the anterior shoulder was superior to **methylergonovine** administered after delivery of the placenta for the prevention of postpartum hemorrhage.

The half-life of **methylergonovine** is 1-3min, its onset of action 2-5min after IM and 5-10min after oral administration. IM is more effective than PO for the treatment of atony; the IV route is usually avoided unless the dose is diluted and infused slowly due to potential hypertension (perhaps causing stroke or MI) or vascular/tissue damage due to extravasation. There are potential interactions of **methylergonovine** and vasoactive agents, which perhaps have been administered to treat hemorrhagic hypotension. Therefore, there must be communication between the obstetrician and anesthesiologist at an operative delivery with unexpected blood loss before the **methylergonovine** is given. The combination of **oxytocin** and **methylergonovine** is more effective than **oxytocin** and **misoprostol** with fewer side effects. Given late postpartum, **methylergonovine** accelerates involution but enhances maternal cramping. A combination of **misoprostol** and **methylergonovine** is an extremely efficient abortifacient in the 2nd trimester. Doses in excess of 2mg can be associated with hallucinations.

Side effects include MI, N/V, diarrhea, headache, hallucinations, hypertension, chest pain, tinnitus, nasal congestion, hematuria, dyspnea, thrombophlebitis, and dizziness.

Fetal Considerations .....

There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **methylergonovine** crosses

the human placenta. Rodent teratogenicity studies have not been performed. Inadvertent administration during pregnancy is followed by tetanic contractions and fetal bradycardia.

Breastfeeding Safety

There are no adequate reports or well-controlled studies in nursing women. The concentrations of **methylergonovine** in human breast milk are clinically insignificant. While some reports suggest **methylergonovine** may decrease milk production, it has been used for decades PO tid or qid up to 1w to prevent postpartum hemorrhage without adverse effects on either lactation or the newborn.

Drug Interactions

There are rare reports of serious adverse events associated with the use of certain ergot alkaloids (e.g., **dihydroergotamine, ergotamine**) and potent CYP3A4 inhibitors, resulting in vasospasm leading to cerebral ischemia and/or ischemia of the extremities. Although there are no reports of such interactions with **methylergonovine** alone, potent CYP3A4 inhibitors (e.g., **clarithromycin, erythromycin, troleandomycin**), HIV protease or reverse transcriptase inhibitors (e.g., **delavirdine, indinavir, nelfinavir, ritonavir**), or azole antifungals (e.g., **itraconazole, ketoconazole, voriconazole**) should not be given with **methylergonovine.** Less potent CYP3A4 inhibitors (e.g., **clotrimazole, fluconazole, fluoxetine, fluvoxamine,** grapefruit juice, **nefazodone, saquinavir, zileuton**) may be administered with caution. These examples are incomplete, and the prescriber should consider the effects on CYP3A4 of other agents being considered for concomitant use with **methylergonovine.**

References

Amant F, Spitz B, Timmerman D, et al. Br J Obstet Gynaecol 1999; 106:1066-70.
Andersen B, Andersen LL, Sorensen T. Acta Obstet Gynecol Scand 1998; 77:54-7.
Arabin B, Ruttgers H, Kubli F. Geburtshilfe Frauenheilkd 1986; 46:215-20.
Bugalho A, Bique C, Pereira C, et al. Acta Obstet Gynecol Scand 1996; 75:270-3.
Caliskan E, Meydanli MM, Dilbaz B, et al. Am J Obstet Gynecol 2002; 187:1038-45.
de Groot AN. Eur J Obstet Gynecol Reprod Biol 1996; 69:31-6.
de Groot AN, van Dongen PW, Vree TB, et al. Drugs 1998; 56:523-35.
Fujimoto M, Takeuchi K, Sugimoto M, Maruo T. Acta Obstet Gynecol Scand 2006; 85:1310-4.
Fujiwara Y, Yamanaka O, Nakamura T, et al. Jpn Heart J 1993; 34:803-8.
Hammer M, Bostrom K, Borgvall B. Gynecol Obstet Invest 1990; 30:91-3.
Hogerzeil HV, Walker GJ. Eur J Obstet Gynecol Reprod Biol 1996; 69:25-9.
Ko WJ, Ho HN, Chu SH. Int J Cardiol 1998; 63:81-4.
Mantyla R, Kanto J. Int J Clin Pharmacol Ther Toxicol 1981; 19:386-91.
Moise KJ Jr, Carpenter RJ Jr. J Reprod Med 1988; 33:771-3.
Scapin F, Calistri D, Tronconi G, et al. Gynecol Obstet Invest 1983; 15:185-90.
Vogel D, Burkhardt T, Rentsch K, et al. Am J Obstet Gynecol 2004; 191:2168-73.
Yaegashi N, Miura M, Okamura K. Int J Gynaecol Obstet 1999; 64:67-8.

Summary	**Pregnancy Category: C** **Lactation Category: S** • There are no indications for **methylergonovine** during a continuing pregnancy. • While **oxytocin** remains the drug of choice to prevent and treat postpartum uterine atony, **methylergonovine** rapidly treats most women should **oxytocin** fail.

Methylphenidate—(Concerta; Metadate CD; Metadate ER; Ritalin; Ritalin LA; Ritalin-SR)

International Brand Name—Attenta (Australia); Concerta (Colombia); Concerta XL (England, Ireland); Medikinet (Germany); Metadate E.R. (Israel); Penid (Korea); Rilatine (Belgium); Ritalina (Ecuador); Ritaline (France); Ritaphen (South Africa); Rubifen (Costa Rica, Dominican Republic, El Salvador, Guatemala, New Zealand, Panama, Singapore, Spain, Thailand); Tranquilyn (England, Ireland)

Drug Class	Amphetamines; CNS stimulants
Indications	ADHD, narcolepsy
Mechanism	Unknown (CNS stimulation)
Dosage with Qualifiers	ADHD—begin 20mg PO qd before the AM meal; increase 20mg PO qw; max 60mg qd Narcolepsy—begin 5-10mg PO bid; increase 10mg/d q7d *NOTE: do not crush/chew.* • **Contraindications**—hypersensitivity to drug or class, glaucoma, Tourette's syndrome, anxiety, MAOI <14d • **Caution**—hypertension, seizure disorder, psychosis, CV disease, alcohol/drug abuse
Maternal Considerations	There are no adequate reports or well-controlled studies of **methylphenidate** in pregnant women. The clinical experience consists of limited case reports of narcolepsy and substance abuse. ***Side effects*** include seizures, growth suppression, psychosis, leukopenia, thrombocytopenic purpura, Tourette's syndrome, exfoliative dermatitis, drug dependency, arrhythmia, erythema multiforme, neuroleptic malignant syndrome, cerebral arteritis, hepatic dysfunction, nervousness, insomnia, abdominal pain, N/V, blurred vision, tachycardia, motor tics, weight loss, angina, rash, fever, urticaria, drowsiness, and dyskinesia.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **methylphenidate** crosses the human placenta, and limited human data do not indicate a significant risk of structural abnormalities. However, maternal abuse of **pentazocine** and **methylphenidate** is associated with preterm birth, IUGR, and evidence of neonatal withdrawal. Rodent teratogenicity studies reveal skeletal abnormalities in rabbits treated with 40× the MRHD. IUGR was seen in lower doses. Lastly, rodent studies suggest a possible impact on brain development.
Breastfeeding Safety	There is no published experience in nursing women. **Methylphenidate** enters human breast milk, but the kinetics remain to be detailed.

Drug Interactions

Should be used cautiously with pressor agents (e.g., **guanethidine**) because of possible effects on BP.
May inhibit the metabolism of coumarin anticoagulants, anticonvulsants (e.g., **phenobarbital, phenytoin, primidone**), and some antidepressants (TCAs and SSRIs). It may be necessary to adjust the dosage and monitor plasma drug concentrations (or, in the case of coumarin, coagulation times).
Serious adverse events are reported when used with **clonidine.**
Should not be used in patients being treated (currently or within the preceding 2w) with MAOIs.

References

Archer T, Fredriksson A, Sundström E, et al. Pharmacol Toxicol 1988; 63:233-9.
Debooy VD, Seshia MM, Tenenbein M, Casiro OG. Am J Dis Child 1993; 147:1062-5.
Hackett LP, Kristensen JH, Hale TW, et al. Ann Pharmacother 2006; 40:1890-1.
Hoover-Stevens S, Kovacevic-Ristanovic R. Clin Neuropharmacol 2000; 23:175-81.
Spigset O, Brede WR, Zahlsen K. Am J Psychiatry 2007; 164:348.

Summary

Pregnancy Category: C
Lactation Category: U

- **Methylphenidate** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Methylprednisolone—(Medlone; Medrol; Metrocort Summicort)

International Brand Name—A-Methapred (Israel); Esametone (Italy); Firmacort (Italy); Medixon (Indonesia); Mednin (Taiwan); Medrate (Germany); Medrone (England, Ireland); Metidrol (Indonesia); Metycortin (Germany); Solomet (Finland); Urbason (Austria, Bulgaria, Czech Republic, Germany, Netherlands, Spain, Switzerland); Urbason Retard (Belgium, Bulgaria, Germany, Italy)

Drug Class

Corticosteroids

Indications

Inflammatory disorders, congenital adrenal hyperplasia, rheumatic disorders, collagen vascular diseases, allergy, respiratory diseases, hematologic disorders, acute exacerbations of MS

Mechanism

Unknown

Dosage with Qualifiers

Inflammatory disorders—2-60mg PO qd
Congenital adrenal hyperplasia—2-60mg PO qd
Rheumatic disorders, adjunctive treatment—2-60mg PO qd
Collagen vascular diseases—2-60mg PO qd
Allergy—2-60mg PO qd
Respiratory diseases—2-60mg PO qd
Hematologic disorders—2-60mg PO qd
MS (acute exacerbations)—200mg PO qd ×7d, then 80mg PO qod ×1mo

NOTE: 4mg ***methylprednisolone*** *= 5mg* ***prednisolone****.*

- **Contraindications**—hypersensitivity to drug or class, systemic fungal infection
- **Caution**—CHF, seizure disorder, diabetes, hypertension, osteoporosis, tuberculosis, hepatic dysfunction

Maternal Considerations

Methylprednisolone is effective treatment for a wide range of disorders that occur during pregnancy. The large number prevents a detailed list here. Most synthetic corticosteroids are absorbed rapidly and completely when administered orally and are eliminated by the liver through the action of the enzyme CYP3A4. Smaller amounts are eliminated by the kidney (10-30%). The elimination t/2 is short (e.g., in nonpregnant adults, 2.3 ± 0.5h); however, the biologic activity is much longer (12-36h). **Methylprednisolone** is effective and believed safe during pregnancy for the treatment of acute asthma, lupus, nephrotic syndrome with mixed connective tissue disease, immune glomerulonephritis, alloimmune thrombocytopenia, immune thrombocytopenia, inflammatory bowel disease, Bell's palsy, and gestational herpes, and for a "stress" dose in labor and delivery to chronically suppressed patients, among many other uses. Other inflammatory disorders such as de Quervain's disease of pregnancy can be treated successfully. It has been suggested that 1st trimester hyperemesis gravidarium refractory to conventional treatments can be treated with **methylprednisolone.** However, a recent RCT concluded that the addition of parenteral and oral **methylprednisolone** to the treatment of women with hyperemesis gravidarum did not reduce the need for rehospitalization later in pregnancy. Steroids may also be useful in reducing the severity and speeding the recovery of women who develop atypical preeclampsia, or HELLP syndrome.
Methylprednisolone reduces the risk of ovarian hyperstimulation during ovulation induction for *in vitro* fertilization.
Side effects include immunosuppression, menstrual irregularities, hypertension, peptic ulcer, CHF, adrenal insufficiency, steroid psychosis, pancreatitis, pseudotumor cerebri, N/V, headache, dizziness, dyspepsia, mood swings, insomnia, anxiety, hypokalemia, edema, appetite change, skin changes, acne, cushingoid features, hyperglycemia, and ecchymosis.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. **Methylprednisolone** does not cross the placenta. However, a recent RCT concluded that high-dose **methylprednisolone** reduces fetal exposure to hyperthermia and inflammation, but increases the rate of neonatal asymptomatic bacteremia. Stress-dose corticosteroid use in labor should trigger consideration of a screening neonatal blood culture. Rodent teratogenicity studies have not been performed, but there is no clinical evidence it is teratogenic. The effect of bolus doses of **methylprednisolone** on the fetus is unknown.

Breastfeeding Safety

There are no adequate reports or well-controlled studies in nursing women. It is unknown whether **methylprednisolone** enters human breast milk. What little evidence exists suggests the quantity of corticosteroid excreted into breast milk is not clinically relevant for the newborn.

Drug Interactions

Mutual inhibition of metabolism occurs with concurrent use of **cyclosporine** and **methylprednisolone.** Convulsions are reported with use of **methylprednisolone** and **cyclosporine.**
Hepatic enzymes such as **phenobarbital, phenytoin,** and **rifampin** may increase the clearance of **methylprednisolone** and may require increases in **methylprednisolone** dose to achieve the desired response.
Troleandomycin and **ketoconazole** may inhibit the metabolism of **methylprednisolone** and thus decrease its clearance. The dose of **methylprednisolone** should be titrated to avoid toxicity.

May increase the clearance of chronic high-dose **aspirin** leading to decreased salicylate levels or increase the risk of toxicity when the **methylprednisolone** is withdrawn.
The effect on oral anticoagulants is variable. There are reports of enhanced as well as diminished effects of anticoagulant when given concurrently with corticosteroids. Therefore, coagulation indices should be monitored to maintain the desired anticoagulant effect.

References

Avci S, Yilmaz C, Sayli U. J Hand Surg 2002; 27:322-4.
Faedda R, Palomba D, Satta A, et al. Clin Nephrol 1995; 44:367-75.
Fischer T, Wallukat G, Schneider MP, et al. Eur J Obstet Gynecol Reprod Biol 2001; 97:255-7.
Futami H, Kodaira M, Furuta T, et al. J Gastroenterol 1998; 33:408-11.
Goetzl L, Zighelboim I, Badell M, et al. Am J Obstet Gynecol 2006; 195:1031-7.
Horita Y, Tsunoda S, Inenaga T, et al. Nephron 2001; 89:354-6.
Isler CM, Barrilleaux PS, Magann EF, et al. Am J Obstet Gynecol 2001; 184:1332-7.
Lainas T, Petsas G, Stavropoulou G, et al. Fertil Steril 2002; 78:529-33.
Lockshin MD, Sammaritano LR. Scand J Rheumatol Suppl 1998; 107:136-8.
Magann EF, Perry KG Jr, Meydrech EF, et al. Am J Obstet Gynecol 1994; 171:1154-8.
Mallmann F, Fernandes AK, Avila EM, et al. Braz J Med Biol Res 2002; 35:39-47.
Mari I, Pouchot J, Grasland A, Vinceneux P. Presse Med 2000; 29:2213-5.
Martin JN Jr, Perry KG Jr, Blake PG, et al. Am J Obstet Gynecol 1997; 177:1011-7.
Moore LE, Martin JN Jr. J Perinatol 2001; 21:456-8.
Ozsoylu S. Am J Obstet Gynecol 1998; 178:1368.
Ponnighaus JM, Ziegler H, Kowalzick L. Zentralbl Gynakol 1998; 120:548-50.
Radoncic E, Delmis J, Pfeifer D, Mayer D. Acta Med Croatica 2000; 54:125-7.
Safari HR, Alsulyman OM, Gherman RB, Goodwin TM. Am J Obstet Gynecol 1998; 178:1054-8.
Safari HR, Fassett MJ, Souter IC, et al. Am J Obstet Gynecol 1998; 179:921-4.
Schlembach D, Munz W, Fischer T. J Perinat Med 2000; 28:502-5.
Yost NP, McIntire DD, Wians FH Jr, et al. Obstet Gynecol 2003; 102:1250-4.

Summary

Pregnancy Category: C
Lactation Category: S (likely)

- **Methylprednisolone** is generally considered safe during pregnancy and lactation for recognized medical indications.

Methyltestosterone—(Android; Androral; Fopou; Forton; Madiol; Metandren; Metestone; Oreton Methyl; Primotest; Testo-B; Testred; Vigorex; Virilon; Virormone)

International Brand Name—Enarmon (Japan); Teston (Greece); Testotonic ''B'' (Israel); Testovis (Italy)

Drug Class	Androgens; Hormones
Indications	Breast cancer
Mechanism	Unknown
Dosage with Qualifiers	Breast cancer—50-200mg PO qd; alternatively 25-100mg buccal qd • **Contraindications**—hypersensitivity to drug or class, pregnancy • **Caution**—renal, cardiac, and hepatic dysfunction
Maternal Considerations	**Methyltestosterone** is used with modest results for the treatment of endometriosis in infertile women. It is used for palliation with advancing inoperable breast cancer known or believed to be estrogen-sensitive. **Methyltestosterone** is also used in combination with estrogen to enhance libido in women. There are no adequate reports or well-controlled studies of **methyltestosterone** in pregnant women, nor are there indications for its use. ***Side effects*** include amenorrhea, breast tenderness, edema, virilism, hypertension, hepatic dysfunction, N/V, hirsutism, cholestatic jaundice, decreased/increased libido, hypercholesterolemia, clitoral enlargement, acne, leukopenia, hypercalcemia, and polycythemia.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **methyltestosterone** crosses the human placenta. It does increase placental estradiol synthesis *in vitro*. Animal studies (rodents, dog) reveal pseudohermaphroditism in female fetuses exposed to **methyltestosterone.**
Breastfeeding Safety	There is no published experience in nursing women. It is unknown whether **methyltestosterone** enters human breast milk. It is ineffective for suppressing lactation.
Drug Interactions	C-17–substituted derivatives of testosterone, such as methandrostenolone, have been reported to decrease the anticoagulant requirements of patients receiving oral anticoagulants. Use with **oxyphenbutazone** may result in elevated serum levels of **oxyphenbutazone.** The metabolic effects of androgens may decrease blood glucose levels and insulin requirements.
References	Biggs JS, Hacker N, Andrews E, Munro C. Med J Aust 1978; 2:23-5. Hammond MG, Hammond CB, Parker RT. Fertil Steril 1978; 29:651-4. Kawashima K, Nakaura S, Nagao S, et al. Endocrinol Jpn 1977; 24:77-81. Shane BS, Dunn HO, Kenney RM, et al. Biol Reprod 1969; 1:41-8.

Summary	**Pregnancy Category: X** **Lactation Category: U** • **Methyltestosterone** is contraindicated during pregnancy.

Methysergide—(Deseril; Sansert)

International Brand Name—None identified.

Drug Class	Ergot alkaloids
Indications	Migraine headache, diarrhea secondary to carcinoid
Mechanism	Nonspecific 5-HT antagonist
Dosage with Qualifiers	Migraine headache—begin 2mg PO qd; typical dose 4-8mg PO qd; drug-free interval of 3-4w q6mo Diarrhea (carcinoid)—begin 2mg PO tid; typical dose 4-16mg PO tid • **Contraindications**—hypersensitivity to drug or class, arteriosclerosis, renal or hepatic dysfunction, hypertension, CAD, collagen disease, valvular heart disease • **Caution**—retroperitoneal fibrosis, pulmonary insufficiency
Maternal Considerations	**Methysergide** is a semisynthetic, ergot ergometrine alkaloid derivative that constricts cranial and peripheral blood vessels. It is used prophylactically to treat migraine headache. There are no adequate reports or well-controlled studies of **methysergide** in pregnant women. Despite the limited clinical data to provide guidance, **methysergide** is generally considered contraindicated during pregnancy because of its vasoconstrictive effects. ***Side effects*** include retroperitoneal, pleural, pulmonary, or cardiac fibrosis; thickening of the aortic root; aortic and mitral valve fibrosis; N/V; diarrhea; heartburn; abdominal pain; insomnia; drowsiness; mild euphoria; dizziness; ataxia; light-headedness; hyperesthesia; facial flush; telangiectasia; increased hair loss; peripheral edema; neutropenia; eosinophilia; arthralgia; and myalgia.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **methysergide** crosses the human placenta. Rodent studies reveal evidence of embryotoxicity and bradycardia when administered at high doses. It is suspected that the toxic effects are vascularly mediated, and not a direct myocardial effect.
Breastfeeding Safety	There is no published experience in nursing women. It is unknown whether **methysergide** enters human breast milk.
Drug Interactions	**Methysergide** may reverse the analgesic activity of narcotic analgesics. Use with vasoconstrictor agents (e.g., ergot alkaloids, **sumatriptan, nicotine** [e.g., smoking]) may enhance vasoconstriction.
References	Noguchi H. Nippon Sanka Fujinka Gakkai Zasshi 1986; 38:1026-32. Roberts GT, Rand MJ. Mutat Res 1978; 50:317-25. Silberstein SD. Cephalalgia 1998; 18:421-35.

Summary

Pregnancy Category: X
Lactation Category: U

- **Methysergide** is generally considered contraindicated during pregnancy and lactation.
- There are alternative agents for which there is more experience regarding use during pregnancy and lactation.

Metoclopramide—(Reglan)

International Brand Name—Ametic (South Africa); Apo-Metoclop (Canada); Aputern (Japan); Betaclopramide (South Africa); Bondigest (Colombia); Carnotprim Primperan (Mexico); Cerucal (Germany); Clopamon (South Africa); Clopan (Italy); Clopram (South Africa); Dibertil (Belgium, Russia); Emetal (Thailand); Emitasol (Korea); Emperal (Bulgaria, Denmark); Enzimar (Colombia); Gastrobi (Korea); Gastronerton (Germany); Gastrosil (Germany, Russia, Switzerland); Gavistal (Indonesia); Gensil (Thailand); Hemesis (Peru); Imperan (Argentina); Maril (Hong Kong, Thailand); Maxeron (India); MCP-Beta Tropfen (Germany); Meclomid (Mexico); Mepramide (Indonesia); Meramide (Thailand); Metagliz (Costa Rica, Dominican Republic, El Salvador, Guatemala, Honduras, Nicaragua, Panama); Metamide (New Zealand); Metlazel (Israel); Metoclor (Japan, Thailand); Metocobil (Italy); Metocyl (Hong Kong); Metolon (Indonesia, Malaysia); Metopram (Finland); Metram (Hong Kong); Nausil (Thailand); Neopramiel (Japan); Netaf (Argentina); Nilatika (Indonesia); Normastin (Indonesia); Opram (Indonesia); Perinorm (India, South Africa); Pharmyork (Greece); Plasil (Argentina, Colombia, Costa Rica, Dominican Republic, Ecuador, El Salvador, Guatemala, Honduras, Israel, Italy, Mexico, Nicaragua, Panama, Philippines, South Africa, Thailand); Pramin (Australia, Israel, Taiwan); Pramotel (Mexico); Primperan (Austria, Bulgaria, Colombia, Ecuador, Germany, Hong Kong, Ireland, Italy, Japan, Malaysia, Mexico, Peru, Poland, Slovenia, South Africa, Taiwan); Primperil (Argentina); Prinparl (Japan); Prowel (Taiwan); Pulin (Singapore); Reliveran (Argentina); Setin (South Africa); Sotatic-10 (Indonesia); Terperan (Japan); Tomid (India); Vertivom (Indonesia); Vomitrol (Indonesia); Zumatrol (Indonesia)

Drug Class

Antiemetics; Antivertigo agents; Gastrointestinals

Indications

N/V, N/V associated with chemotherapy, GERD, gastroparesis (diabetes)

Mechanism

Stimulates GI motility

Dosage with Qualifiers

N/V—5-10mg PO/IM/IV q6-8h
N/V (chemo)—1-2mg/kg IV/PO q2-4h
GERD—5-15mg PO/IV/IM qac, qhs
Gastroparesis (diabetes)—10mg IV/PO qac, qhs

NOTE: may be given 30min before meals; adjust dose based on CrCl.

- **Contraindications**—hypersensitivity to drug or class, pheochromocytoma, seizure disorder, GI bleeding, GI obstruction, concomitant usage of drugs likely to cause extrapyramidal reactions
- **Caution**—cirrhosis, CHF, renal or hepatic dysfunction, Parkinson's disease, hypertension, psychosis, depression, breast cancer

Maternal Considerations

N/V are common during the 1st trimester. **Metoclopramide** effectively reduces the incidence and severity, but may be associated with an increased risk of preterm delivery. It is unclear whether this relationship is related to **metoclopramide** or to the underlying disease. The insufficient data on the safety of **metoclopramide** makes it a second-line agent for the treatment of hyperemesis or gastroesophageal reflux. **Metoclopramide** is highly effective controlling N/V during surgery in women undergoing cesarean section. It reduces gastric secretions but does not decrease the quantity of narcotics used to control pain postoperatively. In contrast, **metoclopramide** significantly reduces the duration of labor and the total PCA **morphine** requirements of women undergoing prostaglandin-induced abortion. To reduce

the risk of dystonia, patients may be premedicated with **diphenhydramine. Metoclopramide** is also helpful for the treatment of migraine, and enhances erythropoiesis in women with Diamond-Blackfan anemia.
Side effects include suicidal ideation, seizures, neutropenia, agranulocytosis, bronchospasm, dystonic reactions, galactorrhea, amenorrhea, hypotension, changes in libido, tardive dyskinesia, CHF, hypotension, hypertension, arrhythmia, porphyria, methemoglobinemia, diarrhea, irritability, urinary frequency, anxiety, rash, dizziness, hyperprolactinemia, urticaria, insomnia, headache, confusion, and neuroleptic malignant syndrome.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. **Metoclopramide** crosses the human placenta, though the kinetics remain to be elucidated. Its use in the 1st trimester does not appear to be associated with an increased risk of malformations, spontaneous abortions, or decreased fetal birth weight. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically.

Breastfeeding Safety

Metoclopramide transfer was examined in 18 women who were 8-12w postpartum. It was detected in all samples, typically with an M:P ratio >1. However, **metoclopramide** was found in only 1 of the 5 neonates studied. Exposure of the child ranged from 6-24 mcg/kg/day in the early puerperium to 1-13 mcg/kg/day in the late puerperium. These quantities are considerably less than the therapeutic dose of 500 mcg/kg/day recommended for children. **Metoclopramide** is said to augment milk production without altering the prolactin or sodium concentrations. However, one RCT in women delivered prematurely concluded it does not improve breast milk volume or the duration of breastfeeding.

Drug Interactions

GI effects are antagonized by anticholinergic drugs and narcotic analgesics.
Additive sedative effects may occur if given with alcohol, sedatives, hypnotics, narcotics, or tranquilizers.
Releases catecholamines in patients with essential hypertension, which suggests it should be used cautiously, if at all, in patients receiving MAOIs.
May decrease absorption from the stomach (e.g., **digoxin**) but increase the rate and/or extent of absorption from the small bowel (e.g., **acetaminophen, cyclosporine,** ethanol, **levodopa, tetracycline**).

References

Aube M. Neurology 1999; 53:S26-8.
Berkovitch M, Elbirt D, Addis A, et al. N Engl J Med 2000; 343:445-6.
Berkovitch M, Mazzota P, Greenberg R, et al. Am J Perinatol 2002; 19:311-6.
Biervliet FP, Maguiness SD, Hay DM, et al. Hum Reprod 2001; 16:581-3.
Broussard CN, Richter JE. Drug Saf 1998; 19:325-37.
Danzer BI, Birnbach DJ, Stein DJ, et al. Reg Anesth 1997; 22:424-7.
Gabay MP. J Hum Lact 2002; 18:274-9.
Hagen EM, Farbu E, Bindoff L. Tidsskr Nor Laegeforen 2001; 121:2162-3.
Hansen WF, McAndrew S, Harris K, Zimmerman MB. Obstet Gynecol 2005; 105:383-9.

Kauppila A, Arvela P, Koivisto M, et al. Eur J Clin Pharmacol 1983; 25:819-23.
Magee LA, Mazzotta P, Koren G. Am J Obstet Gynecol 2002; 185:S256-61.
Pfaffenrath V, Rehm M. Drug Saf 1998; 19:383-8.
Poortinga E, Rosenthal D, Bagri S. Psychosomatics 2001; 42:153-6.
Riggs KW, Rurak DW, Taylor SM, et al. J Pharm Sci 1990; 79:1056-61.
Rosenblatt WH, Cioffi AM, Sinatra R, Silverman DG. Anesth Analg 1992; 75:760-3.
Sorensen HT, Nielsen GL, Christensen K, et al. Br J Clin Pharmacol 2000; 49:264-8.
Stefos T, Sotiriadis A, Tsirkas P, et al. Acta Obstet Gynecol Scand 2001; 80:34-8.
Stuart JC, Kan AF, Rowbottom SJ, et al. Anaesthesia 1996; 51:415-21.

Summary

Pregnancy Category: B
Lactation Category: S

- **Metoclopramide** complements other antiemetic drugs for the management of N/V during pregnancy. It is a second-line agent.
- **Metoclopramide** increases prolactin secretion both during labor and postpartum. These properties make it a useful galactagogue.

Metolazone—(Diulo; Metenix; Mykrox; Zaroxolyn)

International Brand Name—Barolyn (Finland); Diondel (Spain); Diulo (Hong Kong, Portugal); Metenix 5 (England); Normelan (Japan); Xuret (England, Ireland)

Drug Class

Antihypertensives; Diuretics; Thiazides

Indications

CHF, peripheral edema, hypertension

Mechanism

Inhibits resorption of sodium and chloride in the proximal convoluted tubule

Dosage with Qualifiers

Zaroxolyn (see NOTE)
CHF—5-20mg PO qd
Peripheral edema—5-20mg PO qd
Hypertension—2.5-5mg PO qd
Mykrox (more rapid bioavailability; see NOTE)
Hypertension—begin 0.5mg PO qd; max 1mg PO qd

NOTE: Mykrox and other brands of metolazone are not therapeutically equivalent. Consult the package insert.

- **Contraindications**—hypersensitivity to drug, class, or sulfonamides; hyponatremia; hypokalemia; anuria; hepatic coma
- **Caution**—hypersensitivity to thiazide, renal or hepatic dysfunction, gout

Maternal Considerations

The use of diuretics in an otherwise healthy woman is inappropriate and exposes mother and fetus to unnecessary hazard. Diuretics do not prevent the development of preeclampsia, and there is no evidence that they are useful in the treatment of those with the disease. (See **Chlorothiazide.**)

Side effects include hyponatremia, hypokalemia, hypomagnesemia, hypercalcemia, agranulocytosis, aplastic anemia, neuropathy, pancreatitis, hypotension, dizziness, headache, palpitations, fatigue, dyspepsia, N/V, constipation, anorexia, muscle cramps, rash, photosensitivity, hyperuricemia, and urticaria.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **metolazone** crosses the human placenta. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically. (See **Chlorothiazide.**)

Breastfeeding Safety

There are no adequate reports or well-controlled studies in nursing women. **Metolazone** enters human breast milk, but the kinetics remain to be elucidated. (See **Chlorothiazide.**)

Drug Interactions

Furosemide and probably other loop diuretics given with **metolazone** can cause unusually large or prolonged losses of fluid and electrolytes.
The hypotensive effects of ethanol, barbiturates, and narcotics may be potentiated by the volume contraction associated with **metolazone.**
Diuretic-induced hypokalemia can increase sensitize the myocardium to digitalis. Serious arrhythmias can result.
Corticosteroids or ACTH may increase the risk of hypokalemia and increase salt and water retention.
May increase serum **lithium** levels.
Diuretic-induced hypokalemia may increase the neuromuscular blockade of curariform drugs (e.g., **tubocurarine**). It may be advisable to discontinue **metolazone** 3d before elective surgery.
Salicylates and other NSAIDs may decrease the antihypertensive effect.
Methenamine efficacy may be decreased due to urinary alkalizing effect.
Thiazide-like diuretics may affect the response to oral anticoagulants; dose adjustments may be necessary.

References

There are no current relevant references. (See **Chlorothiazide.**)

Summary

Pregnancy Category: B
Lactation Category: U

- **Thiazide** diuretics are contraindicated during pregnancy except in women with CHF.
- There are alternative agents for which there is more experience regarding use during pregnancy and lactation.

Metoprolol—(Betalor; Bloxan; Cardoxone; Lopressor; Metolar; Seloxen; Toprol XL)

International Brand Name—Apo-Metoprolol (Canada); Beatrolol (Malaysia); Beloc (Argentina, Austria, Colombia, Germany); Beloc Duriles (Austria); Beloc Zok (Germany, Switzerland); Betaloc (Canada, China, England, Hong Kong, Hungary, India, Ireland, Korea, Malaysia, New Zealand, Philippines, Poland, Russia, Taiwan, Thailand); Betaloc CR (New Zealand); Betaloc Zok (Colombia, Hong Kong, Poland, Singapore, Taiwan); Betazok (Philippines); Betoprolol (Colombia); Cardeloc (Thailand); Cardiosel (Indonesia, Philippines); Cardiostat (Philippines); Cardiotab (Philippines); CP-Metolol (Hong Kong); Denex (Hong Kong, Malaysia, Singapore, Thailand); Jutabloc (Germany); Kenaprol (Mexico); Lofarbil (Greece); Lopresor (Argentina, Austria, Belgium, Bulgaria, Canada, Chile, Colombia, Czech Republic, England, Germany, Greece, Indonesia, Ireland, Italy, Japan, Mexico, Netherlands, Paraguay, Portugal, Russia, South Africa, Spain, Turkey, Uruguay, Venezuela); Lopresor Oros (Taiwan); Lopresor Retard (Austria, Bulgaria, Greece, Italy, Portugal, Switzerland); Lopresor SR (England); Lopressor (Brazil, France); Meto-Hennig (Germany); Metohexal (Australia); Metolol (Australia, Thailand); Metopress Retard (Israel); Metoprim (Philippines); Metoprogamma (Germany); Metostad (Philippines); Metrol (Australia); Minax (Hong Kong, Taiwan); Montebloc (Philippines); Neobloc (Israel); Prolaken (Mexico); Prolol SR (Korea); Ritmolol (Mexico); Sefloc (Hong Kong, Thailand); Selokeen (Netherlands); Seloken (Belgium, Denmark, Finland, France, Indonesia, Italy, Japan, Mexico, Norway, Spain, Sweden); Seloken Retard (Austria, Italy); Seloken Zoc (Finland, Mexico, Sweden); Seloken-Zok (Mexico); Selopral (Finland); Selo-zok (Denmark, Norway); Selozok (Belgium, Denmark); Selozok LP (France); Slow-Lopresor (New Zealand); Toprol XL (Australia); Vasocardin (China)

Drug Class	Adrenergic antagonists; β-Blockers
Indications	Hypertension, acute MI, angina
Mechanism	Selective β_1-adrenergic antagonist
Dosage with Qualifiers	Hypertension—50-200mg PO bid Acute MI—begin 5mg IV q2min ×3; after the 3rd dose, begin 50mg PO q6h ×48h; then 100mg PO bid or 25-50mg PO q6h Angina—50-200mg PO bid; max 400mg qd • **Contraindications**—hypersensitivity to drug or class, bronchospastic disease, sinus bradycardia, cardiogenic shock, AV block 1st degree or severe, CHF, hypotension, depressed respiratory function • **Caution**—asthma, diabetes, major surgery, hyperthyroidism
Maternal Considerations	**Metoprolol** is effective for the treatment of mild to moderate chronic hypertension, stable angina, arrhythmia, and post-MI patients. **Metoprolol** was extensively tested during pregnancy and deemed safe. Its clearance is increased during pregnancy, and the dose may require upward revision each trimester. **Metoprolol** is more effective than **methyldopa** in decreasing both systolic and diastolic BP in women with chronic hypertension, but less effective than **nicardipine.** There are many case reports of its use during pregnancy without apparent adverse effects. In principle, the management of an arrhythmia is similar whether the patient is pregnant or not. **Metoprolol** has been used successfully to correct supraventricular arrhythmias. It may also reduce the frequency of migraine headache during pregnancy when given prophylactically. **Metoprolol** is as effective as **propranolol** in controlling symptoms of hyperthyroidism. ***Side effects*** include bradycardia, CHF, bronchospasm, depression, dyspnea, fatigue, dizziness, abdominal pain, dry mouth, agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura, N/V, dyspepsia, flatulence, constipation, diarrhea, pruritus, headache, somnolence, nightmares, insomnia, musculoskeletal pain, blurred vision, decreased libido, and tinnitus.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. **Metoprolol** crosses the human placenta, but does not adversely affect the FHR. Some studies of β-blockers in pregnancy reveal an increased risk of IUGR. While true with **atenolol** and **propranolol,** it is not noted with **metoprolol.** Current study suggests the cause of IUGR is excessive β blockade, producing a decrease in maternal cardiac output. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically. High doses are associated with embryotoxicity.

Breastfeeding Safety

Small quantities of **metoprolol** are excreted into human breast milk. The neonatal plasma level is either very low or undetectable between breastfeeding periods. Feeding 3-4h after the maternal dose further reduces the neonatal risk.

Drug Interactions

Catecholamine-depleting drugs (e.g., MAOIs, **reserpine**) may have an additive effect when given with β-blocking agents. Patients should be observed closely for hypotension or marked bradycardia, which may in turn produce vertigo, syncope, or postural hypotension.

Patients with a history of severe anaphylaxis to a variety of allergens may be more reactive to repeated challenge while taking β-blockers.

Drugs that inhibit CYP2D6 (e.g., **fluoxetine, paroxetine, propafenone, quinidine**) are likely to increase **metoprolol** levels. In healthy subjects with CYP2D6 extensive metabolizer phenotype, use of **quinidine** (100 mg) and **metoprolol** (200 mg) tripled the (*S*-)**metoprolol** concentration and doubled the **metoprolol** elimination t/2.

May exacerbate the rebound hypertension that can follow **clonidine** withdrawal. The β-blocker should be withdrawn several days before the gradual withdrawal of **clonidine.** If replacing **clonidine** by β-blocker therapy, the introduction should be delayed until several days after the **clonidine** was stopped.

References

Benfield P, Clissold SP, Brogden RN. Drugs 1986; 31:376-429.

Feely J, Peden N. Drugs 1984; 27:425-46.

Hogstedt S, Lindberg B, Peng DR, et al. Clin Pharmacol Ther 1985; 37:688-92.

Kaaja R, Hiilesmaa V, Holma K, Jarvenpaa AL. Int J Gynaecol Obstet 1992; 38:195-9.

Kulas J, Lunell NO, Rosing U, et al. Acta Obstet Gynecol Scand Suppl 1984; 118:65-9.

Lindeberg S, Lundborg P, Regardh CG, Sandstrom B. Eur J Clin Pharmacol 1987; 33:363-8.

Lindeberg S, Sandstrom B, Lundborg P, Regardh CG. Acta Obstet Gynecol Scand Suppl 1984; 118:61-4.

Pfaffenrath V, Rehm M. Drug Saf 1998; 19:383-8.

Summary

Pregnancy Category: C

Lactation Category: S

- **Metoprolol** is generally considered safe during pregnancy and lactation for the noted indications and doses.

Metronidazole—(Flagyl)

International Brand Name—Acea Gel (England, Ireland); Acromona (Ecuador); Amevan (Ecuador); Amiyodazol (Mexico); Anaerobex (Austria); Anerobia (Philippines); Apo-Metronidazole (Canada); Arcazol (Taiwan); Arilin (Germany, Switzerland); Ariline (Austria); Asiazole (Thailand); Asuzol (Japan); Biotazol (Mexico); Camezol (South Africa); Clont (Germany); Debetrol (Argentina); Deflamon (Italy); Dumozol (Indonesia); Elyzol (Denmark, Finland, Israel, Norway, Sweden, Switzerland); Endazole (Philippines); Epaq (Mexico); Farnat (Indonesia); Fladex (Indonesia, Singapore); Flagenase (Mexico); Flagesol (Paraguay, Uruguay); Flagizole (Israel); Flagyl (Argentina, Australia, Belgium, Bulgaria, Canada, Chile, Costa Rica, Dominican Republic, Ecuador, El Salvador, England, France, Greece, Guatemala, Honduras, India, Indonesia, Ireland, Israel, Mexico, Netherlands, Nicaragua, Panama, Peru, Philippines, Russia, Spain, Switzerland, Taiwan, Venezuela); Flasinyl (Korea); Flazol (Israel); Frotin (Malaysia, Taiwan); Gynoplix (Hong Kong); Helminzol (Brazil); Ivemetro (Republic of Yemen); Klion (Hungary); Marphazole (Hong Kong); MetroCream (Mexico); MetroGel (Canada, Mexico); Metrogyl (Australia, Brazil, Greece); Metrolag (Israel, Puerto Rico, South Africa, Switzerland, Taiwan); Metrolex (Thailand); Metronidazol McKesson (Costa Rica, Dominican Republic, El Salvador, Guatemala, Honduras, Nicaragua, Panama); Metronide (Australia); Metrozin (Colombia); Metrozine (Indonesia); Nalox (Argentina); Nida (Japan); Noritate (Israel); Noritate Cream (Korea); Nor-Metrogel (Dominican Republic, El Salvador, Guatemala, Panama); Novazole (South Africa); Novonidazole (Canada); Otrozol (Colombia); Patryl (Philippines); Protogyl (Malaysia); Protozol (South Africa); Qualigyl (Hong Kong); Robaz (Philippines, Thailand); Rodazid (Philippines); Rosaced Gel (France); Rozacreme (France); Rozagel (France); Rozex (Austria, Belgium, England, France, Hong Kong, Ireland, Italy, Malaysia, South Africa, Switzerland); Rozex Gel (Israel, Netherlands, Paraguay, Peru, Uruguay, Venezuela); Sharizole (Israel); Supplin (Israel); Takimetol (Japan); Trichex (Austria); Trichozole (New Zealand); Triconex (Philippines); Tricowas B (Spain); Trikacide (Indonesia); Trogiar (Indonesia); Unigo (Hong Kong); Zadstat (England); Zidoval Gel (Israel); Zol (Philippines)

Drug Class	Antibiotics; Antiprotozoals; Dermatologics
Indications	Bacterial infections (anaerobic gram-negative bacilli: *B. fragilis* species *[B. distasonis, B. ovatus, B. thetaiotaomicron, B. vulgatus];* anaerobic gram-positive bacilli: *Clostridium* species and *Eubacterium* species; anaerobic gram-positive cocci: *Peptococcus* species, *Peptostreptococcus* species; other microorganisms: *T. vaginalis*, amebae)
Mechanism	Unknown; inhibits DNA synthesis
Dosage with Qualifiers	Bacterial infections—500mg PO q6-8h ×7-14d; alternative 15mg/kg IV ×1 followed by 7.5mg/kg IV q5h; max 1g/dose Amebic abscess—500-750mg PO tid ×5-10d BV—2g PO ×1, alternative 500mg PO bid ×7d Giardiasis—250mg PO tid ×5-7d; alternative 2g PO qd ×3d *C. difficile* colitis—500mg PO tid ×7-14d; alternative 250mg PO qid ×7-14d Rosacea—topical gel application bid ×9w Vaginal trichomoniasis—2g PO ×1; alternative 500mg PO bid ×7d, 1g PO bid ×1d (partner treatment is critical) *NOTE: available also in gel (0.75%) or cream (0.75%).* • **Contraindications**—hypersensitivity to drug or class, alcohol consumption • **Caution**—hepatic dysfunction, blood dyscrasia, seizures, neuropathies
Maternal Considerations	**Metronidazole** is used widely during pregnancy and has multiple therapeutic benefits. *Bacterial vaginosis:* BV is associated with preterm rupture of membrane, preterm labor and delivery, and postpartum endometritis. Systemic and local therapy with **metronidazole** effectively treats BV. Several large randomized trials seeking to determine whether successful treatment of BV reduced the prevalence of adverse outcomes ended in controversy. Women who deliver preterm with symptomatic BV have a lower risk of preterm birth in a subsequent pregnancy if treated with

metronidazole. Unfortunately, the treatment of women with asymptomatic BV and no prior preterm birth apparently does not alter their preterm delivery rate. High-risk conditions that require treatment of BV with **metronidazole** include women with prior preterm birth, body mass index <19.8kg/m^2, and evidence of endometritis before pregnancy. A "test of cure" should be obtained 1mo later. Small trials suggest that the combination of **ampicillin** and **metronidazole** successfully prolongs pregnancy in women with threatened idiopathic preterm labor. Similar results are reported when **metronidazole** is combined with **erythromycin.** Unfortunately, an appropriately sized RCT comparing **metronidazole** plus **ampicillin** at 24w and intrapartum had no effect on preterm birth despite reducing the prevalence of BV. In several of the RCTs, women with asymptomatic BV who took **metronidazole** before 26w gestation actually had a higher incidence of preterm labor than controls. In another RCT focusing on women with a positive cervical fetal fibronectin in the 2nd trimester, **metronidazole** treatment was associated with a near doubling of the preterm birth rate compared to placebo. BV treatment may offer other benefits. Prophylactic IV **metronidazole** reduces infectious morbidity postoperatively after a clinically indicated cesarean section. Similar results are obtained when **metronidazole** is applied PV. **Metronidazole** also decreases the risk of upper genital tract infection after 1st trimester suction curettage.
Trichomoniasis is associated with an increased incidence of adverse outcomes of pregnancy. A single dose of **metronidazole** cures 90%. The cure rate is higher if both partners are treated. Unfortunately, the treatment of pregnant women with asymptomatic trichomoniasis does not prevent preterm delivery. It is not known whether the result is different for symptomatic disease. Other diseases such as inflammatory bowel disease, *C. difficile* colitis, and anaerobic and protozoal infections are successfully treated during pregnancy with short-term courses of **metronidazole.**
Side effects include seizures, peripheral neuropathy, metallic taste, glossitis, stomatitis, neutropenia, overgrowth of *Candida,* ECG changes, dizziness, vertigo, incoordination, ataxia, confusion, irritability, depression, weakness, insomnia, erythematous rash, flushing, nasal congestion, mucous membrane dryness, fever, dysuria, cystitis, polyuria, incontinence, dyspareunia, decrease of libido, distress, N/V, and headache.

Fetal Considerations

Metronidazole crosses the human placenta. Though achieving an F:M ratio near unity, it does not pose a major teratogenic risk when used in the recommended doses. The safety of drug therapy for inflammatory bowel disease during pregnancy is an important clinical concern. **Metronidazole** appears safe if used for short durations. The possible fetal adverse effects related with long-term exposure as required by this condition remain unknown. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically. Embryotoxicity occurs.

Breastfeeding Safety

Metronidazole is excreted into human breast milk, reaching an M:P ratio greater than unity, but is not associated with adverse effects in breastfed neonates.

Drug Interactions

May potentiate coumarin anticoagulants, resulting in a prolongation of the PT.
Drugs that induce microsomal liver enzymes (e.g., **phenobarbital, phenytoin**) may accelerate the elimination of **metronidazole,**

resulting in reduced plasma levels; impaired clearance of **phenytoin** has also been reported.
Drugs that decrease microsomal liver enzyme activity (e.g., **cimetidine**) may prolong the t/2 and decrease plasma clearance.
Alcoholic beverages may cause abdominal cramps, N/V, headaches, and flushing. Psychotic reactions have been reported in alcoholic patients also taking **disulfiram. Metronidazole** should not be given to patients who have taken **disulfiram** within the last 2w.
In patients stabilized on relatively high doses of **lithium,** short-term oral **metronidazole** therapy has been associated with elevation of serum **lithium** levels and, in a few cases, **lithium** toxicity.

References

Carey JC, Klebanoff MA. Curr Womens Health Rep 2001; 1:14-9.
Carey JC, Klebanoff MA, Hauth JC, et al. N Engl J Med 2000; 342:534-40.
Connell W, Miller A. Drug Saf 1999; 21:311-23.
Crowley T, Low N, Turner A, et al. BJOG 2001; 108:396-402.
Czeizel AE, Rockenbauer M. Br J Obstet Gynaecol 1998; 105:322-7.
Diav-Citrin O, Shechtman S, Gotteiner T, et al. Teratology 2001; 63:186-92.
Einarson A, Ho E, Koren G. Can Fam Physician 2000; 46:1053-4.
Ferris DG, Litaker MS, Woodward L, et al. J Fam Pract 1995; 41:443-9.
Freeman CD, Klutman NE, Lamp KC. Drugs 1997; 54:679-708.
Gerstner G, Kofler E, Huber J. Z Geburtshilfe Perinatol 1980; 184:418-23.
Goldenberg RL, Klebanoff M, Carey JC, Macpherson C. Am J Obstet Gynecol 2001; 185:485-6.
Goldenberg RL, Mwatha A, Read JS, et al; Hptn024 Team. Am J Obstet Gynecol 2006; 194:650-61.
Gulmezoglu AM. Cochrane Database Syst Rev 2002; (3):CD000220.
Hauth JC, Goldenberg RL, Andrews WW, et al. N Engl J Med 1995; 333:1732-6.
James AH, Katz VL, Dotters DJ, Rogers RG. South Med J 1997; 90:889-92.
Klebanoff MA, Carey JC, Hauth JC, et al. N Engl J Med 2001; 345:487-93.
Koumans EH, Markowitz LE, Hogan V. Clin Infect Dis 2002; 35:S152-72.
McDonald HM, O'Loughlin JA, Vigneswaran R, et al. Br J Obstet Gynaecol 1997; 104:1391-7.
McGregor JA, French JI. Obstet Gynecol Surv 2000; 55:S1-19.
[No authors]. Sex Transm Infect 1999; 75 (Suppl 1):S16-8.
[No authors]. Sex Transm Infect 1999; 75 (Suppl 1):S21-3.
Odendaal HJ, Popov I, Schoeman J, et al. S Afr Med J 2002; 92:231-4.
Pitt C, Sanchez-Ramos L, Kaunitz AM. Obstet Gynecol 2001; 98:745-50.
Saling E, Schreiber M, al-Taie T. J Perinat Med 2001; 29:199-211.
Shennan A, Crawshaw S, Briley A, et al. BJOG 2006; 113:65-74.
Svare J, Langhoff-Roos J, Andersen LF, et al. Br J Obstet Gynaecol 1997; 104:892-7.
Woodrow N, Lamont RF. Hosp Med 1998; 59:447-50.
Zhang Y, Zhang Q, Xu Z. Zhonghua Fu Chan Ke Za Zhi 1997; 32:288-92.

Summary

Pregnancy Category: B
Lactation Category: S

- **Metronidazole** is a first-line treatment for BV.
- The interpregnancy treatment of women with a prior preterm birth and symptomatic BV or *T. vaginalis* may reduce the risk of recurrence in a subsequent pregnancy.

- Although there is a strong association between BV, *T. vaginalis,* and preterm birth, the largest randomized trials with **metronidazole** failed to show benefit in the treatment of asymptomatic women.
- The use of **metronidazole** either for the treatment of asymptomatic BV or for the prevention of preterm birth actually increases the risk of preterm birth and should be avoided.

Mexiletine—(Mexitil)

International Brand Name—Mexihexal (Germany); Mexitec (Indonesia); Mexitil (Brazil, India, Japan, Malaysia, South Africa, Taiwan); Mexitilen (Argentina); Mugadine (Taiwan); Tumetil (Venezuela)

Drug Class	Antiarrhythmics, class IB
Indications	Arrhythmia, diabetic neuropathy
Mechanism	Stabilizes membranes and depresses phase 0 action potential
Dosage with Qualifiers	Arrhythmia (ventricular)—200mg PO q8h; alternative 400mg PO, then 200mg PO q8-12h Diabetic neuropathy—begin 150mg qd ×3d, then 300mg qd ×3d followed by 10mg/kg *NOTE: plasma levels >0.5mcg/ml are generally considered therapeutic.* • **Contraindications**—hypersensitivity to drug or class, cardiogenic shock • **Caution**—1st degree AV block, seizure disorder
Maternal Considerations	**Mexiletine** is a local anesthetic structurally similar to **lidocaine** but active orally. There are no adequate reports or well-controlled studies of **mexiletine** in pregnant women. The published experience during pregnancy is limited to a few case reports where the drug was used throughout gestation to treat symptomatic PVCs. The dose requires monitoring to ensure that therapeutic levels are maintained. **Mexiletine** has also been used for the treatment of chronic neuropathic pain. ***Side effects*** include arrhythmia, dyspepsia, dizziness, tremor, insomnia, diarrhea, dyspnea, rash, tinnitus, nervousness, headache, depression, palpitations, dry mouth, arthralgia, fever, anorexia, angina, and fatigue.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **mexiletine** crosses the human placenta. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically. Some embryotoxicity was noted at doses that were multiples of the MRHD.
Breastfeeding Safety	**Mexiletine** is excreted into human breast milk, achieving an M:P ratio greater than unity. However, the neonatal concentration does not reach a clinically relevant level because of the volume of distribution.
Drug Interactions	**Phenytoin** and other hepatic enzyme inducers (e.g., **phenobarbital, rifampin**) may be associated with lower **mexiletine** levels. Monitoring of **mexiletine** plasma levels is recommended.

Cimetidine may increase, decrease, or leave unchanged **mexiletine** levels. Patients should be followed carefully.
Use of **mexiletine** and **theophylline** may increase **theophylline** levels. One controlled study observed a 72% mean increase (range 35-136%) in plasma **theophylline** levels. **Theophylline** plasma levels returns to pre-**mexiletine** values within 48h of discontinuing **mexiletine.** An appropriate adjustment in the **theophylline** dose should be considered.

References

Gregg AR, Tomich PG. J Perinatol 1988; 8:33-5.
Lewis AM, Patel L, Johnston A, Turner P. Postgrad Med J 1981; 57:546-7.
Lownes HE, Ives TJ. Am J Obstet Gynecol 1987; 157:446-7.
Timmis AD, Jackson G, Holt DW. Lancet 1980; 2:647-8.

Summary

Pregnancy Category: C
Lactation Category: S

- **Mexiletine** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Mezlocillin—(Mezlin)

International Brand Name—None identified.

Drug Class

Antibiotics; Penicillins

Indications

Bacterial infections (gram-negative aerobes: *E. coli, Klebsiella* species, *P. mirabilis, P. vulgaris, Enterobacter, Shigella, Morganella morganii, Pseudomonas aeruginosa, Providencia rettgeri, H. influenzae, H. parainfluenzae, Providencia stuartii, Citrobacter* species, *Neisseria* species; gram-positive aerobes: *S. aureus,* β-hemolytic streptococci, *S. pneumoniae, S. faecalis;* anaerobic bacteria: *Peptococcus* species, *Peptostreptococcus* species, *Clostridium* species, *Bacteroides* species, *Fusobacterium* species, *Veillonella* species, *Eubacterium* species)

Mechanism

Bactericidal—inhibits bacterial wall mucopeptide synthesis

Dosage with Qualifiers

Bacterial infections—3-4g IV/IM q4-6h; alternative 200-350mg/kg/d IV in divided doses; max 24g/d

- **Contraindications**—hypersensitivity to drug or class
- **Caution**—bleeding, uremia, hypokalemia

Maternal Considerations

Mezlocillin, alone or in combination with other antibiotics, is effective as treatment or prophylaxis for a variety of diseases during pregnancy, including pyelonephritis, puerperal endomyometritis, and PPROM, or for cesarean section prophylaxis. In several small trials, **mezlocillin** prolonged the latency interval after PPROM. **Mezlocillin** is considered as safe and effective as **cefoxitin** and **clindamycin/gentamicin** for treatment of postpartum endometritis. A single perioperative dose of **mezlocillin** is as effective as a 3-dose regimen of either **mezlocillin** or **cefoxitin** in preventing postoperative endometritis after a cesarean section. Because there is no antibiotic that provides superior postcesarean prophylaxis, the decision is usually based on cost.
Side effects include rash, pruritus, urticaria, drug fever, unpleasant taste, seizures, neutropenia, thrombocytopenia,

hemolytic anemia, leukopenia, pseudomembranous colitis, pain, phlebitis, N/V, eosinophilia, fever, elevated LFTs, and thrombophlebitis.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. **Mezlocillin** crosses the placenta and is found in low concentrations in fetal blood and AF. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically.

Breastfeeding Safety

There are no adequate reports or well-controlled studies in nursing women. Low concentrations of **mezlocillin** are found in human breast milk, too low to achieve a clinically relevant level in the fetus. Other penicillins are generally considered compatible with breastfeeding.

Drug Interactions

See **Piperacillin.**

References

Boemi P, Reitano S, Cilano L, et al. Minerva Ginecol 1989; 41:359-63.
Conturso R, Valsecchi A, De Lalla F. Chemioterapia 1987; 6:611-3.
Crombleholme WR, Green JR, Ohm-Smith M, et al. Am J Reprod Immunol Microbiol 1987; 13:71-5.
Faro S. Obstet Gynecol Clin North Am 1988; 15:685-95.
Faro S, Phillips LE, Baker JL, et al. Obstet Gynecol 1987; 69:760-6.
Jaffe R, Altaras M, Loebel R, Ben-Aderet N. Chemotherapy 1986; 32:173-7.
Johnston MM, Sanchez-Ramos L, Vaughn AJ, et al. Am J Obstet Gynecol 1990; 163:743-7.
Meyrier A, Guibert J. Drugs 1992; 44:356-67.
Pastorek JG 2nd, Sanders CV Jr. Rev Infect Dis 1991; 13(Suppl 9):S752-7.
Saltzman DH, Eron LJ, Tuomala RE, et al. J Reprod Med 1986; 31:709-12.
Singlas E. Nouv Presse Med 1982; 11:373-6.

Summary

Pregnancy Category: B
Lactation Category: S
- **Mezlocillin** is effective treatment and prophylaxis for a variety of bacterial infections during pregnancy.

Miconazole—(Fungoid; Monistat; Ony-Clear; Tara)

International Brand Name—Acorvio (England, Ireland); Acromizol (Ecuador); Aflorix (Argentina); Albistat (Belgium); Aloid (Mexico); Amykon (Germany); Andergin (Italy); Antifungal (Taiwan); Becarin (Malaysia); Brentan (Denmark); Candiplas (Taiwan); Candizol (Israel); Candizol oral (Israel); Covarex (South Africa); Daktar (Germany, Norway, Sweden, Switzerland); Daktarin (Argentina, Austria, Belgium, Brazil, Bulgaria, Chile, Colombia, Costa Rica, Czech Republic, Dominican Republic, Ecuador, El Salvador, England, Finland, France, Greece, Guatemala, Honduras, Ireland, Israel, Italy, Japan, Mexico, Netherlands, Nicaragua, Panama, Paraguay, Peru, Poland, Portugal, Russia, Spain, Switzerland, Taiwan, Uruguay, Venezuela); Decozol (Singapore); Deralbine (Argentina); Derma-Mycotral (Germany); Dermonistat (Israel); Diamifan (Chile); Epi-Monistat (Germany); Escortin (Indonesia); Florid (Japan); Florid D (Japan); Funcort (Thailand); Funga (Hong Kong); Fungares (Indonesia); Fungi-M (Thailand); Fungiquim (Mexico); Fungo (Hong Kong, Singapore); Fungos (Chile); Fungo Vaginal Cream (New Zealand); Fungtopic (Philippines); Gyno-Daktar (Germany); Gyno-Daktarin (Argentina, Austria, Belgium, Bulgaria, Colombia, Costa Rica, Czech Republic, Dominican Republic, Ecuador, El Salvador, England, Finland, France, Guatemala, Honduras, Japan, Mexico, Nicaragua, Panama, Philippines, Portugal, Russia, South Africa, Taiwan, Thailand); Gyno-Monistat (Germany); Gynospor (South Africa); Hairscience Antidandruff Shampoo (Singapore); Huma-Miconazole (Hungary); Liconar (Thailand); Medacter (Greece); Micatin (Canada, Ecuador); Micoffen (Mexico); Miconal (Italy); Micotar Mundgel (Germany); Micotef (Italy); Micozole (Canada); Micreme (New Zealand); Minaza (Thailand); Minazol (Singapore); Miracol (Colombia); Monazole 7 (Canada); Monistat-7 (Australia, Canada); Monistat Derm (Australia); Mycoban (Singapore); Mycoheal Cream (Israel); Mycoheal Oral Gel (Israel); Mycorine (Indonesia); Mykoderm (Germany); Mysocort (Thailand); Nazoderm (Indonesia); Neomicol (Mexico); Nilozanoc (Indonesia); Noxraxin (Thailand); Pitrion (Israel); Podakrin (Taiwan); Ranozol (Thailand); Resolve (Singapore); Resolve Thrush (Australia, Singapore); Resolve Tinea (Malaysia, Singapore); Shinaderm (Philippines); Skindure (Thailand); Tara (Thailand); Tinazol (Malaysia); Zarin (Malaysia); Zolagel (Indonesia); Zole (India)

Drug Class ..... Antifungals; Dermatologics

Indications ..... Yeast and mold infections (*Candida* species: *C. albicans;* dermatophyte genera: *Trichophyton, Microsporum, Epidermophyton;* fungal infections, systemic: coccidioidomycosis, candidiasis, cryptococcosis, petriellidiosis, paracoccidioidomycosis, mucocutaneous candidiasis)

Mechanism ..... Inhibits ergosterol biosynthesis, essential for the fungal cell wall

Dosage with Qualifiers ..... Vulvovaginal candidiasis—numerous dosing schedules reflecting disease, response, concomitant therapy, and commercial brand
T. rubrum (tinea pedis, tinea cruris, tinea corporis)—numerous dosing schedules reflecting disease, response, concomitant therapy, and commercial brand
Epidermophyton floccosum, cutaneous candidiasis (moniliasis), tinea versicolor—numerous dosing schedules reflecting disease, response, concomitant therapy and commercial brand

NOTE: available in intravaginal suppository/cream/soft gel or dermatologic cream forms.
Severe systemic fungal infections—400-1200mg IV q8h

- **Contraindications**—hypersensitivity to drug or class
- **Caution**—unknown

Maternal Considerations ..... *Candida* vaginitis is perhaps the most common female genital tract infection. The vaginal milieu during pregnancy predisposes to *C. albicans* overgrowth. There are no adequate reports or well-controlled studies of **miconazole** in pregnant women. There is controversy whether the various imidazole compounds differ in efficacy for mycotic vaginitis. Studies conducted immediately after **miconazole** was released suggested it was significantly better than **nystatin, clotrimazole,** and **butoconazole** for the treatment of vaginal candidiasis during gestation. However, no RCT substantiates that conclusion. There is no significant difference in cure rates achieved after 7-14d of therapy. Significantly more patients relapsed after cure in the **nystatin** and **clotrimazole** groups than in the **miconazole** groups. **Miconazole** is as effective

as oral therapy with **fluconazole** for vulvovaginal candidiasis. About 25-30% of the oral dose, but less than 0.1% of the vaginal dose, is absorbed. Though women frequently prefer oral medication, **fluconazole** is not recommended during pregnancy. ***Side effects*** include anaphylaxis, thrombocytopenia, cardiac arrest, vulvovaginal burning, itching, hives, rash, irritation, burning, maceration, phlebitis, pruritus, N/V, fever, drowsiness, diarrhea, anorexia, and flushing.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **miconazole** crosses the human placenta, but it has been used successfully in newborns. *In vitro,* **miconazole** effectively inhibits placental and fetal adrenal steroid aromatase. **Miconazole** is absorbed systemically after vaginal application, reaching peak levels approximating 10ng/ml. In contrast, parenteral levels of **miconazole** exceed mcg/ml. Post-marketing studies are reassuring, revealing no excess rates of adverse outcomes. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically. Embryotoxicity is associated with doses that also produce maternal toxicity.

Breastfeeding Safety

There is no published experience in nursing women. It is unknown whether **miconazole** enters human breast milk. However, considering the dose and route, it is unlikely the breastfed neonate of a woman being treated for vaginitis with vaginal applications would ingest clinically relevant amounts.

Drug Interactions

Drugs containing cremophor-type vehicles are known to cause electrophoretic abnormalities of lipoprotein; for example, the values and/or patterns may be altered. These effects are reversible upon discontinuation but are not typically an indication for discontinuation.

Enhancement of anticoagulant drugs may occur with coumarin. In cases of simultaneous treatment with **miconazole** IV and anticoagulant drugs, the anticoagulant effect should be carefully titrated.

Severe hypoglycemia has been reported when oral **miconazole** and oral hypoglycemic agents are used together.

The use of **miconazole** IV and **rifampin** should be avoided since the combination lowers the achieved levels of **ketoconazole. Ketoconazole** increases the blood level of **cyclosporine;** thus, there is a possibility of a similar drug interaction with **miconazole** IV. Blood levels of **cyclosporine** should be monitored if the two drugs are used together.

Use with CNS-active drugs (e.g., **carbamazepine, phenytoin**) may alter the metabolism of one or both drugs. It is not known whether **miconazole** may affect the metabolism of other CNS-active drugs.

References

Ainsworth RE. West J Med 1987; 147:599-600.

Eliot BW, Howat RC, Mack AE. Br J Obstet Gynaecol 1979; 86:572-7.

Hilton AL, Warnock DW, Milne JD, Scott AJ. Curr Med Res Opin 1977-78; 5:295-8.

Mason JI, Carr BR, Murry BA. Steroids 1987; 50:179-89.

McNellis D, McLeod M, Lawson J, Pasquale SA. Obstet Gynecol 1977; 50:674-8.

Qualey JR, Cooper C. J Reprod Med 1975; 15:123-5.

Timonen H. Mycoses 1992; 35:317-20.

Summary

Pregnancy Category: C
Lactation Category: U (**S** likely after vaginal administration)

- **Miconazole** cream is effective for the treatment of pregnant women with confirmed candidiasis.
- **Miconazole** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Midazolam—(Midolam; Versed)

International Brand Name—Dalam (Argentina); Doricum (Venezuela); Dormicum (Argentina, Colombia, Costa Rica, Dominican Republic, Ecuador, El Salvador, England, France, Guatemala, Honduras, India, Ireland, Italy, Mexico, Nicaragua, Panama, Paraguay, Poland, Slovenia, Uruguay); Dormonid (Brazil, Chile, Peru); Fortanest (Indonesia); Fulsed (India, Malaysia, Singapore); Hypnovel (Belgium, Colombia, Costa Rica, Dominican Republic, El Salvador, England, France, Guatemala, Honduras, Ireland, Mexico, Nicaragua, Panama); Ipnovel (Italy); Midacum (Korea); Midazo (Taiwan); Midazol (Israel, Thailand); Midolam (Israel); Miloz (Indonesia); Versed (France)

Drug Class	Anxiolytics; Benzodiazepines; Sedatives
Indications	Sedation
Mechanism	Binds benzodiazepine receptors and enhances GABA effects
Dosage with Qualifiers	Sedation, preoperative—5mg IM 1h preoperatively; alternatively, 0.07-0.08mg/kg IM ×1 Surgical sedation—0.5-1mg IV q2-3min prn; max 5mg General anesthesia induction—0.3mg/kg IV over 20-30sec Mechanical ventilation, sedation—0.02-0.1mg/kg/h IV prn • **Contraindications**—hypersensitivity to drug or class, glaucoma, shock, CNS depression • **Caution**—history of substance abuse, COPD, CHF, renal or hepatic dysfunction
Maternal Considerations	Outpatient surgery demands rapid recovery with minimal delay. The short-acting sedation of **midazolam** makes it one of the most frequently used benzodiazepines for short surgical procedures. It is most appropriate for those who are particularly anxious. Conscious sedation with **midazolam** and **fentanyl** significantly improves patient satisfaction with 1st trimester termination performed under local anesthesia. Similar results are obtained in women undergoing outpatient procedures such as oocyte retrieval procedure or GIFT. In one RCT, intrathecal **midazolam** (2mg) prolonged the postcesarean analgesia when used as an adjunct to **bupivacaine.** In yet another RCT, intrathecal **midazolam** increased the analgesic effect of **fentanyl** without any increase in adverse outcomes. In addition, both the 1 and 2mg doses decreased postoperative N/V. In another double-blind RCT, healthy women received either a combination of 1mcg/kg **fentanyl** and 0.02mg/kg **midazolam** IV, or an equal volume of saline IV at the time of their skin preparation for a **bupivacaine** spinal anesthetic. Fetal outcome measures included Apgar scores, continuous pulse oximetry for 3h, and neurobehavioral scores. Maternal outcomes included catecholamine levels, and recall of anesthesia and delivery. There were no between-group differences of neonatal outcome variables (Apgar score, neurobehavioral scores, continuous oxygen saturation). Mothers in both groups showed no difference in their ability to recall the birth of their babies. **Midazolam** levels are increased during pregnancy suggesting a decrease in CYP3A4 activity. In rodents, **midazolam** suppresses uterine contractility *in vitro.*

Side effects include respiratory and/or cardiac arrest, withdrawal, habituation, N/V, confusion, euphoria, involuntary movements, hypotension, sedation, agitation, retrograde amnesia, hallucinations, marked aggressiveness, ataxia, urticaria, rash, dizziness, metallic taste, dry mouth, and constipation.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. **Midazolam** crosses the human placenta somewhat more slowly than **diazepam,** achieving an F:M concentration ratio approaching unity 30-60min after maternal injection. Postnatally, its elimination t/2 is 6-7h. The reported effects of benzodiazepines on development are inconsistent. Studies in the 1970s suggested 1st trimester exposure to benzodiazepines increased the risk of facial clefts, cardiac malformations, and other multiple malformations. Yet, no syndrome could be described. **Diazepam** and **chlordiazepoxide** were most frequently implicated. However, an increased risk was not confirmed in recent studies. **Midazolam** use during the 3rd trimester or labor may be associated with floppy infant syndrome, or symptoms of neonatal withdrawal. These symptoms vary among mild sedation, hypotonia, apneic spells, cyanosis, impaired metabolic responses to cold stress, and reluctance to suck, and may persist for hours to months after birth.

Breastfeeding Safety

Midazolam is excreted at low concentrations into human breast milk with an M:P ratio approximating 0.15 and less than 0.05% of the maternal dose in 24h. Considering the dose and route, it is unlikely the breastfed neonate would ingest clinically relevant amounts.

Drug Interactions

Sedative effect of **midazolam** is accentuated by any concomitantly administered medication that depresses the CNS, particularly narcotics (e.g., **fentanyl, meperidine, morphine**) and also **secobarbital, propofol, ketamine, nitrous oxide,** and **droperidol.** The dose of **midazolam** should be adjusted accordingly.
Caution is advised with drugs known to inhibit CYP3A4, such as **cimetidine** (not **ranitidine**), **diltiazem, erythromycin, ketoconazole, itraconazole, saquinavir,** and **verapamil.** These drug interactions may result in prolonged sedation due to decreased **midazolam** clearance. In a placebo-controlled study, erythromycin administered 500mg tid for 1w reduced the **midazolam** clearance and doubled the t/2. The effects of **diltiazem** (60mg tid) and **verapamil** (80mg tid) on the pharmacokinetics and pharmacodynamics of **midazolam** were investigated in a 3-way crossover study. The t/2 of **midazolam** increased from 5 to 7h when either drug was taken. **Saquinavir** may reduce the **midazolam** clearance by up to ½ and double the t/2.
CYP3A4 inducers (e.g., **carbamazepine, phenytoin, rifampin**) induce metabolism and markedly decreased C_{max} and AUC of oral **midazolam** in adult studies. **Phenobarbital** is expected to have the same effect.
A 15% decrease in **thiopental** requirements has been noted following use of IM **midazolam** for premedication.
IV **midazolam** decreases the MAC of **halothane** required for general anesthesia.
In neonates, severe hypotension has been reported with concomitant administration of **fentanyl.** This effect has been observed in neonates on an infusion of **midazolam** who received a rapid injection of **fentanyl** and in patients on an infusion of **fentanyl** who have received a rapid injection of **midazolam.**

References

Bach V, Carl P, Crawford ME, et al. Anesth Analg 1989; 68:238-42.

Camann W, Cohen MB, Ostheimer GW. Anesthesiology 1986; 65:441.
Chambrier C, Zayneh E, Pouyau A, et al. Ann Fr Anesth Reanim 1991; 10:81-3.
Frölich MA, Burchfield DJ, Euliano TY, Caton D. Can J Anaesth 2006; 53:79-85.
Hamar O, Garamvolgyi G. Acta Chir Hung 1990; 31:63-8.
Hammadeh ME, Wilhelm W, Huppert A, et al. Arch Gynecol Obstet 1999; 263:56-9.
Hebert MF, Easterling TR, Kirby B, et al. Clin Pharmacol Ther 2008; 84:248-53.
Karsli B, Kaya T, Cetin A. Pol J Pharmacol 1999; 51:505-10.
Martinez-Telleria A, Cano ME, Carlos R. Rev Esp Anestesiol Reanim 1992; 39:379-80.
Matheson I, Lunde PK, Bredesen JE. Br J Clin Pharmacol 1990; 30:787-93.
McElhatton PR. Reprod Toxicol 1994; 8:461-75.
Milki AA, Tazuke SI. Fertil Steril 1997; 68:128-32.
Nitsun M, Szokol JW, Saleh HJ, et al. Clin Pharmacol Ther 2006; 79:549-57.
Prakash S, Joshi N, Gogia AR, et al. Reg Anesth Pain Med 2006; 31:221-6.
Rossi AE, Lo Sapio D, Oliva O, et al. Minerva Anesthesiol 1995; 61:265-9.
Sen A, Rudra A, Sarkar SK, Biswas B. J Indian Med Assoc 2001; 99:683-4.
Soussis I, Boyd O, Paraschos T, et al. Fertil Steril 1995; 64:1003-7.
Tucker AP, Mezzatesta J, Nadeson R, Goodchild CS. Anesth Analg 2004; 98:1521-7.
Valentine JM, Lyons G, Bellamy MC. Eur J Anaesthesiol 1996; 13:589-93.
Wong CY, Ng EH, Ngai SW, Ho PC. Hum Reprod 2002; 17:1222-5.

Summary

Pregnancy Category: D
Lactation Category: S

- **Midazolam** is a useful agent during pregnancy and lactation for the indications cited.

Midodrine—(ProAmatine)

International Brand Name—Amatine (Canada); Gutron (Austria, Czech Republic, France, Germany, Greece, Hong Kong, Hungary, Israel, Italy, New Zealand, Portugal, Russia, Switzerland, Taiwan, Thailand); Metligine (Japan); Midron (Korea)

Drug Class

Adrenergic agonists; α-Agonist

Indications

Hypotension, urinary incontinence

Mechanism

α_1-Adrenergic agonist

Dosage with Qualifiers

Hypotension (orthostatic)—10mg PO tid
Urinary incontinence—2.5mg PO bid or tid

- **Contraindications**—hypersensitivity to drug or class, renal dysfunction, thyrotoxicosis, pheochromocytoma
- **Caution**—hepatic dysfunction, diabetes

Maternal Considerations

Midodrine increases vascular tone and elevates BP. In a single case report, **midodrine** was used successfully to treat postural

orthostatic tachycardia syndrome (POTS), a rare disease characterized by syncope, sinus tachycardia, and orthostasis due to autonomic dysfunction. Rodent studies reveal no effect on uterine contractility *in vitro*.
Side effects include bradycardia, erythema multiforme, pruritus, dysuria, paresthesias, piloerection, anxiety, dry mouth, nervousness, vasodilation, chills, confusion, headache, N/V, hypertension; visual field defect, dry skin, impaired urination, asthenia, backache, flatulence, and leg cramps.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **midodrine** crosses the human placenta. Though no evidence of teratogenicity was found in rodent studies, there was an increased prevalence of embryo resorption and IUGR.

Breastfeeding Safety

There is no published experience in nursing women. It is unknown whether **midodrine** enters human breast milk.

Drug Interactions

Cardiac glycosides may enhance or precipitate bradycardia, AV block, or arrhythmia.
Drugs that stimulate α-adrenergic receptors (e.g., **dihydroergotamine, ephedrine, phenylephrine, phenylpropanolamine, pseudoephedrine**) may enhance or potentiate the pressor effects of **midodrine.** Caution is advised.
α-Adrenergic blocking agents (e.g., **doxazosin, prazosin, terazosin**) may antagonize the effects of **midodrine.**
The potential for supine hypertension should be carefully monitored in patients concomitantly treated with salt-retaining steroid therapy (i.e., **fludrocortisone**), with or without salt supplementation. It may be minimized by either reducing the dose of **fludrocortisone** or decreasing the salt intake prior to initiation of **midodrine.**

References

Glatter KA, Tuteja D, Chiamvimonvat N, et al. Pacing Clin Electrophysiol 2005; 28:591-3.
Pittner H. Arzneimittelforschung 1987; 37:794-6.

Summary

Pregnancy Category: C
Lactation Category: U
- **Midodrine** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.
- Common indicated uses are rarely urgent. Its use can likely be delayed until delivery.

Mifepristone—(Mifeprex; RU-486)

International Brand Name—Mifegest (India); Mifegyne (England, France, Israel, Sweden)

Drug Class

Abortifacients; Stimulants, uterine

Indications

Abortion

Mechanism

Progesterone receptor antagonist

Dosage with Qualifiers

Abortion—200-600mg PO ×1

NOTE: pregnancy <49d from LMP; often combined with ***misoprostol.***

- **Contraindications**—hypersensitivity to drug, class, or prostaglandins; ectopic pregnancy; IUD in place; anticoagulation; corticosteroid use; chronic adrenal failure; bleeding disorder; porphyria; no access to emergent health care; noncompliance with the treatment
- **Caution**—unknown

■ Maternal Considerations

Sheep studies demonstrate that **progesterone** suppresses uterine/placental secretion of PGF-2α, and that critical **progesterone**: estradiol-17β and PGE:PGF-2α ratios are necessary for continuation of the pregnancy. **Mifepristone** causes **progesterone** withdrawal. It is a possible emergency contraceptive after unprotected coitus (10mg) effective for up to 6d after exposure. Low-dose **mifepristone** (either 25mg PO ×1, or 10mg PO ×1 followed by levonorgestrel 1.5mg PO 12h later) is 80% effective. In 1996, the FDA Advisory Committee for Reproductive Health Drugs concluded **mifepristone** was safe and effective for early pregnancy termination. In 2000, the FDA approved **mifepristone** to induce abortion in pregnancies <49d from the LMP. The most popular treatment schedule is **mifepristone** 200-600mg followed 36-48h later by oral **misoprostol** (0.4-0.6mg) in pregnancies up to 49d, and vaginal gemeprost (1.0mg) or **misoprostol** (0.8mg) if the pregnancy dates from 49 to 63d since the LMP. The addition of 2 doses of **misoprostol** beginning 48h after **mifepristone** significantly reduces the ongoing pregnancy rate compared to **mifepristone** alone. In another report, a fixed protocol of 200mg of **mifepristone** PO followed by 0.4mg **misoprostol** PV 2d later was compared to a flexible dosing interval of 1, 2, or 3d between **mifepristone** and **misoprostol.** At the same time, the upper limit of gestational age was increased from 56 to 63 days. The rates of complete abortion were 94.9% and 94.4% (not significant), respectively. Continuing pregnancy was rare (0.7%). β-hCG and **progesterone** concentrations continue to increase for 48h after **mifepristone.** After **misoprostol,** the β-hCG and **progesterone** levels decline in 24h by 70% and 60%, respectively. Treated women should expect some bleeding for 9-16d. Eight percent of treated women bleed 30d or more. The duration of bleeding increases with gestational age at termination. There are only a few randomized studies comparing medical and surgical termination, and the definitions of successful outcome (complete abortion), adverse effects, and complications vary. The three most common reasons a woman chooses a medical abortion are "avoidance of surgery," "avoidance of general anesthesia," and "the method being more natural." The duration of bleeding, degree of blood loss, and frequency of uterine pain, vomiting, and diarrhea are all greater with **mifepristone** abortion. Conversely, the incidence of major complications such as blood transfusion and pelvic infection does not seemingly differ between the two. Surgical complications, such as uterine perforation and cervical tears, are less common in women who choose medical abortion. **Mifepristone** helps preserve fertility and avoid major maternal complications (death, hysterectomy) in women with either cervical or uterine scar ectopic pregnancy. At term, **mifepristone** has a modest impact on cervical ripening if given 24h before labor induction. **Mifepristone** appears to reduce the need for **misoprostol** and **oxytocin** compared with placebo.

Side effects include vaginal bleeding, abdominal cramps, incomplete abortion, fetal malformation, hemorrhage, N/V, anxiety, fever, rigors, dyspepsia, fainting, vaginitis, asthenia, leukorrhea, and insomnia.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. **Mifepristone** does cross the primate placenta. The human experience with continued pregnancy after failed medical termination is limited. Normal outcomes are reported. While Möbius' syndrome is increased after failed **misoprostol** termination, the same cannot be said for **mifepristone.**

Breastfeeding Safety

There are no adequate reports or well-controlled studies in nursing women. It is unknown whether **mifepristone** enters human breast milk. Rodent studies suggest that **mifepristone** enhances lactation.

Drug Interactions

Mifepristone is a substrate for CYP3A4. It is possible that CYP3A4 inhibitors (e.g., **erythromycin,** grapefruit juice, **itraconazole, ketoconazole**) may inhibit its metabolism and increase its serum level. Furthermore, CYP3A4 inducers (e.g., **dexamethasone, rifampin,** St. John's wort, and certain anticonvulsants [**carbamazepine, phenobarbital, phenytoin**]) may increase **mifepristone** metabolism and lower its serum levels. Use of **mifepristone** may lead to an increase in serum levels of other drugs that are CYP 3A4 substrates. Due to the slow elimination of **mifepristone,** such interaction may be observed for a prolonged period after administration. Caution is advised.

References

Ashok PW, Stalder C, Wagaarachchi PT, et al. BJOG 2002; 109:553-60.
Ashok PW, Templeton A, Wagaarachchi PT, Flett GM. BJOG 2002; 109:1281-9.
Bartley J, Baird DT. BJOG 2002; 109:1290-4.
Bygdeman M, Danielsson KG. Drugs 2002; 62:2459-70.
Cabrol D, Carbonne B, Bienkiewicz A, et al. Prostaglandins 1991; 42:71-9.
Changhai H, Youlun G, Jie Y, et al. Contraception 2002; 66:221-4.
Cheng L, Gülmezoglu AM, Oel CJ, et al. Cochrane Database Syst Rev 2004; (3):CD001324.
Ellertson C, Waldman SN. Curr Womens Health Rep 2001; 1:184-90.
Elliott CL, Brennand JE, Calder AA. Obstet Gynecol 1998; 92:804-9.
Fox MC, Creinin MD, Harwood B. Contraception 2002; 66:225-9.
Frydman R, Lelaidier C, Baton-Saint-Mleux C, et al. Obstet Gynecol 1992; 80:972-5.
Heikinheimo O, Leminen R, Suhonen S. Contraception 2007; 76:456-60.
Honkanen H, Ranta S, Ylikorkala O, Heikinheimo O. Hum Reprod 2002; 17:2315-9.
Honkanen H, von Hertzen H. Contraception 2002; 65:419-23.
Jain JK, Dutton C, Harwood B, et al. Hum Reprod 2002; 17:1477-82.
Li FF, Chen YX, Tang JH. Di Yi Jun Yi Da Xue Xue Bao 2002; 22:466-6.
[No authors]. Reprod Freedom News 1996; 5:7-8.
Omokanye S. J Fam Plann Reprod Health Care 2001; 27:102.
Schaff EA, Fielding SL, Eisinger S, Stadalius L. Contraception 2001; 63:251-4.
Schaff EA, Fielding SL, Westhoff C. Contraception 2002; 66:247-50.
Sexton C, Sharp N. Aust N Z J Obstet Gynaecol 2002; 42:211-3.
Soaje M, de Di Nasso EG, Deis RP. J Endocrinol 2002; 172:255-61.
Turner AN, Ellertson C. Drug Saf 2002; 25:695-706.

VonHertzen H, Piaggio G, Ding J, et al. Lancet 2002; 360:1803-10.
Weems YS, Bridges PJ, Sasser RG, et al. Prostaglandins Other Lipid Mediat 2002; 70:195-208.
Weimin W, Wenqing L. Int J Gynaecol Obstet 2002; 77:201-7.
Wing DA, Fassett MJ, Mishell DR. Obstet Gynecol 2000; 96:543-8.
Winikoff B, Dzuba IG, Creinin MO, et al. Obstet Gynecol 2008; 112:1303-10.
Wolf JP, Chillik CF, Itskovitz J, et al. Am J Obstet Gynecol 1988; 159:238-42.
Wolf JP, Sinosich M, Anderson TL, et al. Am J Obstet Gynecol 1989; 160:45-7.

Summary

Pregnancy Category: X
Lactation Category: S

- **Mifepristone** is an effective abortifacient either alone or in combination with a prostaglandin analog.
- **Mifepristone** appears to be an effective emergency contraceptive with a good safety profile.
- **Mifepristone** is contraindicated in women planning to continue pregnancy.
- The fetal impact of continuing the pregnancy after a failed medical termination remains unclear.

Miglitol—(Glyset)

International Brand Name—Diastabol (France, Germany)

Drug Class

α-Glucosidase inhibitor; Antidiabetic agents

Indications

Diabetes mellitus type 2

Mechanism

Reversibly inhibits intestinal α-glucoside hydrolase, decreasing glucose absorption

Dosage with Qualifiers

Diabetes—begin 25mg PO prior to each meal; max 100mg PO tid

- **Contraindications**—hypersensitivity to drug or class, DKA, inflammatory bowel disease, colonic ulceration, intestinal obstruction
- **Caution**—hypoglycemia, loss of diabetic control, renal dysfunction

Maternal Considerations

There are no reports of **miglitol** in pregnant women. Because it inhibits glucose absorption, **miglitol** is additive to the hypoglycemic effect of other agents such as sulfonylureas. There is no evidence that systemic absorption contributes to its effect. Insulin is the currently recommended hypoglycemic agent of choice during pregnancy, though a growing body of work suggests a promising future for some oral hypoglycemic agents. ***Side effects*** include abdominal pain, diarrhea, flatulence, and hypoglycemia.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **miglitol** crosses the human placenta. Considering poor absorption, it is unlikely the

maternal systemic concentration will reach a clinically relevant level. Rodent studies are reassuring, revealing no evidence of teratogenicity, though there was a small increase in IUGR at doses in multiples of those used clinically. Placental transport studies in the rat indicate limited transport even after parenteral administration.

Breastfeeding Safety

There is no published experience in nursing women. The breastfeeding newborn is exposed to less than 0.5% of the maternal dose of **miglitol,** a dose that should not have a clinically relevant effect on the neonate.

Drug Interactions

May enhance **glyburide** clearance and thus reduce its hypoglycemic effect.
Reduces the average plasma **digoxin** level by 19%-28%. However, plasma **digoxin** concentrations were not altered in diabetic patients.
May significantly reduce the bioavailability of **ranitidine** and **propranolol** by 60% and 40%, respectively.
Intestinal absorbents (e.g., charcoal) and digestive enzyme preparations containing carbohydrate-splitting enzymes (e.g., **amylase, pancreatin**) may reduce the effect of **miglitol** and should not be taken together.

References

Ahr HJ, Boberg M, Brendel E, et al. Arzneimittelforschung 1997; 47:734-45.

Summary

Pregnancy Category: B
Lactation Category: S

- **Miglitol** is a potentially attractive agent for use during pregnancy and breastfeeding pending objective study.
- It should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.
- There are alternative agents for which there is more experience regarding use during pregnancy.

Milrinone—(Primacor)

International Brand Name—Coritrope (Indonesia); Corotrop (Austria, Germany, Sweden, Switzerland); Corotrope (Belgium, Colombia, France, Greece, Netherlands, Spain)

Drug Class

Inotropes; Vasodilators

Indications

CHF

Mechanism

Selective inhibitor of the cAMP phosphodiesterase in cardiac and vascular muscle

Dosage with Qualifiers

CHF—load 50mcg/kg IV over 10min, then 0.375mcg/kg/min and titrate to desired response; max 0.75mcg/kg/min

NOTE: renal dosing.

- **Contraindications**—hypersensitivity to drug or class, aortic valve disease, pulmonary valve disease, MI
- **Caution**—atrial fibrillation, atrial flutter, renal dysfunction

Maternal Considerations	**Milrinone** is an inotropic agent for the short-term management of CHF. The published experience during pregnancy is limited to case reports, typically in women with pulmonary hypertension and myocardial decompensation. The results have been mixed. ***Side effects*** include ventricular arrhythmia, ventricular ectopy, headache, chest pain, hypotension, angina, hypokalemia, and thrombocytopenia.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **milrinone** crosses the human placenta. While **milrinone** does cross the baboon placenta, placental transfer in the ewe is low. In the latter, **milrinone** increases uterine blood flow. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically. There was some evidence of embryotoxicity at high doses in rabbits.
Breastfeeding Safety	There is no published experience in nursing women. It is unknown whether **milrinone** enters human breast milk.
Drug Interactions	There is an immediate chemical interaction leading to a precipitate when furosemide is injected into an IV line with **milrinone.**
References	Atkinson BD, Fishburne JI Jr, Hales KA, et al. Am J Obstet Gynecol 1996; 174:895-6. Kitazawa T, Takaoka K, Taneike T. J Auton Pharmacol 1999; 19:65-75. Santos AC, Baumann AL, Wlody D, et al. Am J Obstet Gynecol 1992; 166:257-62. Shimizu T, Takahashi H, Matsumiya N, et al. Masui 2007; 56:949-52.
Summary	**Pregnancy Category: C** **Lactation Category: S** • **Milrinone** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk. • There are alternative agents for which there is more experience regarding use during pregnancy and lactation.

Minocycline—(Arestin; Dynacin; Lederderm; Minocin, Vectrin)

International Brand Name—Akamin (Australia); Borymycin (Malaysia, Philippines, Singapore, Taiwan); Cyclimycin (South Africa); Cynomycin (India); Klinomycin (Germany); Lederderm (Germany); Mestacine (France); Micromycin (Mexico); Minaxen (Hong Kong); Mino-50 (Belgium); Minocin (Austria, Belgium, China, England, Greece, Hong Kong, Indonesia, Ireland, Italy, Korea, Malaysia, Netherlands, Philippines, Portugal, Spain, Switzerland, Taiwan); Minocin G (Taiwan); Minocin MR (Hong Kong); Minocin PF (Malaysia, Singapore); Minoclin (Israel); Minoclir 50 (Germany); Minocyclin (Czech Republic); Minocyclin 50 Stada (Germany); Minogalen (Germany); Minoline (Taiwan); Minomax (Brazil); Minomycin (Japan, South Africa); Minotab 50 (Belgium, New Zealand, South Africa); Mino-Wolff (Germany); Mirosin (Taiwan); Mynocine (France); Romin (South Africa); Skinocyclin (Germany); Spicline (France)

Drug Class	Antibiotics; Tetracyclines
Indications	Bacterial infections (gram-negative microorganisms: *H. influenzae, H. ducreyi* [chancroid], *Yersinia pestis, Francisella tularensis, P. pestis, P. tularensis, Bartonella, Bacteroides* species, *V. comma, V. fetus, Brucella, E. coli, Enterobacter aerogenes, Shigella,*

Klebsiella; gram-positive microorganisms: *S. pyogenes, S. faecalis, S. pneumoniae, S. aureus, N. gonorrhoeae, Listeria monocytogenes, Clostridium* species, *B. anthracis, Fusobacterium fusiforme* [Vincent's infection], rickettsiae, *T. pallidum*, *Actinomyces*, amebiasis)

Mechanism

Bacteriostatic—inhibits protein synthesis

Dosage with Qualifiers

Bacterial infections, acne vulgaris—50mg PO qd to tid
Gonorrhea—100mg PO bid ×5d; alternative 100-200mg ×1 followed by 50mg PO qid
Syphilis—100mg PO bid ×15d
Mycobacterium marinum infection—100mg PO bid ×6-8w

- **Contraindications**—hypersensitivity to drug or class
- **Caution**—renal or hepatic dysfunction

Maternal Considerations

There are no adequate reports or well-controlled studies of **minocycline** in pregnant women. Case reports note its use for the treatment of recurrent pemphigoid gestations. Similar to other tetracyclines, concern has been raised that it might lower the effectiveness of low-dose oral contraceptive agents. (See **Tetracycline.**)
Side effects include thrombocytopenia, hepatotoxicity, neutropenia, Jarisch-Herxheimer reaction, enterocolitis, fatty liver disease, pseudomembranous colitis, skeletal abnormalities, hemolytic anemia, hepatic or renal dysfunction, increased BUN, glossitis, ataxia, vertigo, tinnitus, pseudotumor cerebri, and vaginal candidiasis.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **minocycline** crosses the human placenta. It is unlikely the maternal systemic concentration will reach a clinically relevant level if applied topically for acne. Other tetracyclines cross the human placenta and are associated with tooth discoloration and, in rodents, increased embryo resorption. (See **Tetracycline.**)

Breastfeeding Safety

There are no adequate reports or well-controlled studies in nursing women. It is unknown whether **minocycline** enters human breast milk. Milk discoloration is reported. (See **Tetracycline.**)

Drug Interactions

Patients on anticoagulants may require a lower dose of their anticoagulant because tetracyclines can depress plasma prothrombin activity.
It is advisable to avoid using tetracycline with penicillin since bacteriostatic drugs may interfere with the bactericidal action of penicillin.
May cause fatal renal toxicity when used with **methoxyflurane.**
Minocycline may render oral contraceptives less effective.
Isotretinoin should be avoided shortly before, during, and shortly after **minocycline** therapy as each drug alone has been associated with pseudotumor cerebri.
There is an increased risk of ergotism when ergot alkaloids or their derivatives are given with tetracyclines.

References

Hunt MJ, Salisbury EL, Grace J, Armati R. Br J Dermatol 1996; 134:943-5.
Loo WJ, Dean D, Wojnarowska F. Clin Exp Dermatol 2001; 26:726-7.
See also **Tetracycline.**

Summary

Pregnancy Category: D
Lactation Category: U

- The tetracyclines are generally contraindicated during pregnancy because of fetal tooth discoloration.
- There are alternative agents during pregnancy for almost all indications.

Minoxidil—(Alopexil; Alostil; Loniten; Lonolax; Mintop; Modil; Rogaine)

International Brand Name—Alopexy (France); Alopexyl (France); Alostil (France); Apo-Gain (Canada, Malaysia); Crecisan (Spain); Growell (Singapore); Hairgaine (Israel); Hairgrow (Hong Kong); Hair-Treat (Israel); Hair-Treat Forte (Israel); Headway (New Zealand); Hebald (India); Kapodin (Spain); Kenacin (Paraguay); Locemix (Argentina); Locion EPC (Dominican Republic); Loniten (Australia, Austria, Brazil, Canada, Czech Republic, England, Greece, Hong Kong, Hungary, Ireland, Italy, Malaysia, Poland, Portugal, Russia, South Africa, Spain, Switzerland, Taiwan, Thailand); Lonnoten (Belgium, Finland, Netherlands); Lonolox (Germany); Lonoten (France); Manoxidil (Thailand); Minona (Finland); Minoxi 5 (Hong Kong); Minoxidil Isac (Philippines); Minoxidil MK (Colombia); Minoximen (Italy); Minoxitrim (Singapore); Minoxyl (Korea); Moxidil (Korea); Multigain (India); Neocapil (Switzerland); Neoxidil (Hong Kong, Israel, Singapore); Nuhair (Thailand); Regaine (Austria, Belgium, Brazil, Bulgaria, Chile, Czech Republic, Denmark, Ecuador, England, Finland, France, Germany, Greece, Hong Kong, Hungary, Indonesia, Ireland, Israel, Italy, Malaysia, Mexico, Netherlands, Norway, Peru, Poland, Portugal, Russia, South Africa, Spain, Sweden, Switzerland, Taiwan, Thailand, Venezuela); Regroe (Philippines); Regrou (Indonesia); Regrowth (Thailand); Rehair (Indonesia); Rogaine (Canada); Tiazolin (Colombia); Ylox (Argentina)

Drug Class

Antihypertensives; Vasodilators

Indications

Hypertension, baldness

Mechanism

Unknown; peripheral vessel vasodilator

Dosage with Qualifiers

Hypertension—40mg/d in divided doses; max 100mg PO qd
Baldness (alopecia androgetica)—apply 1ml to scalp bid (2.5% solution)

- **Contraindications**—hypersensitivity to drug or class, pheochromocytoma, pericardial effusion
- **Caution**—renal or hepatic dysfunction, MI

Maternal Considerations

There are no adequate reports or well-controlled studies of **minoxidil** in pregnant women. **Minoxidil** is no longer often used for the treatment of hypertension, but rather is used for balding. Balding can be a normal physiologic occurrence in women taking oral contraceptives or after parturition. It can be treated with either **progesterone** or **minoxidil.** Less than 2% of the topical dose is absorbed systemically. ***Side effects*** include CHF, Stevens-Johnson syndrome, pericardial effusion, angina, edema, tachycardia, hypertrichosis, headache, breast tenderness, paresthesias, weight gain, thrombocytopenia, EEG changes, contact dermatitis, itching, skin irritation, and leukopenia.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **minoxidil** crosses the human placenta. Caudal regression syndrome was reported in a mother taking **minoxidil** long before and during gestation. Fetal hypertrichosis is also reported in fetuses whose mothers used **minoxidil** topically throughout pregnancy. Rodent studies are

reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically. Embryotoxicity was seen with high doses.

Breastfeeding Safety

There are no adequate reports or well-controlled studies in nursing women. **Minoxidil** enters human breast milk, achieving a peak concentration of 50mcg/L 2h after 7.5mg PO. It is unlikely that topically administered drug would result in a clinically relevant milk concentration.

Drug Interactions

Use with **guanethidine** may result in profound orthostatic effects. If at all possible, **guanethidine** should be discontinued well before **minoxidil** is begun. Where this is not possible, **minoxidil** therapy should be started in the hospital and the patient should remain institutionalized until severe orthostatic effects are no longer present or the patient has learned to avoid activities that provoke them.

References

Burke KE. Postgrad Med 1989; 85:52-8, 67-73, 77.
Kaler SG, Patrinos ME, Lambert GH, et al. Pediatrics 1987; 79:434-6.
Valdivieso A, Valdes G, Spiro TE, Westerman RL. Ann Intern Med 1985; 102:135.
Veyrac G, Chiffoleau A, Bailly C, et al. Therapie 1995; 50:474-6.

Summary

Pregnancy Category: C
Lactation Category: S (topical); **U** (oral)
- **Minoxidil** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Mirtazapine—(Remeron)

International Brand Name—Avanza (Australia); Norset (France); Remergil (Germany)

Drug Class

Antidepressants; Tetracyclics

Indications

Depression

Mechanism

Unknown; antagonizes α_2-adrenergic and serotonin receptors

Dosage with Qualifiers

Depression—15-45mg PO qhs; begin 15mg PO qhs

- **Contraindications**—hypersensitivity to drug or class, MAOIs <14d
- **Caution**—advanced age, renal or hepatic dysfunction, mania, hypomania, seizures, CV disease, consumption of alcohol

Maternal Considerations

Depression is common during and after pregnancy, but typically goes unrecognized. Pregnancy is not a reason *a priori* to discontinue psychotropic drugs. **Mirtazapine** is one option for patients unresponsive to or intolerant of SSRIs. Most of the published experience with **mirtazapine** during pregnancy is limited to small case series and epidemiologic surveys.
Side effects include agranulocytosis, orthostatic hypotension, torsades de pointes, increased appetite, weight gain, hypercholesterolemia, dry mouth, somnolence, dyspnea, confusion, tremor, abnormal thinking, abnormal dreams,

	dizziness, asthenia, constipation, flu-like symptoms, elevated LFTs, urinary frequency, myalgia, and back pain.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **mirtazapine** crosses the human placenta. Based on reports from Teratogen Information Services, **mirtazapine** does not appear to increase the baseline rate of major malformations of 1-3%. However, there is an increase in spontaneous losses similar to that reported for other antidepressants. Further, there is a single case report of recurrent neonatal hypothermia through 10d of life.
Breastfeeding Safety	**Mirtazapine** enters human breast milk. Mean relative infant doses for **mirtazapine** and desmethylmirtazapine were 1.5% and 0.4%, respectively. The mean M:P ratio was 1.1 for **mirtazapine** and 0.6 for desmethylmirtazapine. **Mirtazapine** was detected (1.5mcg/L) in only 1 of 4 infants tested.
Drug Interactions	**Mirtazapine** is a substrate for several CYP enzymes, including CYP2D6, 1A2, and 3A4. *In vitro* studies suggest **mirtazapine** is not a potent inhibitor of these enzymes, an indication that it is not likely to have a clinically significant inhibitory effect on the metabolism of other drugs that are substrates for these enzymes. Impairment of cognitive and motor skills is additive to that produced by ethanol and **diazepam.**
References	Brown CS. Obstet Gynecol Clin North Am 2001; 28:241-68. Djulus J, Koren G, Einarson TR, et al. J Clin Psychiatry 2006; 67:1280-4. Kristensen JH, Ilett KF, Rampono J, et al. Br J Clin Pharmacol 2007; 63:322-7. Lennestal R, Kallen B. J Clin Psychopharmacol 2007; 27:607-13. Sokoloven N, Merlob P, Klinger G. Can J Clin Pharmacol 2008; 15:e188-90.
Summary	**Pregnancy Category: C** **Lactation Category: S** • **Mirtazapine** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk. • There are alternative agents for which there is more experience regarding use during pregnancy and lactation.

Misoprostol—(Cytotec)

International Brand Name—Cityl (Colombia); Cyprostol (Austria); Cytolog (India); Cytotec (Argentina, Brazil, Canada, China, Colombia, Ecuador, Hong Kong, Indonesia, Japan, Korea, Malaysia, Mexico, Peru, Taiwan, Thailand); Gastotec (Korea); Gastrul (Indonesia); Gymiso (France); Misel (Korea); Misotrol (Chile); U-Miso (Taiwan)

Drug Class	Abortifacients; Gastrointestinals; Oxytocics; Prostaglandins; Stimulants, uterine
Indications	NSAID-induced gastric ulcer, constipation, cervical ripening, induction of labor, abortion
Mechanism	Inhibits gastric acid secretions; protects gastric mucosa; stimulates uterine contractility

■ Dosage with Qualifiers

NSAID-induced gastric ulcers—100-200mcg PO qid
Constipation—600-2400mcg/d PO bid to qid
Cervical ripening—25mcg vaginally q3-6h; wait at least 4h before initiating **oxytocin;** max 50mcg/dose
Abortion—400mcg PO ×1; may repeat q4-6h

NOTE: take with meals; ***misoprostol*** *is often used with* ***mifepristone*** *for 1st trimester termination.*

- **Contraindications**—hypersensitivity to drug or class, pregnancy (for GI indications)
- **Caution**—childbearing potential (for GI indications), prior cesarean section, myomectomy or other uterine surgery, fetal macrosomia, grand multiparity

■ Maternal Considerations

Misoprostol is a prostaglandin E analog. The only FDA-approved indication is the treatment and prevention of intestinal ulcer disease resulting from NSAID drug use. Although still not approved by the FDA for other indications, **misoprostol** is well studied and widely used for both cervical ripening and the induction of labor during either the 2nd or 3rd trimesters. The route of administration is relevant. At 2min after 600mcg PO in postpartum women, the plasma level is 91.5pg/ml; it peaks at 20min (344pg/ml), and then falls steeply by 120min (27.8pg/ml). **Misoprostol** administered PR generates lower peak levels and a reduction in the prevalence of adverse effects compared with oral drug. The AUC for rectal **misoprostol** is higher by 121pg/h/ml than oral drug; the mean maximum serum concentration is also significantly lower and occurs >20min later than it does for oral drug. Women reported shivering after administration: 76% after 600mcg PO, 56% after 400mcg PR, and 54% after 600mcg PR. The relative risk of shivering in both PR groups is 25% lower than in the PO group. Severe shivering is reduced by 70% in PR groups. Increasing rectal doses may achieve higher efficacy without reducing the acceptability of the treatment.
Early to mid-pregnancy termination: Combined with **mifepristone, misoprostol** is safe and effective for medical termination of early pregnancy. Typically, **misoprostol** is given PV 48h after **mifepristone.** The administration of either 2 doses of **misoprostol** (400mcg) or one dose (800mcg) after **mifepristone** significantly reduces the risk of failed abortion compared to **mifepristone** alone. Vaginal **misoprostol** shortens the time from induction to delivery compared to PO. A wide range of dosing regimens has been suggested for 2nd trimester termination; 400mcg PO or 400mcg PV q4-6h are common. Dosing regimens for the induction of labor generally decrease with advancing gestation (e.g., vaginal **misoprostol:** 13-17w, 200mcg q6h; 18-26w, 100mcg q6h; and greater than 27w, 25-50mcg q4h). **Misoprostol** does not reduce the blood loss and the time for placental expulsion after 2nd trimester termination.
Term pregnancy: **Misoprostol** is commonly used to induce cervical ripening and labor. In August 2000, the manufacturer issued a warning letter to American health care providers cautioning against the use of **misoprostol** in pregnant women secondary to the lack of safety data for its use in obstetric practice. The ACOG took issue with that position, as there were a multitude of studies supporting its use. **Misoprostol** is effective in ripening the cervix and inducing labor at term when given either PV or PO. It is inexpensive and stable at room temperature. Debate continues on the optimal dose, regimen, route of administration, and concurrent use of ancillary ripening methods (laminaria, Foley balloon, **dinoprostone** gel). Low-dose **misoprostol** (25mcg) is effective for cervical ripening and labor

induction. More recently, a single 25mcg outpatient intravaginal dose of **misoprostol** was reported to be effective in decreasing the interval to delivery in women with unfavorable cervices at term. The study, however, was inadequately powered to provide strong comment on safety. Uterine tachysystole is more common after 50mcg or more given vaginally or orally. Clinical trials report increased frequencies of meconium passage, neonatal acidemia, and cesarean delivery due to fetal distress if high doses are used. Some trials report no decrease in the overall rate of cesarean delivery, though the frequency of failed induction as an indication is reduced. **Misoprostol** is effective for the induction of labor in women with PPROM, intrauterine fetal demise, or preeclampsia. A recent randomized trial compared **dinoprostone** to **misoprostol** for the induction of labor in women at high risk for fetal distress. **Misoprostol** and **dinoprostone** proved equally safe for the induction of labor. However, **misoprostol** was more efficient and significantly cheaper. Parity, initial cervical dilation, and gestational age are the most useful predictors of successful cervical ripening and labor induction if administered PV. The most common side effects during labor induction are shivering and uterine tachysystole. Because of the tachysystole, low-dose **oxytocin** may be preferred in the high-risk parturient whose fetus is at increased risk for fetal intolerance to labor. In 2002, the ACOG Committee Opinion on Obstetric Practice concluded the risk of uterine rupture during VBAC is substantially increased by the use of various prostaglandin cervical ripening agents. They are specifically discouraged in favor of mechanical methods. Rectal **misoprostol** (400mcg) may be similar to **oxytocin** (10IU with the anterior shoulder), while either rectal or oral **misoprostol** are significantly less effective than **oxytocin** plus **methylergonovine** for the prevention and treatment of postpartum hemorrhage. **Misoprostol** (800mcg) dissolved in 30ml saline and administered by intraumbilical injection appears to reduce the need for manual removal of a retained adherent placenta, whereas **oxytocin** effectiveness was similar to the injection of saline alone.
Side effects include abortion, uterine rupture, uterine hyperstimulation, diarrhea, constipation, abdominal pain, N/V, flatulence, dyspepsia, hypermenorrhea, dysmenorrhea, and headache.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. **Misoprostol** is associated with a higher rate of uterine hyperstimulation, more variable decelerations, and likely as a result, a higher prevalence of meconium. However, compared to **oxytocin,** there is no increase in the incidence of cesarean section for fetal distress or umbilical acidemia. A recent meta-analysis concluded there was no difference in the frequencies of uterine hyperstimulation with FHR changes whether **misoprostol** was given PO or intravaginally. **Misoprostol** is not embryotoxic or teratogenic in rodents at doses 625× and 63× the MRHD, respectively. Congenital defects after unsuccessful medical abortions are reported, but a mechanism has yet to be demonstrated. Several reports in the literature associate the use of **misoprostol** during the 1st trimester with skull defects, cranial nerve palsies, facial malformations, and limb defects. In rodents, prostaglandins but not **oxytocin** stimulate intestinal smooth muscle.

Breastfeeding Safety

Orally administered **misoprostol** is secreted in colostrum within 1h, but it is essentially undetectable by 5h. The AUC is only 51.4pg/h/ml, or ⅛ of the maternal AUC. It has not been studied in women with established lactation. Though **misoprostil** is

rapidly metabolized, there is no information on whether its active metabolite is excreted.

Drug Interactions

No clinically relevant interactions identified.

References

Abdel-Aleem H, Villar J, Gulmezoglu AM, et al. Eur J Obstet Gynecol Reprod Biol 2003; 108:25-8.
Alfirevic Z. Cochrane Database Syst Rev 2001; (2):CD001338.
Ashok PW, Templeton A, Wagaarachchi PT, Flett GM. BJOG 2002; 109:1281-9.
Barrilleaux PS, Bofill JA, Terrone DA, et al. Am J Obstet Gynecol 2002; 186:1124-9.
Bartley J, Baird DT. BJOG 2002; 109:1290-4.
Bebbington MW, Kent N, Lim K, et al. Am J Obstet Gynecol 2002; 187:853-7.
Carlan SJ, Blust D, O'Brien WF. Am J Obstet Gynecol 2002; 186:229-33.
Dickinson JE, Evans SF. Obstet Gynecol 2003; 101:1294-9.
Elsheikh A, Antsaklis A, Mesogitis S, et al. Arch Gynecol Obstet 2001; 265:204-6.
Ferguson JE 2nd, Head BH, Frank FH, et al. Am J Obstet Gynecol 2002; 187:273-9.
Gómez Ponce de León R, Wing D, Fiala C. Int J Gynaecol Obstet 2007; 99(Suppl 2):S190-3.
Gulmezoglu AM, Forna F, Villar J, Hofmeyr GJ. Cochrane Database Syst Rev 2007; (3):CD000494.
Hall R, Duarte-Gardea M, Harlass F. Obstet Gynecol 2002; 99:1044-8.
Has R, Batukan C, Ermis H, et al. Gynecol Obstet Invest 2002; 53:16-21.
Jain JK, Dutton C, Harwood B, et al. Hum Reprod 2002; 17:1477-82.
Karkanis SG, Caloia D, Salenieks ME, et al. J Obstet Gynaecol Can 2002; 24:149-154.
Khan RU, El-Refaey H. Obstet Gynecol 2003; 101:968-74.
Matonhodze BB, Katsoulis LC, Hofmeyr GJ. J Perinat Med 2002; 30:405-10.
McKenna DS, Ester JB, Proffitt M, Waddell KR. Obstet Gynecol 2004; 104:579-84.
[No authors]. Obstet Gynecol 2002; 99:679-80.
Ozden S, Delikara MN, Avci A, Ficicioglu C. Int J Gynaecol Obstet 2002; 77:109-15.
Pandis GK, Papageorghiou AT, Otigbah CM, et al. Ultrasound Obstet Gynecol 2001; 18:629-35.
Rogers MS, Yuen PM, Wong S. Acta Obstet Gynecol Scand 2007; 86:48-54.
Rozenberg P, Chevret S, Goffinet F, et al. BJOG 2001; 108:1255-62.
Rozenberg P, Chevret S, Senat MV, et al. Am J Obstet Gynecol 2004; 191:247-53.
Sahin HG, Sahin HA, Kocer M. Acta Obstet Gynecol Scand 2002; 81:252-7.
Schaff EA, Fielding SL, Westhoff C. Contraception 2002; 66:247-50.
Shetty A, Danielian P, Templeton A. Am J Obstet Gynecol 2002; 186:72-6.
Shetty A, Mackie L, Danielian P, et al. BJOG 2002; 109:645-50.
Wagaarachchi PT, Ashok PW, Smith NC, Templeton A. BJOG 2002; 109:462-5.
Wing DA. Drug Saf 2002; 25:665-76.
Wing DA, Tran S, Paul RH. Am J Obstet Gynecol 2002; 186:1237-40.
Winikoff B, Dzuba IG, Creinin MD, et al. Obstet Gynecol 2008; 112:1303-10.

Zikopoulos KA, Papanikolaou EG, Kalantaridou SN, et al. Hum Reprod 2002; 17:3079-83.

Summary

Pregnancy Category: X
Lactation Category: U

- **Misoprostol** is an effective adjunct to **mifepristone** for medical abortion during early pregnancy. Two doses of **misoprostol** compared to one significantly reduce the failed abortion rate.
- **Misoprostol** induction of cervical ripening or labor is a common practice.
- Oral **misoprostol** is more convenient than vaginal, but may increase the risk of tachysystole.
- **Misoprostol** should not be used for either ripening or labor induction in women undergoing VBAC as it may increase the risk of uterine rupture.

Mitomycin—(Mutamycin)

International Brand Name—Ametycine (France); Datisan (Argentina); Metomit (Chile); Mitocyna (Paraguay); Mitomicina-C (Portugal); Mitomycin C (Hong Kong, India, Israel); Mitomycin-C (Austria, Bulgaria, Greece, Hungary, Indonesia, Italy, Netherlands, Philippines, Poland, Russia, Spain, Switzerland, Taiwan, Thailand, Turkey); Mitomycin-C Kyowa (Australia, Czech Republic, England); Mitomycine (Belgium); Mixandex (Mexico); Mutamycin (Canada, Denmark, Norway, Portugal, Sweden, Uruguay); Vetio (Argentina)

Drug Class

Antineoplastics, antibiotic

Indications

Stomach and pancreatic cancer

Mechanism

Inhibits DNA synthesis

Dosage with Qualifiers

Stomach cancer—numerous dosing schedules depending on disease, response, and concomitant therapy
Pancreatic cancer—numerous dosing schedules depending on disease, response, and concomitant therapy

- **Contraindications**—hypersensitivity to drug or class, thrombocytopenia, coagulopathy, herpes zoster, renal dysfunction
- **Caution**—unknown

Maternal Considerations

Mitomycin is an alkylating agent used as adjunct therapy and is not recommended as single-agent, primary therapy. There are no adequate reports or well-controlled studies of **mitomycin** in pregnant women.
Side effects include thrombocytopenia, leukopenia, hemolytic-uremic syndrome, renal dysfunction, interstitial pneumonitis, sepsis, N/V, alopecia, anorexia, diarrhea, and cardiac or renal toxicity.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **mitomycin** crosses the human placenta. It crosses the rodent placenta in a limited fashion, reaching F:M ratios less than 10%. In rodents, **mitomycin** is a potent teratogen damaging the preimplantation blastocyst, leading to embryo loss. Later exposure produces a myriad of bony malformations. Its effect is enhanced by caffeine. There are no reports in humans.

Breastfeeding Safety	There is no published experience in nursing women. It is unknown whether **mitomycin** enters human breast milk.
Drug Interactions	No clinically relevant interactions identified.
References	Boike GM, Deppe G, Young JD, et al. Gynecol Oncol 1989; 34:187-90. Nagao T, Saitoh Y, Yoshimura S. Teratology 2000; 61:248-61. Rahman ME, Ishikawa H, Watanabe Y, Endo A. Reprod Toxicol 1996; 10:485-9. Sivak A. Regul Toxicol Pharmacol 1994; 19:1-13.
Summary	**Pregnancy Category: C** **Lactation Category: U** • **Mitomycin** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk. • This drug should be assumed a human teratogen until proved otherwise.

Mitoxantrone—(Novantrone)

International Brand Name—Domitrone (Philippines); Elsep (France); Formyxan (Mexico); Misostol (Paraguay); Mitoxantrona (Peru); Mitoxgen (Argentina); Mitroxone (Mexico); Neotalem (Chile); Norexan (Indonesia); Novantron (Austria, Germany, Switzerland); Novantrone (Belgium, Brazil, Bulgaria, Canada, China, Czech Republic, Denmark, Ecuador, England, Finland, France, Hong Kong, Hungary, Indonesia, Ireland, Italy, Japan, Korea, Malaysia, Netherlands, Norway, Poland, Portugal, Russia, South Africa, Spain, Sweden, Taiwan, Turkey); Oncotron (India); Onkotrone (Australia)

Drug Class	Antineoplastics
Indications	AML, MS
Mechanism	Multiple actions that disturb DNA synthesis
Dosage with Qualifiers	AML—numerous dose schedules depending on disease, response, and concomitant therapy MS—12mg/m^2 IV over 5-15min q3mo *NOTE: an evaluation of LV function and a CBC should precede each dose.* • **Contraindications**—hypersensitivity to drug or class, prior **doxorubicine** exposure, CHF, myelosuppression • **Caution**—unknown
Maternal Considerations	There are no adequate reports or well-controlled studies of **mitoxantrone** in pregnant women. The published experience is limited to several case reports. More recently, **mitoxantrone** has been advocated as a treatment for MS, a disease common in reproductive-age women. ***Side effects*** include seizures, arrhythmia, myocardial toxicity, CHF, myelosuppression, renal failure, N/V, fever, abdominal pain, GI bleeding, alopecia, diarrhea, sepsis, stomatitis, conjunctivitis, pneumonia, UTI, headache, cough, and fungal infection.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **mitoxantrone** crosses the human placenta. In the single report of 1st trimester use, the neonate was growth restricted. Rodent studies are reassuring,

revealing no evidence of teratogenicity, but the doses studied were too low.

Breastfeeding Safety

There is no published experience in nursing women. **Mitoxantrone** enters human breast milk, reaching a significant concentration, though the kinetics remain unclear. It should probably be considered incompatible with breastfeeding pending additional study.

Drug Interactions

No clinically relevant interactions identified.

References

De Santis M, Straface G, Cavaliere AF, et al. Neurotoxicology 2007; 28:696-7.
Jain KK. Expert Opin Investig Drugs 2000; 9:1139-49.
Requena A, Velasco JG, Pinilla J, Gonzalez-Gonzalez A. Eur J Obstet Gynecol Reprod Biol 1995; 63:139-41.

Summary

Pregnancy Category: D
Lactation Category: NS (possibly)
- **Mitoxantrone** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Modafinil—(Provigil)

International Brand Name—Alertec (Canada); Modasomil (Austria); Modavigil (New Zealand); Modiodal (France, Mexico); Provigil (England, Ireland, Israel, Korea, Taiwan); Vigicer (Argentina); Vigil (Germany)

Drug Class

Analeptics; CNS stimulants

Indications

Narcolepsy, MS

Mechanism

Unknown

Dosage with Qualifiers

Narcolepsy—200mg PO qam; max 400mg qd
MS—200mg PO qam; max 400mg qd

NOTE: hepatic dosing.

- **Contraindications**—hypersensitivity to drug or class, LV hypertrophy
- **Caution**—CAD, hypertension, renal or hepatic dysfunction, history of psychosis, alcohol use

Maternal Considerations

The published experience with **modafinil** during pregnancy is limited to a case report. **Modafinil** is an inducer of CYP enzymes. Thus, the effectiveness of oral contraceptives may be reduced during therapy and for 1mo after discontinuation. MS is fairly common in reproductive-age women.
Side effects include arrhythmia, tachycardia, chest pain, MI, headache, N/V, palpitations, insomnia, anxiety, euphoria, rhinitis, pharyngitis, and epistaxis.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **modafinil** crosses the human placenta. Adequate rodent teratogenicity studies have not been performed. Those that have been done suggest an increased rate of embryotoxicity. The manufacturer reports 7 exposures during pregnancy without apparent adverse effects.

Breastfeeding Safety

There is no published experience in nursing women. It is unknown whether **modafinil** enters human breast milk.

Drug Interactions

Absorption may be delayed up to 1h when given with either **methylphenidate** or **dextroamphetamine.**
In a drug interaction study between **modafinil** and **ethinyl estradiol** (200mg/d ×7d followed by 400mg/d ×21d), there was an 11% decrease in C_{max} and 18% decrease in AUC(0-24) of **ethinyl estradiol** (0.035 mg PO plus norgestimate). There was no apparent change in the elimination rate of **ethinyl estradiol.** A single dose of **triazolam** (0.125mg) was also administered on the same days as those for the plasma sampling for **ethinyl estradiol** pharmacokinetics. The mean C_{max} and AUC(0-8) of **triazolam** were decreased by 42% and 59%, respectively, and its elimination t/2 was decreased by approximately 1h after the **modafinil.**
May enhance the clearance of **cyclosporine.**
In vitro studies using human liver microsomes showed that **modafinil** reversibly inhibits CYP2C19 at pharmacologically relevant concentrations. CYP2C19 is also reversibly inhibited, with similar potency, by a circulating metabolite, modafinil sulfone. Although the maximum plasma concentrations of modafinil sulfone are much lower than those of the parent, the combined effect of both could produce sustained partial inhibition of the enzyme. Drugs that are largely eliminated via CYP2C19 metabolism, such as **diazepam, propranolol, phenytoin** (also via CYP2C9), or (*S*-)**mephenytoin,** may have prolonged elimination upon co-administration and may require a dose reduction.
CYP2C19 also provides an ancillary pathway for the metabolism of certain TCAs (e.g., **clomipramine, desipramine**) that are primarily metabolized by CYP2D6. In TCA-treated patients deficient in CYP2D6 (i.e., "poor metabolizers" of debrisoquine; 7-10% of the Caucasian population; similar or lower in other populations), the amount metabolized by CYP2C19 may be substantially increased. **Modafinil** may cause elevation of the levels of the TCAs in this subset of patients.
Use of potent inducers of CYP3A4 (e.g., **carbamazepine, phenobarbital, rifampin**) or inhibitors of CYP3A4 (e.g., **itraconazole, ketoconazole**) could alter the plasma levels of **modafinil.**

References

Williams SF, Alvarez JR, Pecho HF, Apuzzio JJ. Obstet Gynecol 2008; 111:522-4.

Summary

Pregnancy Category: C
Lactation Category: U
- **Modafinil** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Moexipril—(Fampress; Univasc)

International Brand Name—Cardiotensin (Poland); Femipres (Italy); Fempres (Peru); Fempress (Austria, Bulgaria, Germany); Moex (Czech Republic, Denmark, France, Hong Kong, Israel); Perdix (England, Ireland); Tensotec (Malaysia); Univasc (Korea, Philippines)

Drug Class

ACEI/A2R-antagonists; Antihypertensives

Indications

Hypertension

Mechanism	Inhibits ACE
Dosage with Qualifiers	Hypertension—7.5-30mg PO qd • **Contraindications**—hypersensitivity to drug or class, history of ACEI angioedema, hereditary angioedema, idiopathic angioedema, pregnancy • **Caution**—renal artery stenosis, severe cardiac failure, collagen vascular disease, renal dysfunction, hypotension
Maternal Considerations	There is no published experience with **moexipril** during pregnancy. ***Side effects*** include hypotension, postural hypotension, syncope, abdominal pain, constipation, vomiting, appetite change, dry mouth, pancreatitis, hepatic dysfunction, bronchospasm, dyspnea, renal insufficiency, oliguria, drowsiness, sleep disturbances, nervousness, mood changes, anxiety, tinnitus, sweating, malaise, arthralgia, and hemolytic anemia.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **moexipril** crosses the human placenta. Other inhibitors of the renin-angiotensin system cross and can cause fetal renal failure. They are generally considered contraindicated during pregnancy unless there is no other therapeutic option. The same is true for **moexipril.**
Breastfeeding Safety	There is no published experience in nursing women. It is unknown whether **moexipril** enters human breast milk.
Drug Interactions	Hypotension may occur in patients on diuretic therapy when ACEIs are started. The likelihood can be minimized by discontinuing the diuretic for several days or cautiously increasing salt intake before starting **moexipril.** If this is not possible, the starting dose of **moexipril** should be reduced. May increase serum potassium as it decreases aldosterone secretion. Use of potassium-sparing diuretics (e.g., **amiloride, spironolactone, triamterene**) or potassium supplements with ACEIs can increase the risk of hyperkalemia. Increased serum **lithium** levels and symptoms of **lithium** toxicity have been reported in patients receiving ACEIs.
References	There is no published experience in pregnancy or during lactation.
Summary	**Pregnancy Category: C** (1st trimester), **D** (2nd and 3rd trimesters) **Lactation Category: U** • **Moexipril** is likely a human teratogen and should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk, and after other antihypertensive agents have failed. • There are alternative agents for which there is more experience regarding use during pregnancy and lactation.

Molindone—(Moban)

International Brand Name—Moban (Finland, Korea)

Drug Class	Antipsychotics
Indications	Schizophrenia

Mechanism	Unknown (selectively antagonizes dopamine D_2 receptors)
Dosage with Qualifiers	Schizophrenia—begin 50-75mg qd divided tid or qid; increase to 100mg qd every 3-5d; max 225mg/d • **Contraindications**—hypersensitivity to drug or class, CNS depression • **Caution**—seizures
Maternal Considerations	Acute schizophrenia presents several difficult management decisions during pregnancy, and a careful risk:benefit analysis is required. There are no adequate reports or well-controlled studies of **molindone** in pregnant women. The published experience consists of isolated case reports. ***Side effects*** include constipation, extrapyramidal effects, blurred vision, tardive dyskinesia, neuroleptic malignant syndrome, leukopenia, decreased sweating, dry mouth, akinesia, tachycardia, depression, hyperactivity, and euphoria.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **molindone** crosses the human placenta. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically.
Breastfeeding Safety	There is no published experience in nursing women. It is unknown whether **molindone** enters human breast milk.
Drug Interactions	No clinically relevant interactions identified.
References	Kahn JL. Am J Psychiatry 1979; 136:1617-8. Pinkofsky HB. Ann Clin Psychiatry 1997; 9:175-9. Wesp CE Jr, Annitto W, Feinsod R. Am J Psychiatry 1979; 136:975.
Summary	**Pregnancy Category: C** **Lactation Category: U** • **Molindone** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Mometasone—(Elocon; Nasonex)

International Brand Name—Allermax Aqueous (Australia); Asmanex Twisthaler (England, Ireland); Dermotasone (Korea); Dermovel (Indonesia); Ecotone (Japan); Ecural (Germany); Elica (Mexico, Philippines); Elocom (Belgium, Brazil, Bulgaria, Canada, Chile, Colombia, Costa Rica, Czech Republic, Dominican Republic, El Salvador, Guatemala, Honduras, Hungary, Korea, Nicaragua, Panama, Peru, Poland, Russia, Spain, Switzerland); Elocon (Argentina, Austria, Denmark, England, Finland, Greece, India, Indonesia, Ireland, Italy, Netherlands, Norway, Philippines, South Africa, Sweden, Turkey, Uruguay, Venezuela); Elocon Cream (New Zealand); Elocon Ointment (New Zealand); Elocyn (Korea); Elomet (Ecuador, Hong Kong, Malaysia, Mexico, Taiwan, Thailand); Eloson (China); Elox (Indonesia); Flumeta (Japan); Mefurosan (Indonesia); Metaspray (India); Momate (Philippines); Monovel (Colombia, Taiwan); Morecort (Korea); Motaderm (Indonesia); Nasonex (Argentina, Brazil, Chile, Colombia, Ecuador, Israel, Peru, South Africa); Nasonex Nasal Spray (Australia, England, Germany, Hong Kong, Indonesia, Ireland, Korea, Malaysia, Peru, Philippines, Singapore); Novasone Cream (Australia); Novasone Lotion (Australia); Novasone Ointment (Australia); Rinelon (Mexico, South Africa, Thailand); Rivelon (Philippines); Uniclar (Colombia, Mexico)

Drug Class	Corticosteroids; Dermatologics
Indications	Allergic rhinitis, dermatitis
Mechanism	Unknown (anti-inflammatory)

Dosage with Qualifiers

Allergic rhinitis—2 sprays/nostril qd; begin 2w before the allergy season
Dermatitis—apply qd

NOTE: available as spray and cream.

- **Contraindications**—hypersensitivity to drug or class
- **Caution**—unknown

Maternal Considerations

Allergic rhinitis affects ⅓ of women of childbearing age. There are no adequate reports or well-controlled studies of **mometasone** in pregnant women. This agent offers the potential advantage of once-daily dosing. However, **budesonide** is generally considered the preferred agent.
Side effects include adrenal suppression, skin atrophy, dryness, folliculitis, pruritus, irritation, and burning.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **mometasone** crosses the human placenta. There are no documented epidemiologic studies with IN corticosteroids (e.g., **budesonide, fluticasone, mometasone**) during pregnancy. However, inhaled corticosteroids (e.g., **beclomethasone**) are not incriminated as teratogens. Considering the dose and route, it is unlikely the maternal systemic concentration will reach a clinically relevant level.

Breastfeeding Safety

There is no published experience in nursing women. It is unknown whether **mometasone** enters human breast milk. However, considering the indications, dose, and route, it is unlikely the breastfed neonate would ingest clinically relevant amounts.

Drug Interactions

Caution is advised if **ketoconazole** is initiated since **mometasone** plasma levels appear to increase and **cortisol** levels appear to decrease.

References

Abdullah AK, Khan S. J Asthma 2007; 44:1-12.
Mazzotta P, Loebstein R, Koren G. Drug Saf 1999; 20:361-75.

Summary

Pregnancy Category: C
Lactation Category: S (likely)

- **Mometasone** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Moricizine—(Ethmozine. Note: No longer available in the US.)

International Brand Name—None identified.

Drug Class

Antiarrhythmics, class IA, IB, and IC

Indications

Ventricular arrhythmia

Mechanism

Stabilizes membranes and depresses phase 0 action potential

Dosage with Qualifiers

Ventricular arrhythmia—200-300mg PO q8h

- **Contraindications**—hypersensitivity to drug or class, cardiogenic shock, 2nd and 3rd degree AV block
- **Caution**—unknown

Maternal Considerations

Moricizine is a phenothiazine derivative with class IC antiarrhythmic properties. It undergoes extensive first-pass metabolism, has a bioavailability of 34-38%, and is extensively plasma bound. There is no published experience with **moricizine** during pregnancy.

Side effects include arrhythmia, ECG changes, CHF, cardiac arrest, N/V, dizziness, dry mouth, headache, fatigue, palpitations, chest pain, dyspnea, blurred vision, nervousness, insomnia, dysuria, urinary incontinence, kidney pain, decreased libido, leg pain, hyperventilation, apnea, asthma, pharyngitis, cough, sinusitis, anorexia, bitter taste, dysphagia, flatulence, ileus, hypothermia, thrombocytopenia, drug fever, eye pain, rash, pruritus, dry skin, urticaria, swelling of lips and tongue, and periorbital edema.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **moricizine** crosses the human placenta. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically.

Breastfeeding Safety

There are no adequate reports or well-controlled studies in nursing women. **Moricizine** enters human and rodent breast milk, but the kinetics remain to be elucidated.

Drug Interactions

Cimetidine decreased **moricizine** clearance by 49% and increased serum levels 1.4-fold in healthy subjects. Patients on **cimetidine** should have **moricizine** initiated at relatively low doses, not more than 600mg/d.

Theophylline clearance and plasma t/2 were significantly affected whether conventional or sustained-release **theophylline** was given to healthy subjects (clearance increased 44-66% and plasma t/2 decreased 19-33%). Plasma **theophylline** levels should be monitored closely when **moricizine** is initiated or discontinued. Caution is indicated when **moricizine** is used with any drug that affects cardiac electrophysiology as there is a possibility of additive pharmacologic effects.

References

There is no published experience in pregnancy or during lactation.

Summary

Pregnancy Category: B
Lactation Category: U

- **Moricizine** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.
- There are alternative agents for which there is more experience regarding use during pregnancy and lactation.

Morphine—(Avinza; Kadian; MS Contin; MSIR; Oramorph; Roxanol)

International Brand Name—Actiskenan (France); Algedol (Uruguay); Anafil - L.C. (Mexico); Anafil - S.T. (Mexico); Anamorph (Australia); Contalgin (Denmark); Continue DR (Korea); Dolcontin (Finland, Sweden); Dolcontin Depottab (Norway); Duralmor (Mexico); Duromorph (England, Ireland); Graten (Mexico); Kapanol (Australia); Kapanol LP (France); La Morph (New Zealand); Longphine SR (Korea); MCR (Israel); M.Elson (Hong Kong); M-Eslon (Canada, Chile, Ecuador, Peru); Meslon (Colombia); M.I.R. (Israel); M-Long (Germany); Morcontin Continus (India); Morficontin (Greece); Morphanton (Germany); Morphgesic SR (England, Ireland); Morphine Mixtures (Australia); Moscontin (France); M S Contin (Canada); MS Contin (Australia, Belgium, Canada, Italy, Netherlands); MS-Contin (Korea); MSI (Germany); MSIR (Canada); MS Mono (Australia); MSP (Israel); MST 10 Mundipharma (Germany); MST 30 Mundipharma (Germany); MST 60 Mundipharma (Germany); MST 100 Mundipharma (Germany); MST 200 Mundipharma (Germany); MST Continus (Argentina, Brazil, Bulgaria, Czech Republic, England, Hungary, Indonesia, Ireland, Israel, Malaysia, Mexico, New Zealand, Philippines, Poland, Puerto Rico, Spain, Taiwan); MST Continus Retard (Switzerland); Mundidol Retard (Austria); Oramorph (England, Ireland); Ra-Morph (New Zealand); Relimal (Philippines); Sevredol (New Zealand); S-Morphine (Korea); SRM-Rotard (Singapore); Statex (Canada, Singapore); Vendal (Uruguay)

Drug Class	Analgesics, narcotic
Indications	Severe pain
Mechanism	Binds to opiate receptors
Dosage with Qualifiers	Pain—2.5-10mg IV slowly over 5-15min; alternative 5-20mg IM/SC or 10-30mg PO q4h Post–cesarean section analgesia—*intrathecal:* 100-250mcg; *epidural:* 2-5 mg *NOTE: do not use solution if dark, discolored, or contains precipitate.* • **Contraindications**—hypersensitivity to drug or class, respiratory depression, asthma, ileus • **Caution**—COPD, head injury, CNS depression, seizure disorder, acute pancreatitis, pseudomembranous colitis, hypotension, hepatic or renal dysfunction, biliary disease, alcoholism
Maternal Considerations	**Morphine** is one of the most frequently used opioids for pain control during human parturition. The elimination t/2 of **morphine** is shorter and the plasma clearance quicker in parturients than in nonpregnant women. **Morphine** as part of an epidural or PCA regimen is common. It is also administered intrathecally after cesarean section for relief of postoperative pain for the first 48h. XR epidural **morphine** provides superior and prolonged postcesarean analgesia compared to conventional epidural **morphine** with no significant increases in adverse events. The addition of small dose to the spinal component of the continuous spinal epidural improves the effectiveness of epidural labor analgesia and reduces the need for pain medications over 24h, but results in a small increase in nausea. Epidural **morphine** significantly reduces the incidence of headache and the need for a blood patch after dural puncture. There is a long clinical experience supporting the relative safety of **morphine** for the listed indications. The combination of small doses of opioids and **bupivacaine** for spinal anesthesia eliminates intraoperative discomfort and reduces postoperative analgesic requirements in women undergoing either vaginal or cesarean delivery. The two most frequently used agents are **fentanyl** and **morphine.** The intrathecal injection of 150mcg intensifies the intraoperative hypothermic effect of **bupivacaine** spinal anesthesia for cesarean section patients. PCA, which provides pain relief through

self-administration of IV doses of opioids, is widely available and advocated as an effective analgesic modality. **Morphine** PCA offers a good quality of analgesia with minimal side effects during both the ante- and postnatal periods. **Morphine** does not affect the spontaneous contractility *in vitro* of human myometrium. It is one of the most frequently used opioids to achieve pain relief during an ambulatory surgical procedure. Patients receiving **morphine** and **diazepam** are to be cautioned against operating machinery or driving.
Side effects include addiction, seizures, respiratory depression, hypotension, shock, apnea, cardiac arrest, bradycardia, toxic megacolon, ileus, abdominal pain, miosis, itching, dry mouth, decreased libido, biliary spasm, paresthesias, pruritus, itching, flushing, urinary retention, and asthenia.

Fetal Considerations

Morphine readily crosses the term human placenta. Rapid maternal clearance shortens the fetal exposure. The concentration of free **morphine** in umbilical venous blood after delivery is significantly associated with the dose-delivery interval and has a significant effect on the need for neonatal resuscitation. Alterations in fetal biophysical profile parameters such as fetal breathing movements and fetal heart rhythm should be expected as **morphine** decreases fetal heart variability and breathing frequency. It is not clear whether **morphine** decreases gross or fine fetal movements. Placental retention of **morphine** may prolong fetal exposure, explaining at least in part its prolonged effect on fetal behavior relative to the maternal concentration. **Morphine** has been combined with benzodiazepines (e.g., **diazepam**) for the relief of pain and anxiety during fetal surgical procedures. While there is no evidence **morphine** is a human teratogen, uncontrolled retrospective studies of neonates chronically exposed to other opioids note reduced brain volume at birth that normalizes during the 1st month of life. Infants born to opioid-abusing mothers are more often SGA, and have decreased ventilatory responses to CO_2 and increased risk of SIDS. Neonatal abstinence syndrome due to opiate withdrawal produces sleep/wake abnormalities, feeding difficulties, weight loss, and seizures. Rodent teratogen studies have not been performed. Other rodent studies suggest *in utero* exposure causes long-term alterations in adult brain and behavior. These changes affect both the NE and opioid systems of several brain areas, including those involved in memory, stress responses, and the maintenance of homeostatic balance with the external environment.

Breastfeeding Safety

Morphine is excreted in human breast milk, and the M:P AUC ratio after parenteral administration approximates 2.5:1. The amount taken by the neonate depends on the maternal plasma concentration, quantity of milk ingested, and the extent of first-pass metabolism. In general, **morphine** is preferred to **meperidine** in breastfeeding women. Intrathecal **morphine** is not associated with clinically relevant maternal plasma and milk **morphine** concentrations. The colostrum concentration of **morphine** and its active metabolites in women using PCA after cesarean delivery is small, supporting the safety of breastfeeding in mothers using a **morphine** PCA.

Drug Interactions

The administration of **morphine** XR liposome injection 3min after a 3ml test dose (**lidocaine** 1.5% and **epinephrine** 1:200,000) increases peak serum concentrations of **morphine.** Increasing the interval between drugs to at least 15min minimizes this interaction.

The concurrent use of other CNS depressants, including sedatives, hypnotics, general anesthetics, **droperidol,** phenothiazines or other tranquilizers, and ethanol, increases the risk of respiratory depression, hypotension, profound sedation, or coma. When combined therapy is contemplated, the initial dose of one or both agents should be reduced at least 50%.
MAOIs markedly potentiate the action of **morphine,** which should not be used in patients taking MAOIs or within 14d of stopping treatment.
Respiratory depression may delay recovery of spontaneous pulmonary ventilation when neuromuscular blocking agents are also used.
There is an isolated report of confusion and severe respiratory depression when a hemodialysis patient was given both **morphine** and **cimetidine.**
May reduce the efficacy of diuretics by inducing the release of antidiuretic hormone.
May lead to acute urinary retention by causing spasm of the bladder sphincter.
Sustained-release capsules should be swallowed whole and not chewed, crushed, or dissolved due to risk of overdose.

References

Al-Metwalli RR. Anesthesia 2008; 63:847-50.
Bake NE, Bayou F, Boutros MJ, Laxenaire MC. Anesth Analg 2002; 94:184-7.
Carvalho B, Roland LM, Chu LF, et al. Anesth Analg 2007; 105:176-83.
Cowan CM, Kendall JB, Barclay PM, Wilkes RG. Br J Anaesth 2002; 89:452-8.
Farrell T, Owen P, Harrold A. Clin Exp Obstet Gynecol 1996; 23:144-6.
Gerdin E, Salmonson T, Lindberg B, Rane A. J Perinat Med 1990; 18:479-87.
Hui CK, Huang CH, Lin CJ, et al. Anaesthesia 2006; 61:29-31.
Iberia I, Nuns F, Ghana M. Act Med Port 2001; 14:395-8.
Kopecky EA, Ryan ML, Barrett JF, et al. Am J Obstet Gynecol 2000; 183:424-30.
Kopecky EA, Simone C, Knie B, Koren G. Life Sci 1999; 65:2359-71.
McIntosh DG, Rayburn WF. Obstet Gynecol 1991; 78:1129-35.
Oberlander TF, Robeson P, Ward V, et al. J Hum Lact 2000; 16:137-42.
Rawal N, Tomlinson AJ, Gibson GJ, Sheehan TM. Eur J Obstet Gynecol Reprod Biol 2007; 133:30-3.
Robieux I, Koren G, Vandenbergh H, Schneiderman J. J Toxicol Clin Toxicol 1990; 28:365-70.
Slamberova R, Schindler CJ, Pometlova M, et al. Physiol Behav 2001; 73:93-103.
Vasudevan A, Snowman CE, Sundar S, et al. Br J Anaesth 2007; 98:241-5.
Vathy I. Psychoneuroendocrinology 2002; 27:273-83.
Wittels B, Glosten B, Faure EA, et al. Anesth Analg 1997; 85:600-6.
Yoo KY, Lee J, Kim HS, Jeong SW. Anesth Analg 2001; 92:1006-9.

Summary

Pregnancy Category: C
Lactation Category: S

- **Morphine** provides safe and effective analgesia for pregnant and breastfeeding women when used as indicated.

Moxifloxacin—(Avelox)

International Brand Name—Avalox (Brazil, Germany, Israel); Avelon (South Africa); Avelox (Colombia, Hong Kong, Indonesia, Korea, Mexico, Peru, Philippines, Singapore, South Africa, Thailand); Bacterol (Colombia); Izilox (France); Megaxin (Israel); Moxif (India); Vigamox (Thailand)

Drug Class

Antibiotics; Quinolones

Indications

Bacterial infections (aerobic gram-positive: *Enterococcus faecalis,* MSSA, *S. saprophyticus, S. pneumoniae, S. pyogenes;* aerobic gram-negative: *Enterobacter cloacae, E. coli, H. influenzae, H. parainfluenzae, Klebsiella pneumoniae, Legionella pneumophila, Moraxella catarrhalis, P. mirabilis, Pseudomonas aeruginosa;* other microorganisms: *Chlamydia pneumoniae, Mycoplasma pneumoniae*)

Mechanism

Bactericidal—inhibits DNA synthesis

Dosage with Qualifiers

Bacterial infections—400mg PO/IV qd

- **Contraindications**—hypersensitivity to drug or class, ECG modification, concomitant usage of antiarrhythmic medication (class IA, III), age <18y
- **Caution**—advanced age, seizure disorder, CNS disorder, dehydration

Maternal Considerations

There is no published experience with **moxifloxacin** during pregnancy.
Side effects include vaginitis, photosensitivity, pseudomembranous colitis, seizures, increased ICP, headache, psychosis, N/V, diarrhea, abdominal pain, dyspepsia, dizziness, insomnia, agitation, tendonitis, arthralgias, and increased LFTs.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **moxifloxacin** crosses the human placenta. Animal studies in rodents and dogs reveal that fetal exposure to quinolone antibiotics is associated with an acute arthropathy of the weight-bearing joints. Although arthropathy has only rarely been observed in humans, the toxicity observed in immature animals has led to the restricted use of quinolones in pregnant women. There was no evidence of teratogenicity in monkeys fed 2.5× the MRHD, though there was an increase in IUGR. Recent studies conclude that the use of fluoroquinolones during embryogenesis is not associated with an increased risk of major malformations.

Breastfeeding Safety

There is no published experience in nursing women. It is unknown whether **moxifloxacin** enters human breast milk. It is excreted into rodent milk.

Drug Interactions

Quinolones form chelates with alkaline earth and transition metal cations that may interfere with absorption, generating systemic concentrations lower than desired. **Moxifloxacin** should be taken at least 4h before or 8h after these agents.
Quinolones, including **moxifloxacin,** are reported to enhance the anticoagulant effects of **warfarin** or its derivatives. In addition, infectious disease and its accompanying inflammatory process, age, and general status of the patient are risk factors for increased anticoagulant activity. Thus, the PT, INR, or other suitable anticoagulation tests should be closely monitored if a quinolone is administered along with **warfarin** or its derivatives.

The concomitant administration of an NSAIDs with some quinolones may increase the risks of CNS stimulation and convulsions.

References

There is no published experience in pregnancy or during lactation.

Summary

Pregnancy Category: C
Lactation Category: U

- **Moxifloxacin** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.
- There are alternative agents for which there is more experience regarding use during pregnancy and lactation.

Nabumetone—(Nabuco; Relafen)

International Brand Name—Aflex (Thailand); Anfer (Thailand); Arthaxan (Germany); Bumetone (Korea, Thailand); Consolan (Denmark); Deku (Taiwan); Goflex (Indonesia); Labuton (Taiwan); Mebutan (Netherlands); Nabentac (Korea); Nabone (Thailand); Nabonet (Thailand); Nabuco (Israel); Nabuflam (India); Naburen (Colombia); Nabuser (Italy); Nacton (Korea); Nadorex (Colombia); Naflex (Thailand); Nametone (Thailand); Noac (Uruguay); No-Ton (Taiwan); Prodac (Korea); Relafen (Canada, Korea); Relif (Spain); Relifen (Japan, South Africa); Relifex (Brazil, Bulgaria, Costa Rica, Czech Republic, Denmark, Dominican Republic, Ecuador, El Salvador, England, Finland, Greece, Guatemala, Honduras, Hong Kong, Hungary, Ireland, Italy, Mexico, Nicaragua, Panama, Philippines, Poland, Sweden, Taiwan, Thailand, Turkey); Relisan (South Africa); Relitone (South Africa); Subuton (Taiwan); Tanleeg (Taiwan); Tontec (Taiwan); Unimetone (Korea)

Drug Class

Analgesics, non-narcotic; NSAIDs

Indications

Osteoarthritis or rheumatoid arthritis, anti-inflammatory

Mechanism

Inhibits cyclooxygenase and lipoxygenase, reducing prostaglandin synthesis

Dosage with Qualifiers

Osteoarthritis—1g PO qd or bid
Rheumatoid arthritis—1g PO qd or bid
Anti-inflammatory—1g bid ×7-14d; begin 2g/d ×1d; max 2g/d

- **Contraindications**—hypersensitivity to drug or class, NSAID-induced asthma
- **Caution**—nasal polyps, GI bleeding, hypertension, CHF

Maternal Considerations

There is no published experience with **nabumetone** during pregnancy.
Side effects include thrombocytopenia, GI bleeding, renal failure, Stevens-Johnson syndrome, interstitial nephritis, hepatotoxicity, agranulocytosis, abdominal pain, diarrhea, constipation, increased sweating, nervousness, insomnia, somnolence, tinnitus, cholestatic jaundice, duodenal ulcer, dysphagia, gastric ulcer, gastroenteritis, increased appetite, increased LFTs, melena, edema, urticaria, rash, dizziness, and headache.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **nabumetone** crosses the human placenta. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically. There is evidence, however, of increased embryo resorption.

Breastfeeding Safety

There is no published experience in nursing women. It is unknown whether **nabumetone** enters human breast milk.

Drug Interactions

Caution should be exercised with **warfarin** since enhancement has been observed in association with other NSAIDs.
There is more rapid absorption if administered with food or milk; however, the total amount in the plasma is unchanged.

References

There is no published experience in pregnancy or during lactation.

Summary

Pregnancy Category: C
Lactation Category: U

- **Nabumetone** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.
- There are alternative agents for which there is more experience regarding use during pregnancy and lactation.

Nadolol—(Corgard)

International Brand Name—Apo-Nadol (Hong Kong); Apo-Nadolol (New Zealand); Corgard (Argentina, Belgium, Brazil, Canada, Chile, Colombia, England, France, Greece, Ireland, Italy, Kenya, Malaysia, Mexico, Nigeria, Peru, Philippines, Poland, Russia, South Africa, Spain, Switzerland, Taiwan, Tanzania, Turkey, Uganda, Uruguay, Venezuela, Zambia); Farmagard (Indonesia); Nadic (Japan); Solgol (Austria, Germany, Spain)

Drug Class	Adrenergic antagonists; β-Blockers
Indications	Hypertension, angina, arrhythmia, headache prophylaxis (vascular)
Mechanism	Nonselective β-adrenergic receptor antagonist
Dosage with Qualifiers	Hypertension—begin 20-40mg/d; increase 40-80mg qd ×2-14d; max 240-320mg/d Angina—begin 20-40mg/d; increase 40-80mg qd ×3-7d; max 160-240mg/d Arrhythmia—60-640mg PO qd Headache prophylaxis (vascular)—20-80mg PO qd; max 120mg/d • **Contraindications**—hypersensitivity to drug or class, sinus bradycardia, asthma, 2nd-3rd degree AV block • **Caution**—diabetes mellitus, hepatic failure, CHF
Maternal Considerations	**Nadolol** is a nonselective β-blocker offering the advantage of once-daily dosing. There are no adequate reports or well-controlled studies of **nadolol** in pregnant women. The published literature is limited to scattered case reports. In one instance, it was used to treat hypertension associated with primary hyperaldosteronism. ***Side effects*** include fatigue, dizziness, slurred speech, bradycardia, rash, CHF, bronchospasm, constipation, dry mouth, nausea, diarrhea, weight gain, cough, nasal stuffiness, sweating, tinnitus, facial swelling, and blurred vision.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **nadolol** crosses the human placenta. Other drugs in this class do cross. Scattered case reports suggest fetal exposure may increase the risk of cardiorespiratory depression, mild hypoglycemia, and IUGR. The long duration of action of **nadolol** and the fact that it is only 30% protein bound make it less desirable during pregnancy than other β-blockers such as **propranolol. Nadolol** crosses the rodent placenta. Rodent studies are generally reassuring, revealing no evidence of teratogenicity despite the use of doses higher than those used clinically. There is evidence of embryotoxicity and IUGR.
Breastfeeding Safety	**Nadolol** is excreted into human breast milk. It is estimated the nursing newborn would ingest 2-7% of the daily maternal dose. Thus, there is a small but real potential for a clinical effect depending upon neonatal clearance. If a woman elects to continue nursing while taking **nadolol,** the child should be observed for evidence of β blockade.
Drug Interactions	May exaggerate the hypotension induced by general anesthetic agents. May enhance hypoglycemia or hyperglycemia; adjust antidiabetic drug dosage accordingly.
References	Fox RE, Marx C, Stark AR. Am J Obstet Gynecol 1985; 152:1045-6.

Devlin RG, Duchin KL, Fleiss PM. Br J Clin Pharmacol 1981; 12:393-6.
Solomon CG, Thiet M, Moore F Jr, Seely EW. J Reprod Med 1996; 41:255-8.
Wilson AL, Matzke GR. Drug Intell Clin Pharm 1981; 15:21-6.

Summary

Pregnancy Category: C
Lactation Category: S (likely)

- **Nadolol** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.
- There are alternative agents for which there is more experience regarding use during pregnancy and lactation.

Nafcillin—(Nafcil; Nallpen; Unipen)

International Brand Name—Vigopen (Philippines)

Drug Class

Antibiotics; Penicillins

Indications

Bacterial infections, especially penicillinase-producing *Staphylococcus*

Mechanism

Bactericidal—inhibits cell wall synthesis

Dosage with Qualifiers

Bacterial infections—500mg-2g IV/IM q4-6h; max 12g/d IM or 20g/d IV

NOTE: hepatic and renal dosing; concurrent administration of ***nafcillin*** *and* ***probenecid*** *increases and prolongs serum levels.*

- **Contraindications**—hypersensitivity to drug or class
- **Caution**—cephalosporin allergy, renal or hepatic dysfunction, neonate

Maternal Considerations

Nafcillin is a penicillinase-resistant penicillin eliminated primarily by nonrenal routes, namely hepatic inactivation and excretion in the bile. There are no adequate reports or well-controlled studies of **nafcillin** in pregnant women. The published literature consists of scattered case reports. Other penicillins have proved safe during pregnancy.
Side effects include pain, swelling, inflammation, interstitial nephritis, pseudomembranous colitis, hepatotoxicity, seizures, tissue necrosis, N/V, diarrhea, candidiasis, urticaria, thrombophlebitis, neutropenia, leukopenia, thrombocytopenia, hypokalemia, and rash.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **nafcillin** crosses the human placenta. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically.

Breastfeeding Safety

There is no published experience in nursing women. It is unknown whether **nafcillin** enters human breast milk. It is generally considered compatible with breastfeeding. **Nafcillin** is frequently used for the treatment of mastitis of cows.

Drug Interactions

Tetracycline may antagonize the bactericidal effect of penicillins and should be avoided.

High-dose regimens (e.g., 2g q4h) may decrease the effects of **warfarin** for up to 30d after the **nafcillin** has been discontinued. The PT should be monitored closely.
May cause subtherapeutic **cyclosporine** levels. **Cyclosporine** levels should be monitored when used with **nafcillin**.

References

Takeba K, Fujinuma K, Miyazaki T, et al. J Chromatogr 1998; 812:205-11.

Summary

Pregnancy Category: B
Lactation Category: S (likely)
- **Nafcillin** is an alternative for the treatment of puerperal mastitis.
- There are alternative agents if necessary during pregnancy for almost all indications.

Naftifine—(Naftin)

International Brand Name—Exoderil (Austria, Bulgaria, Costa Rica, Dominican Republic, El Salvador, Germany, Greece, Guatemala, Honduras, Hong Kong, Hungary, Indonesia, Malaysia, Nicaragua, Panama, Poland, Russia, Taiwan, Turkey); Jia Mei (Taiwan); Suadian (Italy)

Drug Class

Antifungals; Dermatologics

Indications

Fungal and candidal infections (fungal infections: *T. rubrum, T. mentagrophytes, T. tonsurans; Epidermophyton floccosum, M. canis, M. audouini, M. gypseum; Candida* species: *C. albicans*), skin infections

Mechanism

Inhibits biosynthesis of ergosterol, and thus the fungal cell wall

Dosage with Qualifiers

Skin infections—apply to affected area qd

NOTE: available as 1% cream or gel.

- **Contraindications**—hypersensitivity to drug or class
- **Caution**—unknown

Maternal Considerations

There is no published experience with **naftifine** during pregnancy.
Side effects include burning, dryness, erythema, and itching.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **naftifine** crosses the human placenta. Considering the dose and route, it is unlikely the maternal systemic concentration will reach a clinically relevant level. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically.

Breastfeeding Safety

There is no published experience in nursing women. It is unknown whether **naftifine** enters human breast milk. However, considering the dose and route, it is unlikely to pose a clinically significant risk to the breastfeeding neonate.

Drug Interactions

No clinically relevant interactions identified.

References

There is no published experience in pregnancy or during lactation.

Summary

Pregnancy Category: B
Lactation Category: U
- **Naftifine** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Nalbuphine—(Nubain)

International Brand Name—Bufigen (Mexico); Nalbufina (Uruguay); Nalcryn SP (Mexico); Nubain (Austria, Brazil, Bulgaria, Canada, Costa Rica, Czech Republic, Dominican Republic, Ecuador, El Salvador, England, Germany, Greece, Guatemala, Honduras, Hungary, Netherlands, New Zealand, Nicaragua, Panama, Philippines, Poland, Switzerland, Taiwan, Thailand, Venezuela); Nubaina (Argentina); Nubain SP (Mexico); Onfor (Argentina, Paraguay)

Drug Class

Analeptics; Narcotic agonist-antagonists

Indications

Pain, anesthesia (adjunct)

Mechanism

Binds to opiate receptors

Dosage with Qualifiers

Pain—10mg IV/IM/SC q3-6h prn; max 20mg/dose or 160mg/d
Anesthesia (adjunct)—0.25-0.5mg/kg prn; begin 0.3-3mg/kg IV

- **Contraindications**—hypersensitivity to drug or class
- **Caution**—opiate dependency; renal, hepatic, or pulmonary dysfunction; biliary surgery; sulfite allergy

Maternal Considerations

Nalbuphine (formerly marketed as Nubain) is a synthetic opioid agonist-antagonist analgesic commonly used for intrapartum analgesia. Its potency is essentially equivalent to **morphine** on a milligram basis. **Nalbuphine** acts within minutes after IV administration, and <15min after SC or IM injection; the duration of analgesia ranges from 3 to 6h. There are no well-controlled studies of **nalbuphine** in pregnant women. It is, however, a popular agent for analgesia during labor, comparable to **meperidine.** Concerns for fetal safety were raised by a pharmaceutical company that no longer manufactures **nalbuphine** (see *http://www.fda.gov/medwatch/safety/2005/aug_PI/Nubain_PI.pdf*). There is insufficient information to support these concerns or to recommend any change in the administration of this medication for analgesia in labor. Due to its ability to bind the same opiate receptor as **morphine,** IV **nalbuphine** is sometimes used for the treatment of intrathecal **morphine**-induced pruritus after cesarean delivery.
Side effects include headache, nervousness, depression, restlessness, crying, feeling of floating, hostility, unusual dreams, confusion, euphoria, faintness, hallucinations, dysphoria, feeling of heaviness, numbness, tingling, dizziness, bradycardia, hypotension, respiratory depression, dyspepsia, N/V, sweating, dry mouth, urticaria, cramps, dyspnea, asthma, bitter taste, speech difficulty, urinary urgency, blurred vision, pruritus, and substance abuse.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. **Nalbuphine** crosses the human placenta, achieving an F:M ratio approximating 0.75. **Nalbuphine** decreases the number of FHR accelerations and variability, but does not affect the fetal response to vibroacoustic stimulation. The neonatal t/2 is estimated at 4h. **Nalbuphine** can cause respiratory depression, and should be used with caution in women delivering preterm. Rodent studies are reassuring, revealing no evidence of

teratogenicity or IUGR despite the use of doses higher than those used clinically.

Breastfeeding Safety

The mean and maximum **nalbuphine** milk concentrations are 42 ± 26 and 61 ± 26ng/ml, respectively. Assuming a milk volume of 150ml/kg/d, the mean and maximum doses a breastfed neonate would ingest in 1 day are 7.0 ± 3.2 and 9.0 ± 3.8mcg/kg/d. That equates to a relative infant dose of 0.59 ± 0.27% of the weight-adjusted maternal daily dose.

Drug Interactions

No clinically relevant interactions identified.

References

Committee on Obstetric Practice, American College of Obstetricians and Gynecologists. Obstet Gynecol 2007; 110:449.
Charuluxananan S, Kyokong O, Somboonviboon W, et al. Anesth Analg 2001; 93:162-5.
Culebras X, Gaggero G, Zatloukal J, et al. Anesth Analg 2000; 91:601-5.
Frank M, McAteer EJ, Cattermole R, et al. Anaesthesia 1987; 42:697-703.
Giannina G, Guzman ER, Lai YL, et al. Obstet Gynecol 1995; 86:441-5.
Jacqz-Aigrain E, Serreau R, Boissinot C, et al. Ther Drug Monit 2007; 29:815-8.
Nicolle E, Devillier P, Delanoy B, et al. Eur J Clin Pharmacol 1996; 49:485-9.
Poehlmann S, Pinette M, Stubblefield P. J Reprod Med 1995; 40:707-10.
Sherer DM, Cooper EM, Spoor C, et al. Am J Perinatol 1994; 11:367-8.
Somrat C, Oranuch K, Ketchada U, et al. J Obstet Gynaecol Res 1999; 25:209-13.
Wischnik A, Wetzelsberger N, Lucker PW. Arzneimittelforschung 1988; 38:1496-8.

Summary

Pregnancy Category: B
Lactation Category: S

- **Nalbuphine** is a popular labor analgesic and an efficacious treatment of side effects secondary to epidural **morphine.**

Nalidixic acid—(Enexina; Faril; Nalidixio; Nalydixine; NegGram; Nevigramon; Notricel; Urodic; Winlomylon)

International Brand Name—Acidix (Mexico); Anasiron (Japan); Betaxina (Italy); Gramazine (Taiwan); Gramoneg (India, Thailand); Granexin (Israel); Mictral (Ireland); Mytacin (Japan); Nal-Acid (Greece); Nali 500 (Uruguay); Nalidix (Israel); Nalidixin (Italy); Nalix (Mexico); Nalixone (Mexico); Naluril (Brazil); Negacide (Taiwan); Negadix (India); Neg-Gram (Italy); Neggram (Canada, Korea); Negram (Bulgaria, Denmark, Finland, France, Germany, Ireland, Israel, Norway, Russia, Sweden, Turkey); Nevigramon (Poland); Nogram (Germany); Perry (Taiwan); Puromylon (South Africa); Urineg (Indonesia); Wintomylon (Argentina, Chile, Colombia, Costa Rica, Dominican Republic, Ecuador, El Salvador, Guatemala, Honduras, Hong Kong, Malaysia, Mexico, Nicaragua, Panama, Peru, Philippines, South Africa, Thailand); Youdix (Japan)

Drug Class

Antibiotics; Quinolones

Indications

Bacterial infections (aerobic gram-positive: *Enterococcus faecalis,* MSSA, *S. saprophyticus, S. pneumoniae, S. pyogenes;* aerobic gram-negative: *Enterobacter cloacae, E. coli, H. influenzae,*

H. parainfluenzae, Klebsiella pneumoniae, Legionella pneumophila, Moraxella catarrhalis, P. mirabilis, Pseudomonas aeruginosa; other microorganisms: *Chlamydia pneumoniae, Mycoplasma pneumoniae*)

Mechanism

Bactericidal—inhibits DNA synthesis

Dosage with Qualifiers

Bacterial infections—1g PO qid; alternatively, 2g PO qd for chronic suppression

- **Contraindications**—hypersensitivity to drug or class, seizures
- **Caution**—renal or hepatic dysfunction, impaired pulmonary function, CV disease, excessive sunlight exposure

Maternal Considerations

Asymptomatic bacteriuria is common during pregnancy. Perhaps ⅓ of affected pregnant women will develop symptomatic disease (hemorrhagic cystitis or pyelonephritis). **Nalidixic acid** is one treatment alternative for asymptomatic bacteriuria of pregnancy. ***Side effects*** include vaginitis, photosensitivity, pseudomembranous colitis, seizures, increased ICP, headache, psychosis, N/V, diarrhea, abdominal pain, dyspepsia, dizziness, insomnia, agitation, tendonitis, arthralgia, and elevated LFTs.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. **Nalidixic acid** crosses the human placenta, though the kinetics remain to be elucidated. Rodent and canine teratogenicity studies reveal the older quinolones such as **nalidixic acid,** flumequine, and pipemidic acid are associated with acute arthropathy of the weight-bearing joints. Although arthropathy is rare in adult humans, toxicity was observed in immature animals, leading to the restricted use of these agents during pregnancy. More recent studies conclude that **nalidixic acid** is not associated with any increased risks of spontaneous abortion, prematurity, IUGR, or postnatal disorders. A small increase in the risk of pyloric stenosis cannot be excluded.

Breastfeeding Safety

Nalidixic acid is excreted into human breast milk. However, the nursing newborn would ingest <0.05% of the maternal dose.

Drug Interactions

Nitrofurantoin interferes with the therapeutic action of **nalidixic acid.**
Cross-resistance has been observed only with oxolinic acid.
May enhance oral anticoagulants by displacing significant amounts from serum albumin binding sites.
A false-positive reaction for glucose may occur due to the liberation of glucuronic acid from the metabolites excreted when either Benedict's or Fehling's solutions or Clinitest Reagent Tablets are used to test the urine of women taking **nalidixic acid.** However, a colorimetric test for glucose based on an enzyme reaction (e.g., Clinistix Reagent Strips or Tes-Tape) will not give a false-positive reaction.
Incorrect values may be obtained for urinary 17-keto and ketogenic steroids because of an interaction between the drug and the *m*-dinitrobenzene used in the assay. In such cases, the Porter-Silber test for 17-hydroxycorticoids should be used.

References

Czeizel AE, Sorensen HT, Rockenbauer M, Olsen J. Int J Gynaecol Obstet 2001; 73:221-8.
[No authors]. Prescrire Int 1999; 8:29-31.
Pedler SJ, Bint AJ. Drugs 1987; 33:413-21.
Peiker G, Traeger A. Pharmazie 1983; 38:613-5.
Traeger A, Peiker G. Arch Toxicol Suppl 1980; 4:388-90.

Summary

Pregnancy Category: C
Lactation Category: S
- **Nalidixic acid** should be used during pregnancy only if the benefit justifies the potential perinatal risk.
- It is a reasonable first-line drug for the treatment of asymptomatic bacteriuria during the 2nd and 3rd trimesters.

Nalmefene—(Cervene; Revex)

International Brand Name—None identified.

Drug Class

Antidotes; Narcotic agonist-antagonists

Indications

Opiate overdose, postoperative opiate reversal

Mechanism

Opiate receptor antagonist

Dosage with Qualifiers

Opiate overdose—0.5mg IV; over 70kg, dose individually; max 1.5mg
Postoperative opiate reversal—0.25mcg/kg IV; increase 0.25mcg/kg increments q2-5min; max 1mcg/kg IV

- **Contraindications**—hypersensitivity to drug or class
- **Caution**—renal or hepatic dysfunction, opiate addiction, concomitant usage of cardiotoxic drugs

Maternal Considerations

Nalmefene is a long-acting opioid antagonist used for the treatment of overdose. It was also used to provide long-term relief from side effects of intrathecal **morphine.** However, it failed in one prospective trial to reduce the incidence of pruritus and N/V and the level of sedation, but increased the need for supplemental analgesics.
Side effects include arrhythmia, tachycardia, bradycardia, fever, postoperative pain, N/V, headache, vasodilation, dizziness, somnolence, confusion, and chills.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **nalmefene** crosses the human placenta. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically.

Breastfeeding Safety

There is no published experience in nursing women. **Nalmefene** is excreted into human breast milk, though the kinetics remain to be elucidated. However, considering the indication and dosing, one-time **nalmefene** use is unlikely to pose a clinically significant risk to the breastfeeding neonate.

Drug Interactions

No clinically relevant interactions identified.

References

Pellegrini JE, Bailey SL, Graves J, et al. AANA J 2001; 69:199-205.

Summary

Pregnancy Category: B
Lactation Category: S (likely)
- **Nalmefene** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.
- There are superior agents to treat the side effects of intrathecal **morphine.**

Naloxone—(Narcan)

International Brand Name—Antioplaz (Argentina); Mapin (Hong Kong, Malaysia); Nalone (France); Naloxon (Germany); Naloxona (Ecuador); Narcan (Belgium, Brazil, Canada, England, Greece, Ireland, Italy, Korea, Netherlands, Philippines, Switzerland, Taiwan, Venezuela); Narcan Neonatal (France); Narcanti (Argentina, Austria, Bulgaria, Czech Republic, Denmark, Finland, Germany, Hungary, Mexico, Norway, Poland, Sweden, Uruguay); Narcotan (India); Naxone (Israel); Zynox (South Africa)

Drug Class	Antidotes; Narcotic agonist-antagonists
Indications	Opiate overdose, postoperative opiate reversal
Mechanism	Antagonizes various opiate receptors (opiate antagonist)
Dosage with Qualifiers	Opiate overdose—0.4-2mg SC/IV/IM q2-3min; if no response by 10min, the diagnosis should be questioned Postoperative opiate reversal—0.1-0.2mg IV q2-3min prn • **Contraindications**—hypersensitivity to drug or class • **Caution**—opiate addiction, renal or hepatic dysfunction, cardiotoxic drugs
Maternal Considerations	**Naloxone** is a popular opioid antagonist. Pregnant heroin users have poor maternal and neonatal outcome. Medically supervised heroin withdrawal is generally discouraged during pregnancy because of the fetal risk and a high likelihood of failure with return to regular illicit heroin use. More recently, a number of withdrawal procedures developed using **naloxone** or **naltrexone** have met with some success in users who continue the antagonist throughout pregnancy. Maternal respiratory arrest is a rare but potentially life-threatening complication associated with intrathecal opioids for labor analgesia. Resuscitation should include IV **naloxone.** Very-low-dose IV **naloxone** is often used to treat neuraxially-injected **morphine**-associated pruritus. It is not effective when given SC as prophylaxis. ***Side effects*** include cardiac arrest, VF, tachycardia, hypertension, hypotension, seizures, N/V, tremor, diaphoresis, pulmonary edema, withdrawal symptoms, and sweating.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **naloxone** crosses the human placenta. **Naloxone** does not alter the placental transfer or clearance of **morphine** in humans. Neonates of women given parenteral opioids in labor that require **naloxone** have lower 1min Apgar scores than neonates whose mothers have epidural analgesia. Physicians practicing in community vs. university hospitals use **naloxone** more often to resuscitate the neonate. It is unclear whether this increased use reflects adherence to the American Academy of Pediatrics' guidelines for resuscitation, or whether the neonates delivered in community hospitals require resuscitation more frequently. Either way, it is clear this practice is poorly supported and should be examined. Porcine studies suggest that increased opioid "tonus" lowers the FHR and decreases fetal movement. **Naloxone** antagonizes the inhibitory effect of **morphine** on fetal heart rhythm and stimulates fetal hypermotility. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically.
Breastfeeding Safety	There are no adequate reports or well-controlled studies in nursing women. It is unknown whether **naloxone** enters human

breast milk. However, considering the indication and dosing, one-time **naloxone** use is unlikely to pose a clinically significant risk to the breastfeeding neonate. Endogenous opioids inhibit **oxytocin** neurons until parturition, and **naloxone** increases **oxytocin** secretion in pregnant rats. In humans, **oxytocin** secretion is inhibited in breastfeeding women by exogenous **morphine** compared to control. **Naloxone** does not reverse the process.

Drug Interactions ..... No clinically relevant interactions identified.

References .....

Douglas AJ, Bicknell RJ, Russell JA. Adv Exp Med Biol 1995; 395:381-94.
Douglas AJ, Leng G, Russell JA. Reproduction 2002; 123:543-52.
Douglas AJ, Neumann I, Meeren HK, et al. J Neurosci 1995; 15:5049-57.
Head BB, Owen J, Vincent RD Jr, et al. Obstet Gynecol 2002; 99:452-7.
Herschel M, Khoshnood B, Lass NA. Pediatrics 2000; 106:831-4.
Hulse GK, O'Neill G, Pereira C, Brewer C. Aust N Z J Obstet Gynaecol 2001; 41:424-8.
Katsiris S, Williams S, Leighton BL, Halpern S. Can J Anaesth 1998; 45:880-3.
Kopecky EA, Simone C, Knie B, Koren G. Life Sci 1999; 65:2359-71.
Leighton BL, Halpern SH. Am J Obstet Gynecol 2002; 186(Suppl):S69-77.
Leighton BL, Halpern SH. Semin Perinatol 2002; 26:122-35.
Lindow SW, Hendricks MS, Nugent FA, et al. Gynecol Obstet Invest 1999; 48:33-7.
Lockington PF, Fa'aea P. Anaesthesia 2007; 62:672-6.

Summary .....

Pregnancy Category: B
Lactation Category: S

- **Naloxone** reverses the effect of narcotics on the fetus and newborn. It should be given within minutes of delivery.

Naltrexone—(ReVia; Trexan)

International Brand Name—Antaxone (Italy, Spain); Celupan (Spain); Nalerona (Chile, Peru); Nalorex (England, France, Ireland, Netherlands); Nemexin (Austria, Denmark, Finland, Germany, Poland, Switzerland); Nodict (India); Nutrexon (Indonesia); Phaltrexia (Indonesia); Regental (Uruguay); Revez (Argentina); Re-Via (Mexico); Revia (Brazil, Denmark, France, Hong Kong, Hungary, Israel, Korea, Taiwan); ReVia (Canada)

Drug Class ..... Antidotes; Narcotic agonist-antagonists

Indications ..... Opiate addiction, alcohol dependence

Mechanism ..... Opioid receptor antagonist

Dosage with Qualifiers .....

Opiate addiction—begin 25mg PO ×1, repeat in 1h if no withdrawal; alternatively 100mg PO qd, then 150mg PO q3d

*NOTE: patient must be opiate free ×7-10d and pass **naloxone** challenge test.*

Alcohol dependence—50mg PO qd

- **Contraindications**—hypersensitivity to drug or class, hepatitis, hepatic failure, opiate use, failed **naloxone** challenge, failed **naltrexone** challenge, acute opiate dependence, acute opiate withdrawal
- **Caution**—unknown

Maternal Considerations

Naltrexone is a synthetic congener of **oxymorphone** with no opioid agonist properties. There are no adequate reports or well-controlled studies of **naltrexone** in pregnant women. Pregnant heroin users have poor maternal and neonatal outcome. Medically supervised heroin withdrawal is generally discouraged during pregnancy because of the fetal risk and a high likelihood of failure with return to regular illicit heroin use. Recently, a number of withdrawal procedures developed using **naloxone** or **naltrexone** have met with some success in users who continue the antagonist throughout pregnancy. More recently, implants have been studied as a vehicle for sustained release. Ovarian failure of hypothalamic origin is a consequence of an inappropriate increase in opioid tone of the neurons that release GnRH in a pulsatile manner. **Naltrexone** administration to these women can lead to pregnancy. After cesarean section, **naltrexone** is effective against the pruritus and vomiting associated with intrathecal **morphine** for analgesia, but shortens the duration of analgesia.

Side effects include suicidal ideation, opiate withdrawal symptoms, insomnia, N/V, headache, anxiety, chills, anorexia, somnolence, constipation, abdominal pain, muscle aches, rash, dizziness, fatigue, restlessness, bone or joint pain, myalgia, and nasal symptoms.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. **Naltrexone** crosses the human and rodent placenta. Rodent studies are generally reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically. There is evidence of embryo and early fetal toxicity. Rodents exposed to **naltrexone** during prenatal life are larger in weight and length, confirming that native opioids are important growth-inhibiting regulators. **Naltrexone** has no behavioral affect on exposed rabbit pups.

Breastfeeding Safety

The excretion of **naltrexone** and its primary metabolite 6,β-naltrexol has been measured in breast milk in one patient—an opiate addict undergoing oral **naltrexone** pharmacotherapy (5mg/d). The calculated infant dose relative to the maternal weight was 0.03% for **naltrexone** and 0.83% (as naltrexone equivalents) for 6,β-naltrexol. Total relative infant dose estimated for the complete 24h dose interval was 1.06%. Only 6,β-naltrexol was detected in infant plasma and at a very low concentration of 1.1mcg/L. These levels should pose little risk to the newborn.

Drug Interactions

Patients taking the XR injectable suspension may not benefit from opioids.

References

Abboud TK, Lee K, Zhu J, et al. Anesth Analg 1990; 71:367-70.
Chan CF, Page-Sharp M, Kristensen JH, et al. J Hum Lact 2004; 20:322-6.
Christian MS. J Clin Psychiatry 1984; 45:7-10.
Hulse G, O'Neil G. Aust N Z J Obstet Gynaecol 2002; 42:569-73.
Hulse GK, O'Neill G, Pereira C, Brewer C. Aust N Z J Obstet Gynaecol 2001; 41:424-8.
McLaughlin PJ, Tobias SW, Lang CM, Zagon IS. Physiol Behav 1997; 62:501-8.
Wildt L, Leyendecker G, Sir-Petermann T, Waibel-Treber S. Hum Reprod 1993; 8:350-8.
Zagon IS, Hurst WJ, McLaughlin PJ. Life Sci 1997; 61:1261-7.
Zagon IS, Hurst WJ, McLaughlin PJ. Life Sci 1998; 62:221-8.

Summary	**Pregnancy Category: C** **Lactation Category: S** (likely) • **Naltrexone** reduces the adverse symptoms associated with **morphine** analgesia, but shortens the duration. • **Naltrexone** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Naphazoline—(Ak-Con; Albalon; Allersol; I-Naphline; Murine; Muro's Opcon; Nafazair; Naphacel; Naphazole; Naphcon Forte; Nazil; Ocu-Zoline; Opcon; Spectro-Con; Vasocon)

International Brand Name—Albalon (Belgium, Hong Kong, South Africa); Albalon Liquifilm (Netherlands, Philippines); Albasol (Chile, Colombia, Ecuador, Peru); All Clear (Hong Kong); Dazolin (Argentina); Idril N sine augentropfen (Germany); Imizol (Italy); Mirafrin (Colombia); Naftazolina (Italy); Naphacel Ofteno (Costa Rica, Dominican Republic, El Salvador, Guatemala, Honduras, Mexico, Nicaragua, Panama); Naphasal (Israel); Naphazolin (Germany); Naphcon (Greece, Israel, South Africa, Venezuela); Naphcon Forte (Belgium, Canada, Thailand); Naphtears (Paraguay, Uruguay); Nazil Ofteno (Costa Rica, Dominican Republic, El Salvador, Guatemala, Honduras, Mexico, Nicaragua, Panama); Privina (Brazil); Rintal (Peru); Vasocon (Canada); Vistalbalon (Germany); Zolin (Peru)

Drug Class	Decongestants; Sympathomimetics
Indications	Ocular congestion
Mechanism	Stimulates α-adrenergic receptors (sympathomimetic)
Dosage with Qualifiers	Ocular congestion—1-2gtt OS/OD q3-4h; max 4 doses/d • **Contraindications**—hypersensitivity to drug or class, glaucoma • **Caution**—CV disease, diabetes mellitus, hyperthyroidism, hypertension
Maternal Considerations	There are no adequate reports or well-controlled studies of **naphazoline** in pregnant women. ***Side effects*** include hyperemia, headache, dizziness, blurred vision, large pupils, increased sweating, weakness, and nervousness.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **naphazoline** crosses the human placenta. Considering the dose and route, it is unlikely the associated maternal systemic concentration will reach a clinically relevant level.
Breastfeeding Safety	There is no published experience in nursing women. It is unknown whether **naphazoline** enters human breast milk. However, considering the indication and dosing, occasional **naphazoline** use is unlikely to pose a clinically significant risk to the breastfeeding neonate.
Drug Interactions	No clinically relevant interactions identified.
References	There are no current relevant references.
Summary	**Pregnancy Category: C** **Lactation Category: S** (likely) • **Naphazoline** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Naproxen—(EC-Naprosyn; Ec-Naprosyn; Flexipen; Napoton; Napren; Naprosyn; Sutony)

International Brand Name—Acusprain (South Africa); Aflamax (Peru); Agilxen (Colombia); Aleve (Paraguay, Poland, Singapore, Uruguay); Alpron (Philippines); Anax (Korea); Anexopen (Greece); Antalgin (Spain); Apo-Naproxen (Canada); Apranax (Bulgaria, France, Israel, Russia, Venezuela); Apraxin (Turkey); Apronax (Colombia, Ecuador, Peru); Artagen (India); Artron (Mexico); Artroxen (Italy); Babel (Korea); Bipronyl (Singapore); Bonyl (Denmark); Complement (Peru); Congex (Argentina); Crysanal (Australia); Dafloxen (Mexico); Daprox (Denmark); Deflamox (Mexico); Diferbest (Mexico); Diocodal (Argentina); Dysmenalgit (Germany); Femex (Netherlands); Flanax (Brazil, Costa Rica, Dominican Republic, El Salvador, Guatemala, Honduras, Nicaragua, Panama, Philippines); Flanax Forte (Peru); Floginax (Italy); Flonax (Peru); Fuxen (Mexico); Gibixen (Italy); Headlon (Japan); Inza (Australia, Hong Kong, Malaysia); Iraxen (Peru); Laraflex (England); Laser (Italy); Lefaine (Philippines); Leniartil (Italy); Licorax (Korea); Nafasol (South Africa); Naixan (Japan); Napolon (Korea); Naposin (Taiwan); Naprius (Italy); Naproflam (Germany); Naprong (Korea); Naprontag (Argentina); Naprorex (Hong Kong); Naprosyn (Canada, Czech Republic, Denmark, Ecuador, England, Finland, Greece, Hong Kong, India, Ireland, Italy, Malaysia, Norway, Peru, Portugal, Russia, Spain, Sweden, Switzerland, Turkey); Naprosyne (Belgium, France, Netherlands); Naprosyn LE (Thailand); Naprosyn LLE (Philippines); Naprosyn LLE Forte (Philippines); Naproxi 250 (Israel); Naproxi 500 (Israel); Naprux (Argentina); Napxen (Thailand); Narma (Japan); Narocin (Israel); Naxen (Canada, Indonesia, Mexico, South Africa); Naxen F (Korea); Naxen-F CR (Korea); Naxopren (Finland); Naxyn 250 (Israel); Naxyn 500 (Israel); Novo-naprox (Canada); Novonaprox (Canada); Nuprafem (Singapore); Nycopren (Austria, Denmark, Finland); Prexan (Italy); Primeral (Italy); Prodilor (Germany); Pronaxen (Malaysia, Sweden); Proxen (Austria, Germany, Spain, Switzerland); Proxen LLE (Taiwan); Proxidol (Israel); Rahsen (Japan); Roxen (Thailand); Sanomed (Philippines); Saritilron (Japan); Seladin (Malaysia); Shiprosyn (Philippines); Sutolin (Taiwan); Synflex (England, Hong Kong, Ireland); Tohexen (Japan); Uniflam (Peru); U-Ritis (Taiwan); Velsay (Mexico); Veradol (Argentina); Vinsen (Thailand); Wintrex (Peru); Xenar (Italy); Xenobid (India)

Drug Class	Analgesics, non-narcotic; NSAIDs
Indications	Osteoarthritis or rheumatoid arthritis, dysmenorrhea, pain, ankylosing spondylitis, anti-inflammatory effect
Mechanism	Inhibits cyclooxygenase and lipoxygenase, leading to reduced prostaglandin synthesis
Dosage with Qualifiers	Osteoarthritis—250-500mg PO bid; max 1500mg/d ×3-5d Rheumatoid arthritis—250-500mg PO bid; max 1500mg/d ×3-5d Dysmenorrhea—250mg PO q6-8h prn; begin 500mg ×1; max 1250mg/d Pain—250-500mg PO bid; max 1500mg/d ×3-5d Ankylosing spondylitis—250-500mg PO bid; max 1500mg/d ×3-5d Anti-inflammatory effect—250-500mg PO bid; max 1500mg/d ×3-5d • **Contraindications**—hypersensitivity to drug or class, NSAID-induced asthma, renal or hepatic dysfunction • **Caution**—GI bleeding, hypertension, CHF, nasal polyps, chronic alcoholic liver disease, anemia
Maternal Considerations	NSAIDs are widely distributed in OTC preparations, and their use during pregnancy is underestimated. About 5% of women report use of either **ibuprofen** or **naproxen** near conception or during pregnancy. It may be combined with **sumatriptan** for the treatment of acute migraine. In a recent prospective case-control study, prenatal **ibuprofen** or **naproxen** use increased the risk of spontaneous abortion by 80% (adjusted hazard ratio 1.8 [95% CI 1.0-3.2]). The association was stronger if the initial use was around conception or if the use lasted more than 1w. **Naproxen** offers no distinct clinical advantage after the 1st trimester over other NSAIDs on the market. It provides analgesic relief similar to **acetaminophen** after vaginal delivery. One randomized trial suggests the addition of regular doses of **naproxen** to prn requests for **acetaminophen-codeine** provides small reductions in

pain on day 2 after cesarean delivery, with the greatest effects at 36h, when pain typically peaks.
Side effects include headache, dyspnea, dizziness, drowsiness, light-headedness, vertigo, skin eruption, ecchymosis, sweating, purpura, edema, palpitations, tinnitus, hearing disturbances, visual disturbances, renal failure, bronchospasm, Stevens-Johnson syndrome, interstitial nephritis, hepatotoxicity, thrombocytopenia, agranulocytosis, constipation, rash, increased hepatic transaminases, urticaria, and fluid retention.

Fetal Considerations

Naproxen crosses the human placenta, achieving an F:M ratio of 0.92 during the 2nd trimester. Fetal levels are dependent on the maternal, as NSAIDs are not metabolized by the fetal kidney. Other NSAIDs can cause premature closure of the fetal ductus arteriosus. While the ductal response to **naproxen** remains to be studied, there are several case reports of neonatal pulmonary hypertension after its use in the 3rd trimester. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically.

Breastfeeding Safety

Although **naproxen** is excreted into human breast milk, the amount of drug transferred is only a small fraction of the maternal dose and should not pose a risk to the nursing newborn.

Drug Interactions

Displaced from its binding sites by **aspirin**, resulting in lower plasma concentrations and peak plasma levels.
NSAIDs reduce the tubular secretion of **methotrexate** in an animal model, possibly increasing the toxicity of **methotrexate.**
NSAIDs may diminish the antihypertensive effect of ACEIs.
NSAIDs may reduce the natriuretic effect of **furosemide** and thiazides. This response is attributed to inhibition of renal prostaglandin synthesis.
Increases the minimum **lithium** concentration some 15% and decreases renal clearance some 20%, presumably secondary to the inhibition of renal prostaglandin synthesis. Patients should be observed carefully for signs of **lithium** toxicity.
The effects of **warfarin** and NSAIDs on GI bleeding are synergistic. Caution is advised even though no significant interactions have been observed in clinical studies with **naproxen** and coumarin-type anticoagulants.
NSAIDs may reduce the antihypertensive effect of β-blockers.
Probenecid increases plasma levels and extends the t/2 significantly.
Use of **naproxen** delayed-release tablets are not recommended with H_2 blockers, **sucralfate,** or intensive antacid therapy due to the increase in gastric pH.

References

Angle PJ, Halpern SH, Leighton BL, et al. Anesth Analg 2002; 95:741-5.
Davies NM, Anderson KE. Clin Pharmacokinet 1997; 32:268-93.
Li DK, Liu L, Odouli R. BMJ 2003; 327:368-73.
Siu SS, Yeung JH, Lau TK. Hum Reprod 2002; 17:1056-9.
Skovlund E, Fyllingen G, Landre H, Nesheim BI. Eur J Clin Pharmacol 1991; 40:539-42.
Talati AJ, Salim MA, Korones SB. Am J Perinatol 2000; 17:69-71.

Summary

Pregnancy Category: B
Lactation Category: S

- **Naproxen** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

- Periconceptual **naproxen** may increase the risk of spontaneous abortion.
- 1st trimester exposure should be minimized until completion of future studies in light of the association with gastroschisis.
- **Acetaminophen** (paracetamol) is the analgesic of choice in the 1st trimester.
- **Naproxen** probably poses minimal risk when taken occasionally outside the 1st trimester.

Naratriptan—(Amerge)

International Brand Name—Amerge (Canada); Antimigrin (Austria); Naragran (Denmark); Naramig (Argentina, Australia, Belgium, Brazil, Bulgaria, Chile, Colombia, England, France, Germany, Ireland, Korea, Mexico, Netherlands, Peru, Singapore, South Africa, Thailand, Uruguay)

Drug Class	Serotonin receptor agonists
Indications	Migraine headache
Mechanism	Selective 5-$HT_{1B/1D}$ agonist
Dosage with Qualifiers	Migraine headache—1-2.5mg PO ×1; may repeat in 4h after 1st dose; max 5mg/d • **Contraindications**—hypersensitivity to drug or class, hypertension, CAD, hepatic failure, significant renal or hepatic dysfunction, MAOIs <14d, ergot derivatives <24h • **Caution**—CVD, mild hepatic dysfunction
Maternal Considerations	Migraine headaches are a frequent complaint during pregnancy, and ergot compounds are generally considered contraindicated. From 55% to 90% of pregnant women experience an improvement in headache symptoms during the 2nd and 3rd trimesters. A higher percentage of women with menstrual migraine find they improve during pregnancy. There are no adequate reports or well-controlled studies of **naratriptan** in pregnant women. The clearance of **naratriptan** is modestly reduced (22%) in women on oral contraceptives; clearance during pregnancy is unstudied. Smoking increases clearance by 1/3. The manufacturer, Glaxo-Wellcome, maintains a registry for post-marketing information on pregnancy outcomes. ***Side effects*** include malaise, fatigue, abnormal ECG, acute MI, stroke, coronary vasospasm, cardiac arrest, palpitations, tachyarrhythmia, hypertensive crisis, colonic ischemia, hyposalivation, vomiting, tracheitis, asthma, pleuritis, tremors, cognitive function disorders, sleep disorders, disorders of equilibrium, anxiety, depression, hallucinations, panic, polyuria, diuresis, and inflammation of the breast, vagina, or bladder.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. Epidemiologic information is limited but reassuring. However, ther is more experience with **sumatriptan**. It is unknown whether **naratriptan** crosses the human placenta. Rodent studies reveal embryotoxicity and skeletal abnormalities at doses producing maternal plasma levels only a few multiples of the MRHD. However, the frequencies of these adverse outcomes are not dose-dependent.

Breastfeeding Safety

There is no published experience in nursing women. It is unknown whether **naratriptan** enters human breast milk. It does enter rodent milk. However, considering the indication and dosing, one-time **naratriptan** use is unlikely to pose a clinically significant risk to the breastfeeding neonate. The patient may choose to pump her breasts for 24h for added safety.

Drug Interactions

Use of ergotamine-containing or ergot-type medications (e.g., **dihydroergotamine, methysergide**) within 24h is contraindicated as there is a theoretical concern the effects may be additive. SSRIs (e.g., **fluoxetine, fluvoxamine, paroxetine, sertraline**) are reported, rarely, to cause weakness, hyperreflexia, and incoordination when co-administered with 5-HT_1 agonists.

References

Evans EW, Lorber KC. Ann Pharmacother 2008; 42:543-9.
Pfaffenrath V, Rehm M. Drug Saf 1998; 19:383-8.

Summary

Pregnancy Category: C
Lactation Category: U

- **Naratriptan** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.
- Physicians are encouraged to register pregnant women under the Naratriptan Pregnancy Registry (1-800-336-2176) for a better follow-up of outcome while under treatment with **naratriptan.**
- There are alternative agents for which there is more experience regarding use during pregnancy and lactation.

Nateglinide—(Starlex)

International Brand Name—Fastic (Korea); Glinate (India); Starlix (Argentina, Brazil, Chile, Colombia, Costa Rica, Dominican Republic, Ecuador, El Salvador, Guatemala, Honduras, Indonesia, Malaysia, Mexico, New Zealand, Nicaragua, Panama, Peru, Philippines, Singapore, Uruguay, Venezuela)

Drug Class

Antidiabetic agents; Biguanides

Indications

Diabetes mellitus type 2

Mechanism

Stimulates pancreatic beta cell insulin release

Dosage with Qualifiers

Diabetes mellitus type 2—begin 30-60mg PO qac if Hb_{A1c} close to normal; use as monotherapy or in combination with **metformin**

NOTE: do not use with insulin secretagogues; take 30min before meal and skip dose if no meal taken.

- **Contraindications**—hypersensitivity to drug or class, diabetes mellitus type 1, DKA
- **Caution**—hepatic dysfunction

Maternal Considerations

Oral agents have rapidly become established viable alternatives during pregnancy in women with type 2 diabetes mellitus. **Nateglinide** is a D-phenylalanine derivative that helps reduce postprandial hyperglycemia. There is no published experience during pregnancy.
Side effects include URI, arthropathy, bronchitis, hypoglycemia, diarrhea, and dizziness.

Fetal Considerations

There is no published experience in human fetuses. It is unknown whether **nateglinide** crosses the human placenta. Rodent studies are generally reassuring, though some note an increase in gallbladder agenesis at doses 40× the MRHD.

Breastfeeding Safety

There is no published experience in nursing women. It is unknown whether **nateglinide** enters human breast milk. It is excreted into rodent milk, and the maternal administration of high doses slows pup weight gain. It is unknown whether the reduced growth reflects only maternal hypoglycemia.

Drug Interactions

NSAIDs, salicylates, MAOIs, and nonselective β-adrenergic-blocking agents may potentiate the hypoglycemic action of **nateglinide.**
Thiazides, corticosteroids, thyroid products, and sympathomimetics may reduce the hypoglycemic action of **nateglinide.**

References

There is no published experience in pregnancy or during lactation.

Summary

Pregnancy Category: C
Lactation Category: U

- There are superior agents for use during pregnancy, notably **glyburide** and **metformin.**
- **Nateglinide** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Nedocromil—(Alocril; Tilade)

International Brand Name—Alocril (Canada); Telavist (France, Israel); Tilade (Brazil, Canada, Indonesia, New Zealand); Tilade CFC Free (Australia)

Drug Class

Allergy; Mast cell stabilizers

Indications

Asthma, chronic; allergic conjunctivitis

Mechanism

Inhibits release of various inflammatory cell mediators

Dosage with Qualifiers

Asthma, chronic—2 puffs INH qid
Allergic conjunctivitis—1-2gtt OS/OD bid

NOTE: 2% solution; may reduce dose 50% if clinical improvement.

- **Contraindications**—hypersensitivity to drug or class, acute asthma attack
- **Caution**—unknown

Maternal Considerations

There is no published experience with **nedocromil** during pregnancy. **Nedocromil** is effective long-term maintenance therapy for bronchial asthma.
Side effects include bronchospasm, headache, bitter taste, cough, pharyngitis, rhinitis, bronchitis, dyspnea, N/V, dry mouth, dyspepsia, and fatigue.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **nedocromil** crosses the human placenta. Considering the dose and route, it is unlikely the maternal systemic concentration will reach a clinically relevant level. Rodent studies are reassuring, revealing no evidence of

	teratogenicity or IUGR despite the use of doses higher than those used clinically.
Breastfeeding Safety	There is no published experience in nursing women. It is unknown whether **nedocromil** enters human breast milk. However, considering the indication and dosing, occasional **nedocromil** use is unlikely to pose a clinically significant risk to the breastfeeding neonate.
Drug Interactions	No clinically relevant interactions identified.
References	There is no published experience in pregnancy or during lactation.
Summary	**Pregnancy Category: B** **Lactation Category: U** • **Nedocromil** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk. • There are alternative agents for which there is more experience regarding use during pregnancy and lactation.

Nefazodone—(Serzone)

International Brand Name—Nefadar (Germany); Serzone (Brazil, New Zealand, South Africa); Serzonil (Israel)

Drug Class	Antidepressants
Indications	Depression
Mechanism	Inhibits norepinephrine and 5-HT reuptake; antagonizes 5-HT receptor
Dosage with Qualifiers	Depression—begin 100mg PO bid, 150-300mg PO bid; max 600mg/d • **Contraindications**—hypersensitivity to drug or class, active hepatic disease, MAOI <14d, **cisapride** use • **Caution**—unknown
Maternal Considerations	Depression is common during and after pregnancy, but typically goes unrecognized. Pregnancy is not a reason *a priori* to discontinue psychotropic drugs. The serotonin reuptake inhibitors are first-line treatment for most depressive and anxiety disorders. **Nefazodone** is unrelated to SSRIs, TCAs, or MAOIs. There is limited published experience with **nefazodone** during pregnancy. It has been used to treat postpartum depression. ***Side effects*** include hepatotoxicity, seizures, hypomania, hepatic failure, insomnia, asthenia, dizziness, light-headedness, headache, dry mouth, dyspepsia, constipation, diarrhea, pharyngitis, abnormal vision, blurred vision, confusion, orthostatic hypotension, increased appetite, and paresthesias.
Fetal Considerations	There is no published experience in human fetuses. It is unknown whether **nefazodone** crosses the human placenta. A prospective case-control study was reassuring, revealing no evidence of an adverse fetal effect. Rodent studies are generally reassuring, revealing no signs of teratogenicity or IUGR despite the use of doses higher than those used clinically. There is an unexplained increase in early pup death.

Breastfeeding Safety

There are no adequate reports or well-controlled studies in nursing women. **Nefazodone** enters human breast milk, and neonatal drowsiness, lethargy, and poor feeding that resolves when breastfeeding stops are reported. If the mother elects to breastfeed, the infant should be monitored for possible adverse effects, the drug given at the lowest effective dose, and breastfeeding avoided at times of peak drug levels.

Drug Interactions

Use with another drug that is highly protein bound may cause increased free concentrations of that drug, potentially resulting in adverse events. Conversely, adverse effects could result from displacement of **nefazodone** by other highly bound drugs.

In one steady-state pharmacokinetics study of healthy volunteers, **nefazodone** (250mg bid) triggered a marked increase in the **buspirone** concentration (up to 20-fold in C_{max} and up to 50-fold in AUC). Subjects receiving **nefazodone** (250mg bid) and **buspirone** (5mg bid) experienced light-headedness, asthenia, dizziness, and somnolence. These events were also noted with either drug alone.

There were no changes in the pharmacokinetic parameters for **fluoxetine** or its metabolite norfluoxetine when **fluoxetine** (20mg qd) and **nefazodone** (200mg bid) were given. Nor were there changes in the pharmacokinetic parameters of **nefazodone.** However, the mean AUC levels of the two biologically active **nefazodone** metabolites increased 3- to 6-fold and 1.3-fold, respectively. When administered to subjects receiving **fluoxetine** for 1w, there was an increased prevalence of transient adverse events such as headache, light-headedness, nausea, or paresthesia. Patients who are switched from **fluoxetine** to **nefazodone** without an adequate washout period can experience similar transient adverse events. Because of the long t/2 of **fluoxetine** and its metabolites, this washout period may range from 1 to several weeks.

Use with **carbamazepine** increases the steady-state C_{max} and AUC of **carbamazepine** (23% and 23%, respectively), while the steady-state C_{max} and AUC of the **carbamazepine** metabolite, 10,11-epoxycarbamazepine, decreased by 21% and 20%, respectively. Co-administration significantly reduced the steady-state C_{max} and AUC of **nefazodone** by 86% and 93%, respectively. As a result, it is recommended **nefazodone** not be used in combination with **carbamazepine**.

When given to CYP2D6 extensive metabolizers, the C_{max}, C_{min}, and AUC for **digoxin** were increased by 29%, 27%, and 15%, respectively. **Digoxin** had no effects on the pharmacokinetics of **nefazodone** and its active metabolites. Caution should be exercised when **nefazodone** and **digoxin** are used together.

Use with **propranolol** (40mg bid) reduced by 30% and 14% the C_{max} and AUC for **propranolol,** respectively. The kinetics of **nefazodone** and its metabolites were unaffected. No change in dosing of either drug is necessary.

Caution should be used if **nefazodone** is given with HMG-CoA reductase inhibitors that are metabolized by CYP3A4 (e.g., **atorvastatin, lovastatin, simvastatin**). Increases of 20-fold in the concentrations of **simvastatin** and 3- to 4-fold in those of **atorvastatin** are presumably due to the inhibition of CYP3A4 by **nefazodone** as, in the same study, **nefazodone** had no effect on the plasma concentrations of **pravastatin,** which is not metabolized by CYP3A4. There are rare reports of rhabdomyolysis in patients receiving the combination of **nefazodone** and either **simvastatin** or **lovastatin,** also a substrate of CYP3A4. Since metabolic interactions are unlikely between **nefazodone** and HMG-CoA reductase inhibitors that undergo

little or no metabolism by CYP3A4 (e.g., **fluvastatin**, **pravastatin**), dosage adjustments should not be necessary. There are reports of increased concentrations of **cyclosporine** and **tacrolimus** into toxic ranges when patients received these drugs with **nefazodone.** Both **cyclosporine** and **tacrolimus** are substrates of CYP3A4. Blood concentrations of the immunosuppressive agent should be monitored and dosage adjusted accordingly.

References

Dodd S, Buist A, Burrows GD, et al. J Chromatogr B Biomed Sci Appl 1999; 730:249-55.
Einarson A, Bonari L, Voyer-Lavigne S, et al. Can J Psychiatry 2003; 48:106-10.
Yapp P, Ilett KF, Kristensen JH, et al. Ann Pharmacother 2000; 34:1269-72.

Summary

Pregnancy Category: C
Lactation Category: NS (possibly)

- **Nefazodone** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.
- There are alternative agents for which there is more experience regarding use during pregnancy and lactation.

Nelfinavir—(Viracept)

International Brand Name—Viracept

Drug Class

Antivirals; Protease inhibitors

Indications

HIV infection

Mechanism

Protease inhibitor

Dosage with Qualifiers

HIV infection—1250mg PO with food bid in combination with other antiretroviral agents; alternatively, 750mg PO tid

NOTE: do not mix with juice or acidic food.

- **Contraindications**—hypersensitivity to drug or class; use of **amiodarone, astemizole,** ergot derivatives, **midazolam, pimozide, quinidine,** and **rifampin;** phenylketonuria
- **Caution**—hepatic dysfunction

Maternal Considerations

The incidence of both the AIDS syndrome and opportunistic infections has declined over the last few years due to advances in drug regimens. HAART consisting of 3-5 agents is the current standard of care in the US for the management of HIV infection during pregnancy because of its high efficacy. Some study protocols use **nelfinavir** as the protease inhibitor. The treatment of HIV during pregnancy dramatically reduces the risk of mother-to-child transmission in proportion to the maternal viral load. Pregnancy increases clearance. In one steady-state study of 20 women on a HAART regimen including **nelfinavir** (1250mg bid) and two NRTIs, during the 3rd trimester median **nelfinavir** AUC (0-12 h) was 25.8mcg/h/ml vs. 32.5mcg/h/ml in the control group. Median oral clearance (CL/F) was significantly higher in pregnant women (48.5 L/h vs. 38.5 L/h), but the difference disappeared when CL/F was adjusted for body weight. Trough concentration was also significantly ($p < .01$) lower during

pregnancy (median 0.8mcg/ml vs. 1.5mcg/ml). The elimination t/2 of **nelfinavir** during pregnancy was 3.7h (range 1.4-6.6h), compared with 5.2h (range 3.1-10.1h) in the control group. A smaller study led to a similar conclusion. These results indicate that women in the later stages of pregnancy may be exposed to subtherapeutic concentrations of **nelfinavir** if the dosage or frequency is not adjusted. This increased clearance takes some time to return to the prepregnant values. In one study of 9 pregnant women, clearance was unaltered compared to the puerperium. Careful monitoring for hepatotoxicity during therapy with **nelfinavir** is recommended. The association between combination antiviral therapy with protease inhibitors and an increased risk of very low birth weight requires confirmation. **Nelfinavir**-related GI symptoms and hyperglycemia may be more common during pregnancy.
Side effects include N/V, flatulence, diarrhea, hepatitis, seizures, rash, asthenia, abdominal pain, arthralgia, myalgias, myopathy, dyslipidemia, hyperglycemia, leukopenia, thrombocytopenia, and pruritus.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. Like most protease inhibitors, **nelfinavir** crosses the human placenta but achieves only subtherapeutic levels. In one study, the **nelfinavir** F:M concentration ratio was 25% for maternal concentrations of 0.1-2.5mg/L between 31 and 41w gestation. In another study, cord blood concentrations were below the limit of assay detection in 10 of 40 samples for **nelfinavir** and 10 of 16 AF samples. The transfer is probably limited by a high degree of plasma protein binding and backward transport by placental P-glycoprotein. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically.

Breastfeeding Safety

Nelfinavir enters human breast milk, but the M:P ratio ranges from 6% to 24%. Breastfeeding is contraindicated in HIV-infected nursing women where formula is available to reduce the risk of neonatal transmission.

Drug Interactions

Inhibits CYP3A. Use with drugs primarily metabolized by CYP3A (e.g., dihydropyridine calcium channel blockers, HMG-CoA reductase inhibitors, immunosuppressants, **sildenafil**) may result in increased plasma concentrations of the other drug that could increase or prolong both its therapeutic and adverse effects.
Lovastatin and **simvastatin** have the potential for serious reactions such as risk of myopathy, including rhabdomyolysis.
Increases **atorvastatin** concentration; use the lowest possible dose of **atorvastatin** with careful monitoring, or consider another HMG-CoA reductase inhibitor (e.g., **fluvastatin, pravastatin**).
Rifampin may lead to loss of antivirologic efficacy and resistance to **nelfinavir** or to other co-administered antiretroviral agents.
St. John's wort *(Hypericum perforatum)* may lead to loss of antivirologic efficacy and resistance to **nelfinavir** or to other co-administered antiretroviral agents.
Use with **indinavir** increases the concentrations of both **nelfinavir** and **indinavir.**
Ritonavir increases the concentration of **nelfinavir.**
Increases the concentration of **saquinavir.**
Use of **delavirdine** increases the concentration of **nelfinavir** but decreases the concentration of **delavirdine.**
Nevirapine decreases the **nelfinavir** C_{min}.
Carbamazepine and **phenobarbital** each decrease **nelfinavir** concentration and render it ineffective.

Decreases the **phenytoin** concentration; monitor and adjust as indicated.
Use with **rifabutin** increases the **rifabutin** concentration but either decreases (750mg tid) or has no effect (1250mg bid) on **nelfinavir** concentrations. The dose of **rifabutin** should be reduced by half when given with **nelfinavir;** the 1250mg bid dose is the preferred.
Decreases **methadone** concentration; the dosage of **methadone** may need to be increased.
Decreases **ethinyl estradiol** concentation; alternative or additional contraceptive measures should be used when oral contraceptives and **nelfinavir** are co-administered.
Increases **azithromycin** concentration; close monitoring for known side effects (e.g., liver enzyme abnormalities and hearing impairment) is warranted.
Increases **fluticasone** concentration; consider alternatives to **fluticasone,** particularly for long-term use.

References

Chappuy H, Tréluyer JM, Rey E, et al. Am J Obstet Gynecol 2004; 191:558-62.
Colebunders R, Hodossy B, Burger D, et al. AIDS 2005; 19:1912-5.
Hill JB, Sheffield JS, Zeeman GG, Wendel GD Jr. Obstet Gynecol 2001; 98:909-11.
Hirt D, Urien S, Jullien V, et al. Br J Clin Pharmacol 2007; 64:634-44.
Jordan R, Gold L, Cummins C, Hyde C. BMJ 2002; 324:757.
Kosel BW, Beckerman KP, Hayashi S, et al. AIDS 2003; 17:1195-9.
Marzolini C, Rudin C, Decosterd LA, et al. AIDS 2002; 16:889-93.
Mirochnick M, Dorenbaum A, Holland D, et al. Pediatr Infect Dis J 2002; 21:835-8.
Read JS, Best BM, Stek AM, et al. HIV Med 2008; 9:875-82.
Timmermans S, Tempelman C, Godfried MH, et al; Dutch HMF Study Group. AIDS 2005; 19:795-9.
Tuomala RE, Shapiro DE, Mofenson LM, et al. N Engl J Med 2002; 346:1863-70.
van Heeswijk RP, Khaliq Y, Gallicano KD, et al. Clin Pharmacol Ther 2004; 76:588-97.
Villani P, Floridia M, Pirillo MF, et al. Br J Clin Pharmacol 2006; 62:309-15.

Summary

Pregnancy Category: B
Lactation Category: NS

- HAART consisting of 3-5 agents is the current standard of care in the US for the management of HIV infection during pregnancy because of its high efficacy.
- The clearance of **nelfinavir** increases significantly during pregnancy, and plasma concentrations should be monitored.
- Pregnant women require careful monitoring for hepatotoxicity during antiretroviral therapy.
- Physicians are encouraged to register pregnant women under the Antiretroviral Pregnancy Registry (1-800-258-4263) for a better follow-up of the outcome while under treatment with **nelfinavir.**

Neomycin—(Mycifradin; Myciguent; Neo-Rx; Qrp)

International Brand Name—Gemicina (Mexico); Mycifradin (England, Ireland, South Africa); Neomicina (Spain); Neomycin (Israel); Neomycine Diamant (France); Nivemycin (England)

Drug Class

Aminoglycosides; Antibiotics

Indications

Hepatic coma, bacterial infections (aerobic gram-negative: *Enterobacter cloacae, E. coli, Klebsiella, Enterobacter)*

Mechanism

Bactericidal—inhibits protein synthesis reducing ammonia forming bacteria in the gut

Dosage with Qualifiers

Hepatic coma—4-12g/d PO; minimize protein in diet
Bacterial infections—apply topically qd to tid; max 1w

NOTE: available in combination with ***bacitracin*** *and polymyxin B as Neosporin.*

- **Contraindications**—hypersensitivity to drug or class, GI obstruction, inflammatory and ulcerative GI disease, severe dermatologic diseases
- **Caution**—hepatic dysfunction

Maternal Considerations

There are no adequate reports or well-controlled studies of **neomycin** in pregnant women. **Neomycin** is poorly absorbed in the bowel, though repeated dosing can lead to accumulation especially in the inner ear. Clearance can take weeks. The CDC recommends the use of a selective broth culture to improve detection of genital tract or anorectal carriage of GBS in pregnant women. The addition of **neomycin** to **nalidixic acid** in a selective broth medium improves the sensitivity of screening cultures for the detection of GBS carriage in women.
Side effects include N/V, diarrhea, malabsorption syndrome, nephrotoxicity, ototoxicity, and neuromuscular blockage.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **neomycin** crosses the human placenta. While there is no evidence that it is a human teratogen, some aminoglycosides (e.g., **streptomycin**) have been associated with irreversible deafness after *in utero* exposure. Considering the dose and route, it is unlikely the maternal systemic concentration will reach a clinically relevant level after topical administration. Rodent teratogenicity studies have not been performed. **Neomycin** is used for prophylaxis of ophthalmia neonatorum, though efficacy has not been tested through clinical trials.

Breastfeeding Safety

There are no adequate reports or well-controlled studies in nursing women. It is unknown whether **neomycin** enters human breast milk. **Neomycin** is excreted into both ovine and rat breast milk. However, considering the indication and dosing, occasional topical use is unlikely to pose a clinically significant risk to the breastfeeding neonate.

Drug Interactions

Caution should be used in concurrent or serial administration of other neurotoxic and/or nephrotoxic drugs because of possible enhancement of the nephrotoxicity and/or ototoxicity.
Caution should also be used in concurrent or serial administration of other aminoglycosides and polymyxins because they may enhance nephrotoxicity and/or ototoxicity and potentiate **neomycin's** neuromuscular blocking effects.

Oral **neomycin** inhibits the GI absorption of penicillin V, oral vitamin B_{12}, **methotrexate,** and **5-fluorouracil.** The absorption of **digoxin** also appears to be inhibited. Serum **digoxin** levels should be monitored.
Oral **neomycin** may enhance the effect of coumarin by decreasing vitamin K availability.

References

Assadian O, Assadian A, Aspock C et al. Wien Klin Wochenschr 2002; 114:194-9.
Czeizel AE, Rockenbauer M, Olsen J, Sorensen HT. Scand J Infect Dis 2000; 32:309-13.
Dunne WM Jr. J Clin Microbiol 1999; 37:3705-6.
Dunne WM Jr, Holland-Staley CA. J Clin Microbiol 1998; 36:2298-300.
Scheer M. Arzneimittelforschung 1976; 26:778-81.

Summary

Pregnancy Category: D
Lactation Category: S (topical), **U** (oral)
- **Neomycin** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Neostigmine—(Prostigmin)

International Brand Name—Prostigmin (Argentina, Australia, Canada, Czech Republic, Ecuador, Germany, Ghana, Indonesia, Israel, Kenya, Malaysia, Netherlands, Puerto Rico, Tanzania, Thailand, Uganda, Zambia); Prostigmina (Italy); Prostigmine (Belgium, Costa Rica, Dominican Republic, Ecuador, El Salvador, France, Guatemala, Honduras, Israel, Mexico, Nicaragua, Panama); Tilstigmin (India); Vagostin (Taiwan)

Drug Class

Cholinesterase inhibitors; Musculoskeletal agents

Indications

Myasthenia gravis, neuromuscular reversal, urinary retention

Mechanism

Inhibits cholinesterase activity

Dosage with Qualifiers

Myasthenia gravis treatment—15-375mg PO qd; 10mg SC/IV/IM qd; 0.5-2.5mg SC/IV/IM q2-3h prn; max 375mg PO qd
Myasthenia gravis diagnosis—0.02mg/kg IM ×1 with **atropine**
Neuromuscular reversal—0.07mg/kg IV, max 5mg; give slow IV push with **atropine** and **glycopyrrolate**
Urinary retention treatment—0.5-1mg SC/IM ×1; if no output after 1h, catheterize bladder and give 0.5mg SC/IM q3h ×5 doses
Urinary retention prophylaxis—0.25mg SC/IM q4-6h ×2-3d; begin immediately postoperatively to prevent bladder distention/atony

NOTE: renal dosing.

- **Contraindications**—hypersensitivity to drug or class, GI obstruction, urinary tract obstruction, peritonitis
- **Caution**—epilepsy, asthma, bradycardia, recent MI, hyperthyroidism, peptic ulcer disease

Maternal Considerations

There are case reports of use of **neostigmine** throughout pregnancy for the treatment of maternal myasthenia gravis. It is also increasingly used for neuraxial anesthesia.
Side effects include cholinergic crisis, cardiac arrest, arrhythmia, respiratory paralysis, bronchospasm, respiratory secretions, salivation, drowsiness, fasciculation, N/V, abdominal pain, flatulence, diarrhea, dizziness, seizures, syncope, hypotension, rash, weakness, flushing, and urinary frequency.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **neostigmine** crosses the human placenta. Twenty to 30% of offspring of women suffering from myasthenia gravis have transient neonatal motor symptoms, suggesting maternal antibodies cross the placenta. Newborns with myasthenia gravis require **neostigmine** until complete recovery of the motor handicap. Rodent teratogenicity studies have not been performed.

Breastfeeding Safety

There are no adequate reports or well-controlled studies in nursing women. It is unknown whether **neostigmine** enters human breast milk. However, considering the indications and dosing, occasional use is unlikely to pose a clinically significant risk to the breastfeeding neonate. It is generally considered compatible with breastfeeding.

Drug Interactions

Certain antibiotics, especially **kanamycin, neomycin,** and **streptomycin,** may accentuate neuromuscular block. These antibiotics should be used in the myasthenic patient only where clearly indicated, and then with careful adjustment of adjunctive anticholinesterase dosage.

Local and some general anesthetics, antiarrhythmic agents, and other drugs that interfere with neuromuscular transmission should be used cautiously, if at all, in patients with myasthenia gravis.

References

Chung CJ, Kim JS, Park HS, Chin YJ. Anesth Analg 1998; 87:341-6.

Clark RB, Brown MA, Lattin DL. Anesthesiology 1996; 84:450-2.

Habib AS, Gan TJ. CNS Drugs 2006; 20:821-39.

Klamt JG, Garcia LV, Prado WA. Anaesthesia 1999; 54:27-31.

Licht C, Model P, Kribs A, et al. Nervenarzt 2002; 73:774-8.

Mercier FJ, Benhamou D. Baillieres Clin Obstet Gynaecol 1998; 12:397-407.

Mitchell PJ, Bebbington M. Obstet Gynecol 1992; 80:178-81.

Owen MD, Ozsarac O, Sahin S, et al. Anesthesiology 2000; 92:361-6.

Nelson KE, D'Angelo R, Foss ML, et al. Anesthesiology 1999; 91:1293-8.

Rolbin WH, Levinson G, Shnider SM, Wright RG. Anesth Analg 1978; 57:441-7.

Summary

Pregnancy Category: C
Lactation Category: S

- **Neostigmine** should be used during pregnancy only if the benefit justifies the potential perinatal risk.

Nesiritide—(Natrecor)

International Brand Name—Noratak (Israel)

Drug Class

Cardiovasculars; Natriuretic peptides, type-B human

Indications

Acute CHF

Mechanism

Stimulates cGMP production and thus vascular smooth muscle relaxation

Dosage with Qualifiers

Acute CHF—begin 2mcg/kg IV bolus, then 0.01mcg/kg/min IV; decrease or discontinue if hypotension; max 0.03mcg/kg/min

- **Contraindications**—hypersensitivity to drug or class, cardiogenic shock, systolic BP <90mmHg, cardiac tamponade, restrictive cardiomyopathy, obstructive cardiomyopathy, constrictive pericarditis
- **Caution**—renal dysfunction, hypotension, volume depletion, concomitant use of other hypotensive agents

Maternal Considerations

Nesiritide is human recombinant BNP. There is no published experience with **nesiritide** during pregnancy.
Side effects include hypotension, tachycardia, ventricular extrasystoles, dizziness, elevated creatinine, headache, hypotension, back pain, N/V, insomnia, anxiety, and angina.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **nesiritide** crosses the human placenta. Rodent teratogenicity studies have not been performed.

Breastfeeding Safety

There is no published experience in nursing women. It is unknown whether **nesiritide** enters human breast milk.

Drug Interactions

There is an increase in symptomatic hypotension in patients receiving oral ACEIs.

References

There are no current relevant references.

Summary

Pregnancy Category: C
Lactation Category: U

- **Nesiritide** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.
- There are alternative agents for which there is more experience regarding use during pregnancy and lactation.

Netilmicin—(Netromycin)

International Brand Name—Bactrocin (Thailand); Certomycin (Austria, Germany); Hypobhac (Indonesia); Keunmixin (Philippines); Nelin (Thailand); Neosin (Korea); Nesomicin (Korea); Netcin (Korea, Mexico); Netcin FA (Mexico); Netilacin (Korea); Netilicin (Korea); Netillin (England, Ireland); Netilmicin (Korea); Netilyn (Denmark, Finland, Japan, Norway, Sweden); Netin (Korea); Netrocin (Spain); Netromicina (Brazil, Costa Rica, Dominican Republic, Ecuador, El Salvador, Guatemala, Honduras, Mexico, Nicaragua, Panama, Peru, Portugal, Venezuela); Netromicine (France); Netromycin (Canada, China, Greece, India, Indonesia, Korea, Malaysia, New Zealand, Philippines, South Africa, Switzerland, Taiwan, Thailand); Netromycine (Belgium, Czech Republic, Hungary, Israel, Netherlands, Poland); Netromycin IM IV (Hong Kong); Nettacin (Italy); Vectacin (Japan); Zetamicin (Italy)

Drug Class

Aminoglycosides; Antibiotics

Indications

Bacterial infections of the skin, and respiratory tract, sepsis, intra-abdominal infections (aerobic gram-negative: *Enterobacter cloacae, E. coli, H. influenzae, H. parainfluenzae, Klebsiella* species, *Legionella pneumophila, Moraxella caterrhalis, P. mirabilis;* aerobic gram-positive: *Enterococcus faecalis,* MSSA, *S. saprophyticus, S. pneumoniae, S. pyogenes*)

Mechanism

Bactericidal—inhibits protein synthesis

Dosage with Qualifiers

Bacterial infections—4-6.5mg/kg/IV qd divided q8-12h

- **Contraindications**—hypersensitivity to drug or class
- **Caution**—unknown

Maternal Considerations

There are no adequate reports or well-controlled studies of **netilmicin** in pregnant women. It is the 1st alternative to **gentamicin** for the treatment of brucellosis. There are case reports of its use for listeriosis.
Side effects include nephrotoxicity, ototoxicity, rash, neuromuscular blockade, hypomagnesemia, thrombocytosis, pain at injection site, tinnitus, nystagmus, hearing loss, and elevation of liver enzymes, bilirubin, and alkaline phosphatase.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **netilmicin** crosses the human placenta. While there is no evidence that **netilmicin** is a human teratogen, some aminoglycosides (e.g., **streptomycin**) have been associated with irreversible deafness after *in utero* exposure. Rodent teratogenicity studies have not been performed. Transfer across the term rat placenta appears low. In the guinea pig, **netilmicin** had significantly less effect on the cochlea compared to **gentamicin.** In the rat, the impact of **netilmicin** on renal function after *in utero* exposure is similar to **gentamicin** and greater than **amikacin.**

Breastfeeding Safety

There is no published experience in nursing women. A small amount of **netilmicin** enters human breast milk, but the kinetics remain to be elucidated.

Drug Interactions

No clinically relevant interactions identified.

References

Bonacorsi S, Doit C, Aujard Y, et al. Clin Infect Dis 1993; 17:139-40.
Fujino A, Uda F, Nomura A, Tokiwa T. Jpn J Antibiot 1982; 35:979-86.
Kawasaki H, Yamada Y, Takei T, Akiyoshi M. Jpn J Antibiot 1982; 35:1553-61.
Mallie JP, Coulon G, Billerey C, et al. Kidney Int 1988; 33:36-44.

Summary

Pregnancy Category: D
Lactation Category: U

- **Netilmicin** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.
- There are alternative agents for which there is more experience regarding use during pregnancy and lactation.

Nevirapine—(Viramune)

International Brand Name—Ciplanevimune (Colombia); Nevimune (India)

Drug Class

Antivirals; Non-nucleoside reverse transcriptase inhibitors

Indications

HIV

Mechanism

Inhibits reverse transcriptase

Dosage with Qualifiers

HIV infection—200mg PO qd ×14d; continue treatment with 200mg PO bid in combination with nucleoside antiretrovirals

- **Contraindications**—hypersensitivity to drug or class
- **Caution**—renal or hepatic dysfunction

■ Maternal Considerations

The incidence of both the AIDS syndrome and opportunistic infection has decreased dramatically over the last years because of advances in drug regimens. This is a rapidly changing area. Triple (e.g., **zidovudine, lamivudine, nevirapine**) or quadruple therapy remains the standard of care for the management of HIV infection in adults because of its high efficacy. **Nevirapine**-based HAART (compared mainly with **nelfinavir**-based HAART), western African origin, and lower baseline viral load are associated with shorter times to achieving viral suppression and is probably a regimen of choice. A single dose of **nevirapine** (200mg PO) given at the onset of labor dramatically reduces perinatal HIV transmission in women receiving no other antenatal antiretroviral therapy. It is more effective (in the absence of regular antiretroviral therapy) than an intrapartum and postpartum regimen of **zidovudine** if given to both women at the onset of labor and their newborns within 72h of birth. **Nevirapine** resistance does occur from this approach. However, a single dose of **tenofovir** and **emtricitabine** at delivery reduces resistance to NNRTIs at 6w postpartum by half; therefore, this treatment should be considered as an adjuvant to intrapartum **nevirapine.** Women who receive a single dose of **nevirapine** to prevent perinatal transmission of HIV-1 have higher rates of failure with subsequent **nevirapine**-based antiretroviral therapy than do women without previous exposure to **nevirapine** if the therapy is initiated within 6mo after the single peripartum dose. Maternal risk factors include a low CD_4 cell count and a high viral load at delivery. The addition of **nevirapine** during the labor of women receiving antiretroviral therapy during pregnancy does not further reduce perinatal HIV transmission if cesarean section is available. Cost and identification of women with HIV infection during pregnancy represent a significant problem in many developing countries. As a result, it has been proposed that, in high HIV prevalence areas, ''triple therapy'' be offered routinely to all pregnant women and their infants without prior HIV testing. The association between combination therapy that includes a protease inhibitor and an increased risk of very low birth weight requires confirmation. Hepatotoxicity usually does not manifest before 5mo of therapy.

The WHO takes an incremental approach, recommending countries adopt more effective antiretroviral regimens. The 2006 guidelines include triple-drug antiretroviral treatment for those women who are eligible. Those women who are not eligible for antiretroviral treatment should receive a combination prophylaxis antiretroviral regimen—preferably **zidovudine** from 28w of gestation; **zidovudine, lamivudine,** and a single dose of **nevirapine** during delivery; and **zidovudine** and **lamivudine** for 7d after delivery—to reduce the development of **nevirapine** resistance. Newborn infants should receive a single dose of **nevirapine** and 1-4w of **zidovudine,** depending on the duration of the regimen received by the mother.

Side effects include Stevens-Johnson syndrome, fever, hepatotoxicity, hepatitis, neutropenia, peripheral neuropathy, N/V, abdominal pain, diarrhea, rash, myalgias, headache, arthralgia, and stomatitis.

■ Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. The safety of many approved antiretroviral agents during pregnancy is not established. In contrast to other protease inhibitors, **nevirapine** rapidly crosses the human placenta, reaching an F:M ratio approximating unity. A single 2mg/kg dose administered to the newborn at 48-72h after birth achieves serum **nevirapine** concentrations 10× the *in vitro* 50% inhibitory

concentration against wild-type HIV-1 throughout the 1st week of life. This limited regimen is well-tolerated and reduces the risk of mother-to-child transmission by nearly 50% in women and infants receiving no other antiretrovirals. However, neonatal plasma concentrations decrease more rapidly after maternal **nevirapine** therapy during pregnancy, suggesting *in utero* liver enzyme induction. Infants born <2h after maternal **nevirapine** during labor should receive a dose immediately after birth in addition to the standard infant dose at 48-72h to ensure therapeutic levels.

Breastfeeding Safety

There are no adequate reports or well-controlled studies in nursing women. **Nevirapine** is excreted into human breast milk with an M:P ratio approximating 0.6. Breastfeeding is contraindicated in HIV-infected nursing women when formula is available to reduce the risk of neonatal transmission. However, breastfeeding is essential in some countries, and intrapartum/neonatal **nevirapine** lowers HIV-1 transmission risk in breastfeeding women compared to a short intrapartum/neonatal **zidovudine** regimen. **Nevirapine** is measurable for up to 2w after discontinuation; total **nevirapine** concentrations remain above the 90% inhibitory concentration for 6d, and no differences are observed between breasts. The absolute 8% reduction in transmission at 6-8w is sustained at age 18mo. This simple, inexpensive, well-tolerated regimen has the potential to significantly decrease HIV-1 perinatal transmission in less developed countries. Continued neonatal **nevirapine** prophylaxis appears well-tolerated and further reduces the rate of HIV transmission.

Drug Interactions

Metabolized in the liver by CYP3A4 and 2B6 and is a known inducer of these enzymes. Drugs metabolized by these enzyme systems may have lower than expected plasma levels when used with **nevirapine.**

The *in vitro* interaction between **nevirapine** and **warfarin** is complex. Anticoagulation levels should be monitored frequently.

Significantly decreases **clarithromycin;** however, concentrations of the 14-OH metabolite are increased. Because the overall activity is reduced, options such as **azithromycin** should be considered.

Decreases the concentration of **efavirenz.** Appropriate doses for this combination are not established.

Decreases the concentrations of **ethinyl estradiol/norethindrone.** Thus oral contraceptives and other hormonal methods of birth control should not be used as the sole method of contraception in women taking **nevirapine.** An alternative or additional method of contraception is recommended.

Increases the concentration of **nevirapine.** Patients should be monitored closely for **nevirapine**-associated adverse events when both drugs must be given together.

Decreases **indinavir** such that an increased dosage may be required.

Decreases **ketoconazole** concentrations and may reduce its efficacy.

Decreases **lopinavir** when given as the **lopinavir/ritonavir** combination. It is recommended to increase the dose of **lopinavir/ritonavir** to 533/133mg bid when given with **nevirapine.**

May decrease **methadone** levels, requiring increased dosages to prevent symptoms of opiate withdrawal.

Decreases the concentration of the **nelfinavir** M8 metabolite and the **nelfinavir** C_{min}. The appropriate dose for nelfinavir in combination with **nevirapine** has not been established.

Modestly increases the concentration of **rifabutin** and its metabolite. Some patients may experience large increases and may be at higher risk for **rifabutin** toxicity. Caution should be used.

Rifampin decreases the concentration of **nevirapine.** The combination should not be used because it may reduce the

efficacy of the drug. Physicians needing to treat patients co-infected with tuberculosis and using a **nevirapine**-containing regimen may use **rifabutin** instead.
Decreases the concentration of **saquinavir.** Appropriate doses for this combination are not established, but an increase in the dose of **saquinavir** may be required.
May decrease the concentrations of **amiodarone, carbamazepine, cisapride, clonazepam, cyclophosphamide, cyclosporine, diltiazem, disopyramide, ergotamine, ethosuximide, fentanyl, itraconazole, lidocaine, nifedipine, sirolimus, tacrolimus,** and **verapamil.**

References

Bennetto-Hood C, Aldrovandi GM, King JR, et al. Clin Infect Dis 2007; 45:391-4.
Brocklehurst P, Volmink J. Cochrane Database Syst Rev 2007; (1):CD003510.
Chi BH, Sinkala M, Mbewe F, et al. Lancet 2007; 370:1698-705.
Chung MH, Kiarie JN, Richardson BA, et al. Antivir Ther 2008; 13:799-807.
Cunningham CK, Chaix ML, Rekacewicz C, et al. J Infect Dis 2002; 186:181-8.
Dao H, Mofenson LM, Ekpini R, et al. Am J Obstet Gynecol 2007; 197(3 Suppl):S42-55.
Dorenbaum A, Cunningham CK, Gelber RD, et al. JAMA 2002; 288:189-98.
Edwards SG, Larbalestier N, Hay P, et al. HIV Med 2001; 2:89-91.
Eshleman SH, Jackson JB. AIDS Rev 2002; 4:59-63.
European Collaborative Study, Patel D, Cortina-Borja M, Thorne C, Newell ML. Clin Infect Dis 2007; 44:1647-56.
Hankins C. Reprod Health Matters 2000; 8:87-92.
Jackson JB, Musoke P, Fleming T, et al. Lancet 2003; 362:859-68.
Lockman S, Shapiro RL, Smeaton LM, et al. N Engl J Med 2007; 356:135-47.
McGowan JP, Shah SS. Curr Opin Obstet Gynecol 2000; 12:357-67.
Mirochnick M. Ann N Y Acad Sci 2000; 918:287-97.
Mirochnick M, Clarke DF, Dorenbaum A. Clin Pharmacokinet 2000; 39:281-93.
Mirochnick M, Dorenbaum A, Blanchard S, et al. J Acquir Immune Defic Syndr 2003; 33:153-6.
Mirochnick M, Siminski S, Fenton T, et al. Pediatr Infect Dis J 2001; 20:803-5.
Morris L, Pillay C, Gray G, McIntyre J. SADJ 2001; 56:614-6.
Pacifici GM. Early Hum Dev 2005; 81:647-54.
Podzamczer D, Fumero E. Expert Opin Pharmacother 2001; 2:2065-78.
Shetty AK, Coovadia HM, Mirochnick MM, et al. J Acquir Immune Defic Syndr 2003; 34:482-90.

Summary

Pregnancy Category: C
Lactation Category: NS

- **Nevirapine** given at the onset of labor and to newborns within 72h of birth is more effective than intrapartum and postpartum **zidovudine** for women who have not received the regular antiretroviral therapy during prenatal period.
- Its combined use with other antiretrovirals (e.g., HAART) is the preferred regimen for most HIV infected women during pregnancy.
- Physicians are encouraged to register pregnant women under the Antiretroviral Pregnancy Registry (1-800-258-4263) for a better follow-up of the outcome while under treatment with **nevirapine.**

Niacin—(Acido Nicotinico; Akotin; Niaspan; Nicolar; Niconacid; Nicotinic Acid; Nikacid; Nikotime; Novo-Niacin; Slo Niacin; Span Niacin; Vitaplex; Wampocap)

International Brand Name—Acido Nicotinico (Colombia); Akotin 250 (Argentina); Apo-Nicotinic Acid (New Zealand); Cardene (England, Ireland, Netherlands); Natinate (Thailand); Niaspan (England, Ireland); Nicangin (Sweden); Nicobid (Hong Kong); Nicotabs (Thailand); Nyclin (Japan, Taiwan); Pepevit (Mexico)

Drug Class ..... Antihyperlipidemics; Vitamins/minerals

Indications ..... Hypercholesterolemia, mixed dyslipidemia, hypertriglyceridemia, pellagra

Mechanism ..... Decreases hepatic LDL/VLDL production and triglyceride esterification, inhibits lipolysis, increases lipoprotein lipase activity

Dosage with Qualifiers .....

Hypercholesterolemia—begin 250mg PO qd, increase 250mg q4-7d based on effect/tolerance; max 6g/d
Mixed dyslipidemia—begin 500mg/d PO qhs ×4w, then 1g/d q4w; max 2g/d
Hypertriglyceridemia—begin 500mg/d PO qhs ×4w, then 1g/d q4w; max 2g/d
Pellagra—300-500mg PO qd; available SC

*NOTE: **aspirin** may reduce the flushing; LFTs at baseline, q6-12w ×1y, then q3-6mo; do not cut/crush/chew.*

- **Contraindications**—hypersensitivity to drug or class, bleeding, hypotension, active ulcer disease, severe hepatic dysfunction
- **Caution**—gout, mild hepatic dysfunction, diabetes mellitus, CAD, hypotension

Maternal Considerations .....

Niacin is a water-soluble B-complex vitamin with essential roles in lipid metabolism, tissue respiration, and glycogenolysis. The higher death rate from pellagra in women compared to men is attributed to an estrogen-mediated decrease in the formation of **niacin** from tryptophan. Pregnancy imposes a metabolic stress, which grows with advancing gestation. The recommended dose of niacinamide (a by-product of **niacin**) varies between 15 and 17mg/d, and it is usually found in prenatal vitamins. There are no adequate reports or well-controlled studies of **niacin** in pregnant women. Despite routine vitamin supplementation, a high percentage of vitamin A, B_6, B_{12}, **niacin**, and **thiamine** hypovitaminemia occurs during pregnancy. **Niacin** deficiency is particularly common during the 1st trimester and its prevalence increases subsequently. Combination deficits of **niacin**, **thiamine**, and vitamins A, B_6, and B_{12} occur in each trimester. There is no evidence that supplementation changes pregnancy outcome. **Niacin** deficiencies were once thought associated with preeclampsia and hyperemesis gravidarium, but these associations were not confirmed by well-designed studies.
Side effects include rhabdomyolysis, atrial fibrillation, cardiac arrhythmias, orthostatic hypotension, dyspepsia, vomiting, peptic ulceration, elevated LFTs, jaundice, diarrhea, flushing, dry skin, decreased glucose tolerance, gout, hyperuricemia, macular edema, amblyopia, and headache.

Fetal Considerations .....

There are no adequate reports or well-controlled studies in human fetuses. **Niacin** crosses the human placenta, though the

kinetics remain to be elucidated. Rodent teratogenicity studies have not been conducted.

Breastfeeding Safety

There are no adequate reports or well-controlled studies in nursing women. **Niacin** is excreted into human breast milk. It is not known whether supplementation increases both the milk and neonatal concentration. **Niacin** is generally considered compatible with breastfeeding.

Drug Interactions

May potentiate the effects of ganglionic blocking agents and vasoactive drugs, resulting in postural hypotension.
About 98% of available **niacin** is bound to **colestipol**, with 10-30% binding to **cholestyramine,** suggesting at least 4-6h elapse between the ingestion of bile acid–binding resins and use of **niacin.**
Ethanol or hot drinks may increase flushing and pruritus and should be avoided around the time of **niacin** ingestion. Vitamins or other nutritional supplements containing large doses of niacin or related compounds such as nicotinamide may potentiate the adverse effects of **niacin.**

References

Baker H, DeAngelis B, Holland B, et al. J Am Coll Nutr 2002; 21:33-7.
Deodhar AD, Rajalakshmi R, Ramakrishnan CV. Acta Paediatr Scand 1964; 53:42-8.
Hart BF, McConnell WT. Am J Obstet Gynecol 1943; 46:283-7.
Hobson W. J Hyg 1948; 46:198-216.

Summary

Pregnancy Category: C
Lactation Category: S
- **Niacin** is a component of most prenatal vitamins.
- Many pregnant women are deficient despite supplementation.

Nicardipine—(Cardene)

International Brand Name—Antagonil (Germany); Cardene (England, Ireland, Netherlands); Cardene SR (England, Netherlands); Cardepine (Philippines); Cardepine SR (Malaysia); Cardibloc (Singapore); Cardipene (Thailand); Convertal (Peru); Dacarel (Ecuador); Dagan (Spain); Flusemide (Spain); Karden (Austria); Lincil (Costa Rica, Dominican Republic, El Salvador, Guatemala, Honduras, Nicaragua, Panama, Spain); Loxen (France, Indonesia); Nicardal (Italy); Nicodel (Japan); Nimicor (Italy); Perdipina (Italy); Perdipine (China, Japan, Korea, Taiwan); Perdipine LA (China, Japan); Ranvil (Italy); Ridene (Mexico); Rycarden (Denmark, Sweden); Rydene (Belgium); Saf Card (Indonesia); Vasodin (Thailand)

Drug Class

Antiarrhythmics; Antihypertensives; Calcium channel blockers

Indications

Hypertension, angina

Mechanism

Inhibits calcium influx into vascular smooth muscle and myocardium

Dosage with Qualifiers

Hypertension—20-40mg PO tid; max 40mg PO tid
Angina—begin 20mg PO tid; max 40mg PO tid
Acute hypertension—5mg/h, increase 2.5mg/h q5-15min prn, titrate down to effect

NOTE: hepatic dosing.

- **Contraindications**—hypersensitivity to drug or class, aortic stenosis
- **Caution**—renal or hepatic dysfunction, CHF, cardiac conduction disease

■ Maternal Considerations

Hypertension during pregnancy: Hypertension remains a significant cause of maternal and fetal morbidity and death. Severe hypertension during pregnancy (BP >170/110mmHg) should be treated immediately to improve both maternal and fetal outcome. An uncontrolled reduction in BP may lead to coma, stroke, MI, acute renal failure, and death. Pregnancy further complicates the treatment of an acute hypertensive episode because an acute decrease in BP might adversely affect the fetus. Thus, the goal is not just to decrease BP, but to do so with minimal adverse effects while preserving organ function. Randomized trials reveal that **nicardipine** is safe and effective for the treatment of severe hypertension during pregnancy. It is more efficient than **metoprolol** and similar to **labetalol.** Although the definitive treatment for severe preeclampsia remains delivery, some practitioners attempt to temporize in hopes of reducing the complications of prematurity. Preliminary study indicates that long-term treatment with **nicardipine** for severe preeclampsia is effective and safe. **Nicardipine** has also been used during pregnancy to treat hypertension due to pheochromocytoma and autonomic hyperreflexia.

Preterm labor: **Nicardipine** abolishes *in vitro* contractility of the smooth muscle strips. It causes a modest decline in systolic (9mmHg) and diastolic (7mmHg) pressures in normotensive patients as peripheral resistance falls. The reflex increase in HR is usually small, but may occasionally be pronounced. One prospective clinical trial concluded that **nicardipine** is an effective, safe, and well-tolerated tocolytic agent. It arrests preterm labor more rapidly than **magnesium sulfate,** and women treated with **nicardipine** have fewer adverse medication effects and episodes of recurrent preterm labor compared to those treated with **magnesium sulfate.** Treatment-related maternal hypotension was not associated with fetal distress. In another trial, **nicardipine** led to a greater percentage of women delivering more than 7d after diagnosis compared to **salbutamol,** and there were fewer maternal side effects. **Nicardipine** seems especially attractive in women with hypertension, diabetes mellitus, or maternal cardiomyopathy. A relationship between oral **erythromycin** and sudden cardiac death was reported in patients also receiving strong inhibitors of CYP3A such as nitroimidazole antifungal agents, **diltiazem, verapamil,** and **troleandomycin;** each doubles, at least, the AUC for a CYP3A substrate. The potential implication for obstetrics is real with the growing use of **nicardipine** as a tocolytic agent in women who may also be treated with antibiotics for PPROM. Though not included in the referenced study, **nicardipine** is also a substrate for CYP3A, suggesting the likelihood for some interaction is high.

See **Nifedipine.**

Side effects include edema, flushing, asthenia, malaise, N/V, dyspnea, palpitations, tachycardia, dizziness, dry mouth, constipation, nervousness, nocturia, ECG abnormalities, and orthostatic hypotension.

■ Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. In one study of 10 preeclamptic women, **nicardipine** was measured in maternal and umbilical cord blood. There was a median F:M ratio of 0.15 (umbilical artery) and 0.17 (umbilical vein). The highest cord concentration after maternal dosage of 4.5mg/h was a subtherapeutic 18ng/ml. Thus, adverse fetal reactions are unlikely due to a direct **nicardipine** effect. Consistent with these observations, transfer across the nonhuman primate placenta is poor, and there is no effect on fetal CV parameters after maternal administration. **Nicardipine** may have

some beneficial effect on fetoplacental blood flow resistances in animals and humans. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically. Embryotoxicity occurred at doses 50× the MRHD.

Breastfeeding Safety

Nicardipine levels were determined in 34 breast milk samples from 7 preeclamptic women receiving IV **nicardipine.** **Nicardipine** was undetectable in 82% of samples. In 6 samples from 4 women with doses ranging from 1 to 6.5mg/h, milk **nicardipine** ranged from 5.1 to 18.5ng/ml. The maximum possible exposure of a neonate to **nicardipine** was calculated to be less than 300ng/d, which is an insignificant fraction of the therapeutic dose used in neonates.

Drug Interactions

Cimetidine increases **nicardipine** plasma levels. Patients receiving the two drugs concomitantly should be carefully monitored.
Some calcium blockers increase the concentration of digitalis.
Severe hypotension has been reported during **fentanyl** anesthesia with concomitant use of a β-blocker and a calcium channel blocker. Even though such interactions were not seen during clinical studies with **nicardipine,** an increased volume of circulating fluids might be required if such an interaction were to occur.
Increases **cyclosporine** levels. Plasma **cyclosporine** should be closely monitored, and its dose reduced as necessary.

References

Bartels PA, Hanff LM, Mathot RA, et al. BJOG 2007; 114:230-3.
Carbonne B, Jannet D, Touboul C, et al. Obstet Gynecol 1993; 81:908-14.
Csapo AI, Puri CP, Tarro S, et al. Am J Obstet Gynecol 1982; 142:483-91.
Ducsay CA, Thompson JS, Wu AT, Novy MJ. Am J Obstet Gynecol 1987; 157:1482-6.
Economy KE, Abuhamad AZ. Semin Perinatol 2001; 25:264-71.
Elatrous S, Nouira S, Ouanes Besbes L, et al. Intensive Care Med 2002; 28:1281-6.
Hanff LM, Vulto AG, Bartels PA, et al. J Hypertens 2005; 23:2319-26.
Ichihara J, Izumi H, Koyama Y, et al. Nippon Sanka Fujinka Gakkai Zasshi 1991; 43:1249-54.
Jannet D, Abankwa A, Guyard B, et al. Eur J Obstet Gynecol Reprod Biol 1997; 73:11-6.
Jannet D, Carbonne B, Sebban E, Milliez J. Obstet Gynecol 1994; 84:354-9.
Kasai Y, Tsutsumi O, Taketani Y, et al. J Physiol 1995; 486:373-84.
Larmon JE, Ross BS, May WL, et al. Am J Obstet Gynecol 1999; 181:1432-7.
Marin J, Reviriego J. Arch Int Pharmacodyn Ther 1989; 302:209-19.
Ray WA, Murray KT, Meredith S, et al. N Engl J Med 2004; 351:1089-96.
Seki H, Takeda S, Kinoshita K. Int J Gynaecol Obstet 2002; 76:135-41.

Summary

Pregnancy Category: C
Lactation Category: S

- Calcium channel blockers have excellent safety profiles and a high degree of efficacy for the treatment of acute and chronic hypertension.

- Calcium channel blockers are considered the agents of choice for tocolysis.
- There is more experience with **nifedipine** than **nicardipine** for tocolysis.
- Oral **erythromycin** should probably be avoided in women receiving a calcium channel blocker as a tocolytic agent. **Ampicillin** plus **sulbactam** would be preferred.

Nicotine—(Habitrol; NicoDerm; Nicotrol; ProStep; Quit Spray; Stubit)

International Brand Name—Nicabate (Australia); Nicabate CQ Clear (Australia); Nicabate CQ Lozenges (Australia); Nicabate TTS (New Zealand); Nicobate CQ Clear (Australia); Nicoderm (Canada); Nicolan (Denmark, Mexico); Nicolan Light (Denmark); Nicopass sans sucre menthe fraicheur (France); Nicopass sans sucre reghasse menthe (France); Nicopatch (France); Nicorest (France); Nicorette (Brazil, Bulgaria, Canada, Chile, China, Colombia, Czech Republic, England, Hong Kong, Ireland, Japan, Korea, Malaysia, Mexico, New Zealand, Portugal, Slovenia, Taiwan, Thailand, Turkey, Venezuela); Nicorette Fruit (France); Nicorette Inhaler (Australia); Nicorette Menthe (France); Nicorette Orange (France); Nicorette Orange sans sucre (France); Nicostop (Korea, Portugal); Nicotinell (Australia, Austria, Belgium, Denmark, England, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Netherlands, Norway, Portugal, Sweden, Switzerland); Nicotinell Chewing Gum (Hong Kong, Singapore); Nicotinell Fruit sans sucre (France); Nicotinell Lozenge (Hong Kong); Nicotinell Menthe sans sucre (France); Nicotinell Mint Lozenge (Singapore); Nicotinell TTS (France, Hong Kong, Malaysia, Mexico, New Zealand, Puerto Rico, South Africa, Taiwan, Thailand); Nicotrans (Italy); Nicotrol Gum (New Zealand); Nikofrenon (Germany); Niquitin (Brazil, France, Mexico); Niquitinclear (France); Niquitin CQ (Israel); Niquitin sans sucre (France); Quit Spray (South Africa)

Drug Class	CNS stimulants
Indications	Smoking cessation
Mechanism	Stimulates nicotinic-cholinergic receptors localized in various CNS and peripheral sites
Dosage with Qualifiers	Smoking cessation—begin 21mg/d transdermal patches ×6w, then 14mg/d ×2w, then 7mg/d ×2w; alternatively, 14mg/d ×6w if <100 lb, <1/2ppd, or signs of cardiac disease *NOTE: available in patches that release 7, 14, or 21mg/d.* • **Contraindications**—hypersensitivity to drug or class, nonsmokers, recent history of acute MI, arrhythmia, angina, allergy to menthol, Buerger's disease, Prinzmetal's variant angina, Raynaud's phenomenon, hyperthyroidism, pheochromocytoma, IDDM • **Caution**—CAD, peptic ulcer disease
Maternal Considerations	Cigarette smoking is directly linked to an array of health care problems whose costs to society are staggering. Active and passive maternal smoking has damaging effects in each trimester. Cigarette smoke contains numerous toxins that exert a direct effect on placental and fetal cell proliferation and differentiation. It is the single largest modifiable risk for pregnancy-related morbidity and death in the US. Cigarette smoking increases the rate of subfertility and failed IVF. Addiction to **nicotine** is a primary contributor to tobacco use. **Nicotine** replacement facilitates cessation by relieving the physiologic symptoms of withdrawal. **Nicotine** delivery systems include gum, patch, nasal spray, and vapor inhaler. Because **nicotine** medications do not deliver the toxins and carcinogens delivered by cigarettes, they are considered safer than smoking if used as directed. Women should be advised to stop smoking completely during pregnancy, and that

a simple reduction in the number of cigarettes smoked, or switching to so-called low-tar or low-**nicotine** concentration cigarettes will not significantly reduce the perinatal risks. **Nicotine** patch therapy may help some pregnant smokers, but the success rate during pregnancy is low. Despite the failure of large numbers of treated women to quit, the average birth weight is increased by therapy. The success rate may be enhanced by the addition of an SSRI and formal counseling. Preliminary study suggests women who cannot quit smoking after the 1st trimester metabolize **nicotine** more rapidly than those who can. Thus, the optimal response may be to raise the support level during pregnancy, not lower it. Social support systems can enhance the likelihood of long-term success in women who do quit smoking during pregnancy. The initial dose of **nicotine** during replacement therapy should approximate the dose of **nicotine** being consumed. Intermittent-use formulations of NRT (gum, spray, inhaler) are preferred as the total dose of **nicotine** delivered to the fetus is less than with continuous-use formulations (transdermal patch). ***Side effects*** include ventricular arrhythmia, atrial fibrillation, MI, vasculitis, dependence, local erythema, local pruritus, N/V, diarrhea, insomnia, headache, nervousness, abnormal dreams, dizziness, and rash.

Fetal Considerations

Cigarette smoke contains thousands of chemicals, many of which are well-documented reproductive toxins (e.g., **nicotine,** carbon monoxide, lead). **Nicotine** rapidly crosses the placenta, and the fetuses of mothers who smoke are exposed to higher concentrations than their mothers. Smoking during pregnancy is a major risk factor for spontaneous abortion, preterm placental abruption, IUGR, late fetal death, neonatal polycythemia, and SIDS. The increased miscarriage rate among mothers who smoke may be related to direct adverse effects of **nicotine,** cadmium, or the polyaromatic hydrocarbons on trophoblast invasion and proliferation. The mean reduction in birth weight in infants of smokers is 200g. Recent study indicates a greater prevalence of facial clefts in the offspring of smokers. Longitudinal studies in humans suggest that prenatal exposure to **nicotine** increases the risks for cognitive deficits, ADHD, conduct disorder, criminality in adulthood, and a predisposition of the offspring to abuse tobacco and alcohol. Sheep and human studies reveal that prenatal **nicotine** blunts elements of the fetal cardiorespiratory defense for hypoxia (HR, ventilatory and arousal responses), and has long-term effects on the postnatal breathing pattern. The newborn unable to maximize cardiac output during times of stress is at increased risk for morbidity and possible death. Acute exposure to **nicotine** significantly decreases fetal heart reactivity. Median **epinephrine** and NE concentrations in the umbilical cord are significantly lower in smokers compared with nonsmokers. The significance of this finding is unclear, but could reflect depletion. The finding of increased connective tissue expression in pulmonary vessels of fetal monkeys whose mothers were treated with **nicotine** suggests **nicotine** is transported across the placenta and directly interacts with nicotinic ACH receptors in pulmonary vessels to alter connective tissue expression and produce vascular structural alterations. Rodent studies show that **nicotine** exposure compromises neuronal maturation, leading to long-lasting structural alterations in key brain regions involved with cognition, learning, and memory. Human neonatal **nicotine** withdrawal does occur.

Breastfeeding Safety

Nicotine is excreted in human milk at low concentrations. Milk cotinine (a by-product of **nicotine**) levels do not correlate with

the number of cigarettes smoked. Newborns breastfed by smoking women are exposed not only to environmental (''passive'') smoke, but also by ingesting **nicotine** metabolites and toxic by-products present in the milk. Maternal smoking cessation with the nicotine patch is a safer option than continued smoking. In one study of 15 women, the milk **nicotine** and cotinine concentrations were no different between smoking (mean of 17 cigarettes/d) and the 21mg/d patch, but concentrations were lower when patients were using the 14mg/d and 7mg/d patches. There was also a downward trend in absolute infant dose (nicotine equivalents) from smoking or the 21mg patch through to the 14mg and 7mg patches. Infant milk intake was similar regardless of whether their mothers were smoking or subsequently using the 21mg, 14mg, and 7mg patches.

Drug Interactions

Because of the de-induction of hepatic enzymes after smoking cessation, the following drugs may require a decrease in dosage: **acetaminophen, caffeine, imipramine, oxazepam, pentazocine, propranolol,** or other β-blockers, and **theophylline**.
The extent of absorption and peak plasma concentration is slightly reduced in patients with the common cold/rhinitis. In addition, the T_{max} is prolonged. The use of a nasal vasoconstrictor such as xylometazoline in patients with rhinitis will further prolong the time to peak.
Circulating catecholamines decline after smoking cessation. As a result, the dose of adrenergic agonists (e.g., **isoproterenol**, **phenylephrine**) may need to increase.

References

al-Alawi E, Jenkins D. Ir Med J 2000; 93:175-6.
Anderson HA, Wolff MS. J Expo Anal Environ Epidemiol 2000; 10:755-60.
Dempsey DA, Benowitz NL. Drug Saf 2001; 24:277-322.
Dempsey D, Jacob P 3rd, Benowitz NL. J Pharmacol Exp Ther 2002; 301:594-8.
Fant RV, Owen LL, Henningfield JE. Prim Care 1999; 26:633-52.
Hafstrom O, Milerad J, Sundell HW. Am J Respir Crit Care Med 2002; 166:92-7.
Hafstrom O, Milerad J, Sundell HW. Am J Respir Crit Care Med 2002; 166:1544-9.
Haustein KO. Int J Clin Pharmacol Ther 1999; 37:417-27.
Hellstrom-Lindahl E, Nordberg A. Respiration 2002; 69:289-93.
Ilett KF, Hale TW, Page-Sharp M, et al. Clin Pharmacol Ther 2003; 74:516-24.
Klesges LM, Johnson KC, Ward KD, Barnard M. Obstet Gynecol Clin North Am 2001; 28:269-82.
Koren G. Can Fam Physician 2001; 47:1971-2.
Mitchell EA, Thompson JM, Robinson E, et al. Acta Paediatr 2002; 91:323-8.
Narayanan U, Birru S, Vaglenova J, Breese CR. Neuroreport 2002; 13:961-3.
Nattie E, Kinney H. Am J Respir Crit Care Med 2002; 166:1530-1.
Oncken CA, Henry KM, Campbell WA, et al. Pediatr Res 2003; 53:119-24.
Oncken C, Kranzler H, O'Malley P, et al. Obstet Gynecol 2002; 99:751-5.
Oncken CA, Pbert L, Ockene JK, et al. Obstet Gynecol 2000; 96:261-5.
Paszkowski T, Wojewoda K. Ginekol Pol 2001; 72:945-9.
Roy TS, Seidler FJ, Slotkin TA. J Pharmacol Exp Ther 2002; 300:124-33.
Schroeder DR, Ogburn PL Jr, Hurt RD, et al. J Matern Fetal Neonatal Med 2002; 11:100-7.

Sekhon HS, Proskocil BJ, Clark JA, Spindel ER. Eur Respir J 2004; 23:906-15.
Vagnarelli F, Amarri S, Scaravelli G, et al. Ther Drug Monit 2006; 28:585-8.
Weitzman M, Byrd RS, Aligne CA, Moss M. Neurotoxicol Teratol 2002; 24:397-406.
Wisborg K, Henriksen TB, Jespersen LB, et al. Obstet Gynecol 2000; 96:967-71.

Summary

Pregnancy Category: D
Lactation Category: S

- All pregnant women should be advised to stop smoking completely during pregnancy.
- Pregnant smokers unable to stop smoking without medical treatment can be offered NRT.
- The exposed pregnant woman subjects herself and her pregnancy to risks including IUGR and increased perinatal mortality.
- Prenatal **nicotine** exposure is associated with higher rates of behavior problems (increased activity, decreased attention) diminished intellectual abilities, and school failure.

Nifedipine—(Adalat; Adalat CC; Alonix; Corinfar; Ecodipin-E; Procardia; Procardia XL)

International Brand Name—Adalat (Argentina, Austria, Belgium, Brazil, Bulgaria, Chile, Czech Republic, Denmark, England, Finland, Germany, Greece, Hong Kong, Hungary, Indonesia, Israel, Italy, Japan, Korea, Malaysia, Mexico, Netherlands, Norway, Peru, Philippines, Poland, Portugal, Spain, Sweden, Switzerland, Thailand, Uruguay, Venezuela); Adalat 5 (Australia); Adalat 10 (Australia); Adalat 20 (Australia); Adalat CR (Bulgaria, Greece, Japan, Switzerland, Thailand); Adalat Crono (Italy); Adalate (France); Adalat FT (Canada); Adalat GITS (Hong Kong); Adalat GITS 30 (Philippines); Adalat L (Japan); Adalat LA (England, Malaysia); Adalat LP (France); Adalat Oros (Brazil, Chile, Colombia, Costa Rica, Denmark, Dominican Republic, Ecuador, El Salvador, Finland, Guatemala, Honduras, Indonesia, Korea, Mexico, Netherlands, Nicaragua, Norway, Panama, Paraguay, Spain, Sweden, Taiwan, Uruguay, Venezuela); Adalat P.A. (Canada); Adalat Retard (Austria, Brazil, Chile, Costa Rica, Czech Republic, Dominican Republic, El Salvador, England, Germany, Greece, Guatemala, Honduras, Hong Kong, Indonesia, Malaysia, Mexico, Netherlands, New Zealand, Nicaragua, Panama, Paraguay, Peru, Philippines, Poland, Spain, Thailand); Adefin XL (Australia); Adipine XL (England); Alat (Taiwan); Alonix-S (Taiwan); Alpha-Nifedipine Retard (New Zealand); Angipec (Peru); Antiblut (Peru); Apo-Nifed (Canada); Aprical (Germany); Atanaal Softcap (Taiwan); Calcheck (Philippines); Calcibloc (Philippines); Calcibloc OD (Philippines); Calcigard (India, Thailand); Calcigard Retard (China); Calcilat (England); Calgina (Philippines); Cardifen (South Africa); Cardilat (South Africa); Cardionorm (Philippines); Chronadalate LP (France); Cipilat (South Africa); Citilat (Italy); Coracten (England, Germany, Hong Kong); Coral (Italy); Cordalat (Indonesia); Cordipen (Singapore); Cordipin (Slovenia); Coronpin (Indonesia); Corotrend (Germany, Israel); Denkifed (Philippines); Depin (India); Dignokonstant (Germany); Dilafed (Mexico); Dilcor (Spain); Dipinkor (Indonesia); Duranifin (Germany); Ecodipin (China, Switzerland); Fedcor (Philippines); Fedipin (Indonesia); Fedipine 24 CR (Korea); Fenamon (Hong Kong, Malaysia, Singapore, Taiwan, Thailand); Fenamon SR (Thailand); Glopir (Greece); Hadipine S.R. (Korea); Hexadilat (Denmark); Jutadilat (Germany); Kemolat (Indonesia); Megalat (Israel); Myogard (India); Nadipine (Korea); Nedipin (Taiwan); Nelapine (Philippines); Nelapine Retard (Philippines); Nifangin (Finland); Nifar (South Africa); Nifdemin (Finland); Nifebene (Austria); Nifecard (Australia, Austria, Hong Kong); Nifecor (Germany); Nifedepat (Germany); Nifedicor (Italy); Nifedilat (South Africa); Nifedin (Italy); Nifedine (India); Nifedin SC (Korea); Nifedipres (Mexico); Nifedirex LP (France); Nifehexal (Australia); Nifelat (Argentina, Thailand); Nifelat-Q (Thailand); Nifensar (Peru); Nifensar Retard (Peru); Nifestad (Philippines); Nificard (Thailand); Nifidine (South Africa); Nipin (Singapore); Nipine (Korea); Normadil (Philippines); Novo Nifedin (Canada); Nyefax Retard (New Zealand); Nypine (Australia); Odipin (Philippines); Orix (Greece); Osmo-Adalat (Israel); Pidilat (Germany); Sepamit (Japan); Tibricol (Argentina); Unidipine XL (China); Vascard (South Africa); Vasdalat (Indonesia, Singapore); Vasdalat Retard (Indonesia); Zenusin (Costa Rica, Dominican Republic, Ecuador, El Salvador, Guatemala, Honduras, Malaysia, Nicaragua, Panama, South Africa)

Drug Class ..... Antiarrhythmics; Antihypertensives; Calcium channel blockers

Indications ..... Hypertension, angina

Mechanism

Inhibits Ca^{2+} influx into vascular smooth muscle and myocardium

Dosage with Qualifiers

Hypertension—begin 10mg PO tid, titer to effect; max 180mg/d
Angina, Prinzmetal's—begin 10mg PO tid, titer to effect; max 180mg/d
Angina, variant—begin 10mg PO tid, titer to effect; max 180mg/d

- **Contraindications**—hypersensitivity to drug or class
- **Caution**—CHF

Maternal Considerations

Hypertension during pregnancy: Hypertension remains a significant cause of maternal and fetal morbidity and death. Severe hypertension during pregnancy (BP >170/110mmHg) should be treated immediately to improve both maternal and fetal outcome. An uncontrolled reduction in BP may lead to coma, stroke, MI, acute renal failure, and death. Treatment of an acute hypertensive episode during pregnancy further complicates the process because an acute decrease in BP might adversely affect the fetus. Thus, the goal is not just to decrease BP, but to do so with minimal adverse effects while preserving organ function. **Nifedipine** is proven safe and effective. The antihypertensive effect of **nifedipine** does not correlate with the serum concentration. Given PO or SL, **nifedipine** (8-10mg ×1) has a longer duration of action and is more effective than either IV **hydralazine** (5-10mg ×1) or IV **labetolol** (20mg ×1). In randomized trials, **nifedipine** *retard* was as effective as the rapidly acting formuation, though women given the *retard* form required a 2nd dose more frequently. One approach is to observe the patient 24h to learn the proper timing of **nifedipine.** This is based on the observation that hypertension is more pronounced at night in women with preeclampsia compared to chronic hypertension. Maternal cerebral blood flow is influenced by antihypertensive treatment. A reduction in middle cerebral artery flow velocities after **nifedipine** and **methyldopa** confirms that cerebral vasospasm occurs in preeclamptic women. In contrast to the middle cerebral artery, there is no change in uteroplacental Doppler-determined resistances in severe preeclamptic women treated with **nifedipine.**
Preterm labor: No tocolytic agent actually stops preterm labor or alone improves perinatal outcome. Tocolysis changes perinatal outcome by allowing time for corticosteroid administration. When compared to placebo and any other tocolytic agent, calcium channel blockers and specifically **nifedipine** reduce the number of women giving birth within 48h or 7d of diagnosis. The doses used ranged widely from 30 to 240mg/d until contractions stop; 40mg PO q4-6h seem the typical starting dose. Like all other tocolytic agents, maintenance use offers no added benefit. The frequency of drug discontinuation for adverse effects is also dramatically reduced for **nifedipine** compared to all other tocolytic agents. In steady state, the mean **nifedipine** plasma concentration to achieve tocolysis is about the half of that measured after initial tocolysis. The use of **nifedipine** with **magnesium sulfate** is potentially dangerous; the combination is more frequently associated with severe hypotension, neuromuscular blockade, and cardiac depression. Similar to all other agents, maintenance therapy with oral **nifedipine** after the successful treatment of presumed preterm labor does not alter the timing of delivery. Several case reports note the occurrence of acute MI during the use of **nifedipine** for tocolysis. A short interval between cessation of β-mimetic therapy and the start of **nifedipine** may have had a role. Recently, a relationship

between oral **erythromycin** and sudden cardiac death was reported in patients also receiving strong inhibitors of CYP3A such as nitroimidazole antifungal agents, **diltiazem, verapamil,** and **troleandomycin;** each doubles, at least, the AUC for a CYP3A substrate. The potential implication for obstetrics is real with the growing use of **nifedipine** as a tocolytic agent in women who may also be treated with antibiotics for PPROM. Though not included in the referenced study, **nifedipine** is also a substrate for CYP3A, suggesting the likelihood for some interaction is high.

Pulmonary hypertension: The treatment of pulmonary hypertension during pregnancy remains controversial in part because of its rarity and complexity. Some authors consider PO **nifedipine** and IV **prostacyclin,** guided by right pulmonary artery catheterization and Doppler measurements of cardiac output, effective.

Side effects include flushing, CHF, pulmonary edema, dyspnea, MI, headache, N/V, dizziness, peripheral edema, nervousness, weakness, wheezing, nasal congestion, pruritus, and muscle cramps.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. **Nifedipine** crosses the human placenta, achieving an F:M ratio approximating 0.75. Newborns exposed to **nifedipine** have lower NICU admission rates and lower incidences of RDS, intracranial bleeding, and neonatal jaundice. Part of the benefit, but not all, appears to be prolongation of pregnancy. Placental and fetal cerebral arterial blood flow, fetal systolic and diastolic cardiac function, and the downstream distribution of fetal cardiac output are unaffected by **nifedipine** loading. However, a beneficial effect of **nifedipine** on placental blood flow cannot be excluded. In one study that tested fetuses before and after 48h of **nifedipine** tocolysis, there was a decline in uterine artery and fetal middle cerebral artery Doppler indices 24h after the first dose. Fetal cardiac diastolic function was unaffected and the significant redistribution observed after 24h is likely attributable to altered cerebral blood flow. **Nifedipine** is teratogenic and embryotoxic in rodents, increasing the prevalence of skeletal abnormalities, cleft palate, and IUGR. Its use in subhuman primates is associated with small placentas. In the ewe, **nifedipine** is associated with a fetal acidemia despite little change in uteroplacental blood flows.

Breastfeeding Safety

Nifedipine is excreted into human breast milk, achieving an M:P ratio approximating 0.3. It is unlikely the nursing newborn would ingest a clinically relevant amount.

Drug Interactions

Use with β-blocking agents is usually well tolerated, but there are occasional reports the combination increases the likelihood of CHF, severe hypotension, or exacerbation of angina.

There are isolated reports of elevated **digoxin** levels, suggesting a possible interaction between **digoxin** and **nifedipine.** Use of XR **nifedipine** increased **digoxin** levels in 9 of 12 patients an average of 45%. Thus, it is recommended that **digoxin** levels be monitored closely when initiating, adjusting, and discontinuing **nifedipine.**

There are rare reports of decreased **quinidine.**

There are reports of increased PTs in patients taking coumarin.

In healthy volunteers, **cimetidine** (1000mg/d for 1w) was associated with increased **nifedipine** peak levels (80%) and AUC (74%). The effect is probably mediated by the known inhibition of hepatic CYP3A4 by **cimetidine.**

Grapefruit juice resulted in a 2-fold increase in **nifedipine** AUC and C_{max} with no change in t/2 most likely due to inhibition of

CYP3A4-related first-pass metabolism. Use of **nifedipine** with grapefruit juice is to be avoided.

References

Aali BS, Nejad SS. Acta Obstet Gynecol Scand 2002; 81:25-30.
Benedetto C, Zonca M, Giarola M, et al. Br J Obstet Gynaecol 1997; 104:682-8.
Belfort MA, Saade GR, Suresh M, et al. Am J Obstet Gynecol 1995; 172:1395-403.
Blea CW, Barnard JM, Magness RR, et al. Am J Obstet Gynecol 1997; 176:922-30.
Borghi C, Esposti DD, Cassani A, et al. J Hypertens 2002; 20(Suppl 2):S52-6.
Brown MA, Buddle ML, Farrell T, et al. Am J Obstet Gynecol 2002; 187:1046-50.
Carr DB, Clark AL, Kernek K, Spinnato JA. Am J Obstet Gynecol 1999; 181:822-7.
Danielsson BR, Danielson M, Reiland S. Teratology 1990; 41:185-93.
Easterling TR, Ralph DD, Schmucker BC. Obstet Gynecol 1999; 93:494-8.
Fried G, Liu YA. Acta Physiol Scand 1994; 151:477-84.
Guclu S, Gol M, Saygili U, et al. Ultrasound Obstet Gynecol 2006; 27:403-8.
Guclu S, Saygili U, Dogan E, et al. Ultrasound Obstet Gynecol 2004; 24:761-5.
Haghighi L. Int J Gynaecol Obstet 1999; 66:297-8.
Khedun SM, Maharaj B, Moodley J. Paediatr Drugs 2000; 2:419-36.
King JF, Flenady VJ, Papatsonis DN, et al. Cochrane Database Syst Rev 2003; (1):CD002255.
Kiss H, Egarter C, Asseryanis E, et al. Am J Obstet Gynecol 1995; 172:1052-4.
Kook H, Yoon YD, Baik YH. J Korean Med Sci 1996; 11:250-7.
Kwawukume EY, Ghosh TS. Int J Gynaecol Obstet 1995; 49:265-9.
Lyell DJ, Pullen KM, Mannan J, et al. Obstet Gynecol 2008; 112:1221-6.
Magann EF, Bass JD, Chauhan SP, et al. J Soc Gynecol Investig 1994; 1:210-4.
Manninen AK, Juhakoski A. Int J Clin Pharmacol Res 1991; 11:231-6.
Norman JE, Ward LM, Martin W, et al. J Reprod Fertil 1997; 110:249-54.
Oei SG, Oei SK, Brolmann HA. N Engl J Med 1999; 340:154.
Oei SG, Mol BW, de Kleine MJ, Brolmann HA. Acta Obstet Gynecol Scand 1999; 78:783-8.
Papatsonis DN, Bos JM, van Geijn HP, et al. Am J Ther 2007; 14:346-50.
Papatsonis DN, Kok JH, van Geijn HP, et al. Obstet Gynecol 2000; 95:477-81.
Ray WA, Murray KT, Meredith S, et al. N Engl J Med 2004; 351:1089-96.
Saade GR, Taskin O, Belfort MA, et al. Obstet Gynecol 1994; 84:374-8.
Scardo JA, Vermillion ST, Newman RB, et al. Am J Obstet Gynecol 1999; 181:862-6.
Serra-Serra V, Kyle PM, Chandran R, et al. Br J Obstet Gynaecol 1997; 104:532-7.
Sullivan CA, Morrison JC. Obstet Gynecol Clin North Am 1995; 22:197-214.
Tsatsaris V, Carbonne B. J Gynecol Obstet Biol Reprod 2001; 30:246-51.
Tsatsaris V, Papatsonis D, Goffinet F, et al. Obstet Gynecol 2001; 97:840-7.

Visser W, Wallenburg HC. J Hypertens 1995; 13:791-5.
Yoshida T, Kanamori S, Hasegawa Y. Toxicol Lett 1988; 40:127-32.

Summary

Pregnancy Category: C
Lactation Category: S (likely)

- **Nifedipine** is safe and effective in controlling BP in women with severe preeclampsia.
- Current evidence supports the conclusion that calcium channel blockers, and **nifedipine** specifically, are the most effective tocolytic agents with the highest maternal/fetal safety profile.
- **Nifedipine** should be considered a first-line tocolytic agent.
- Oral **erythromycin** should probably be avoided in women receiving a calcium channel blocker as a tocolytic agent. **Ampicillin** plus **sulbactam** would be preferred.

Nimodipine—(Nimotop)

International Brand Name—Admon (Spain); Eugerial (Argentina, Brazil, Colombia, Peru); Grifonimod (Peru); Irrigor (Peru); Kenzolol (Mexico); Nidip (Colombia); Nimodilat (Argentina); Nimotop (Austria, Belgium, Brazil, Bulgaria, Canada, Chile, China, Colombia, Czech Republic, Denmark, Ecuador, England, Finland, France, Germany, Greece, Hong Kong, Hungary, Indonesia, Ireland, Israel, Italy, Japan, Korea, Malaysia, Mexico, Netherlands, Norway, Paraguay, Peru, Philippines, Poland, Portugal, South Africa, Spain, Sweden, Switzerland, Taiwan, Thailand, Uruguay, Venezuela); Nisom (Colombia); Periplum (Italy); Tropocer (Colombia, Costa Rica, Dominican Republic, El Salvador, Guatemala, Honduras, Nicaragua, Panama); Vasoflex (Chile); Vasotop (India)

Drug Class

Calcium channel blockers

Indications

Subarachnoid hemorrhage with vasospasm

Mechanism

Inhibits Ca^{2+} influx into vascular smooth muscle and myocardium

Dosage with Qualifiers

Subarachnoid hemorrhage—begin 60mg PO q4h within 96h of hemorrhage ×21d

NOTE: hepatic dosing.

- **Contraindications**—hypersensitivity to drug or class
- **Caution**—hepatic dysfunction

Maternal Considerations

Nimodipine is a calcium channel blocker with selective cerebrovascular effect.
Hypertension during pregnancy: Hypertension remains a significant cause of maternal and fetal morbidity and death. Severe hypertension during pregnancy (BP >170/110mmHg) should be treated immediately to improve both maternal and fetal outcome. An uncontrolled reduction in BP may lead to coma, stroke, MI, acute renal failure, and death. Pregnancy further complicates the treatment of an acute hypertensive episode since an acute decrease in BP might adversely affect the fetus. Thus, the goal is not just to decrease BP, but to do so with minimal adverse effects while preserving organ function. Cerebral perfusion pressure may be either high or low in women with preeclampsia and eclampsia. A recent Cochrane review concluded based on a series of adverse outcomes that **nimodipine** should be avoided for this indication. Specifically, it was associated with a higher risk of eclampsia (relative risk [RR] 2.24, 95% CI 1.06-4.73) and respiratory difficulties (RR 0.28, 95% CI 0.08-0.99). **Nimodipine** significantly reduces Doppler-measured resistances of the retinal vessels.

Compared to **magnesium sulfate, nimodipine** increases cerebral perfusion pressure in women with severe preeclampsia. While once suggested as an agent to prevent eclampsia, it is inferior to **magnesium sulfate** as prophylaxis.
Preterm labor: When compared with any other tocolytic agent, calcium channel blockers reduce the number of women giving birth within 48h or 7d of diagnosis. The frequency of drug discontinuation for adverse effects is also dramatically reduced. There are no adequate reports or well-controlled studies of **nimodipine** for tocolysis in pregnant women. It is an effective inhibitor of uterine contractions *in vitro.* Either **nifedipine** or **nicardipine** would be preferable.
Psychiatric disorders: **Nimodipine** may be an alternative to **lithium** in pregnant women with bipolar disorder.
Side effects include hypotension, tachycardia, bradycardia, arrhythmia, ECG abnormalities, AV conduction abnormalities, GI bleeding, thrombocytopenia, thromboembolism, elevated LFTs, diarrhea, edema, dyspnea, headache, rash, dyspepsia, anemia, acne, muscle aches, and flushing.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. **Nimodipine** crosses the human placenta, reaching an F:M ratio approaching unity within several hours. Maternal administration reduces both maternal and fetal cerebral resistances. Rodent studies are somewhat conflicting. Placental transfer is inefficient. Embryotoxicity, teratogenicity, and IUGR are reported in some models, but it occurs in a non–dose-dependent fashion.

Breastfeeding Safety

There are no adequate reports or well-controlled studies in nursing women. **Nimodipine** enters human breast milk. In one case report, the M:P ratio approximated 0.1. It was estimated the breastfed newborn would ingest a clinically insignificant amount ranging between 0.008% and 0.092% of the weight-adjusted maternal dose.

Drug Interactions

The cardiovascular action of other calcium channel blockers may be enhanced.
Cimetidine (1000mg/d for 1w) in a study in healthy volunteers increased the **nimodipine** peak concentration 50% and the AUC 90%, probably secondary to the known inhibition of hepatic CYP3A4 by **cimetidine.**

References

Anthony J, Mantel G, Johanson R, Dommisse J. Br J Obstet Gynaecol 1996; 103:518-22.
Belfort MA, Anthony J, Saade GR. Semin Perinatol 1999; 23:65-78.
Belfort MA, Anthony J, Saade GR, et al. N Engl J Med 2003; 348:304-11.
Belfort MA, Carpenter RJ Jr, Kirshon B, et al. Am J Obstet Gynecol 1993; 169:204-6.
Belfort MA, Saade GR, Moise KJ Jr, et al. Am J Obstet Gynecol 1994; 171:417-24.
Belfort MA, Saade GR, Yared M, et al. Am J Obstet Gynecol 1999; 181:402-7.
Carcas AJ, Abad-Santos F, de Rosendo JM, Frias J. Ann Pharmacother 1996; 30:148-50.
Duley L, Henderson-Smart DJ, Meher S. Cochrane Database Syst Rev 2006; (3):CD001449.
Kaya T, Cetin A, Cetin M, Sarioglu Y. Eur J Pharmacol 1998; 346:65-9.

Kaya T, Cetin A, Cetin M, Sarioglu Y. J Reprod Med 1999; 44:115-21.
Suwelack D, Weber H, Maruhn D. Arzneimittelforschung 1985; 35:1787-94.
Tonks AM. Aust N Z J Surg 1995; 65:693-4.
Yingling DR, Utter G, Vengalil S, et al. Am J Obstet Gynecol 2002; 187:1711-2.

Summary

Pregnancy Category: C
Lactation Category: S (likely)

- **Nimodipine** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.
- There are alternative agents for which there is more experience regarding use during pregnancy and lactation.

Nisoldipine—(Sular)

International Brand Name—Angiolat (Uruguay); Baymycard (Bulgaria, Germany, Japan); Corasol (Chile); Nisoldin (Korea); Syscor (Austria, Belgium, Costa Rica, Dominican Republic, El Salvador, Finland, Greece, Guatemala, Honduras, Italy, Netherlands, New Zealand, Nicaragua, Panama, Spain, Switzerland, Taiwan); Syscor AP (Brazil); Syscor CC (Peru); Syscor MR (England)

Drug Class

Antihypertensives; Calcium channel blockers

Indications

Hypertension

Mechanism

Inhibits Ca^{2+} influx into vascular smooth muscle and myocardium

Dosage with Qualifiers

Hypertension—20-40mg PO qd; max 60mg/d

- **Contraindications**—hypersensitivity to drug or class
- **Caution**—unknown

Maternal Considerations

Hypertension remains a significant cause of maternal and fetal morbidity and death. Severe hypertension during pregnancy (BP >170/110mmHg) should be treated immediately to improve both maternal and fetal outcome. An uncontrolled reduction in BP may lead to coma, stroke, MI, acute renal failure, and death. Treatment of an acute hypertensive episode during pregnancy further complicates the process, because an acute decrease in BP might adversely affect the fetus. Thus, the goal is not just to decrease BP, but to do so with minimal adverse effects while preserving organ function. In one study, **nisoldipine** was used to treat preeclamptic women with severe postpartum hypertension. A rapid and significant fall in BP was seen within 30min, and maintained successfully by repeating **nisoldipine** for the duration of the study period. There were no adverse reactions.
Side effects include vasodilation, headache, palpitation, chest pain, CHF, 1st degree AV block, dizziness, pharyngitis, edema, rash, N/V, increased LFTs, sinusitis, and malaise.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **nisoldipine** crosses the human placenta. **Nisoldipine** was unassociated with changes in the FHR despite maternal bradycardia. Rodent studies conducted at doses that cause maternal toxicity were associated with embryotoxicity.

Breastfeeding Safety	There is no published experience in nursing women. It is unknown whether **nisoldipine** enters human breast milk.
Drug Interactions	**Cimetidine** (400mg bid) increased the AUC and C_{max} of **nisoldipine** 30-45%. **Ranitidine** did not interact significantly with **nisoldipine.** **Quinidine** (648mg bid) decreased the AUC of **nisoldipine** by 26%, but not the C_{max}. The immediate-release, but not the coat-to-core formulation of **nisoldipine,** increased **quinidine** concentrations by about 20%. This interaction was not accompanied by ECG changes and its clinical significance is not known.
References	Belfort MA, Kirshon B. S Afr Med J 1992; 81:267-70.
Summary	**Pregnancy Category: C** **Lactation Category: U** • **Nisoldipine** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk. • There are alternative agents for which there is more experience regarding use during pregnancy and lactation.

Nitrofurantoin—(Furadantin; Furalan; Furan; Furanite; Furantoina; Furatoin; Macrobid; Macrodantin; Nitrofan; Nitrofuracot)

International Brand Name—Furadantin (Austria, England, Germany, India, Ireland, Italy, Norway, Sweden, Switzerland); Furadantina (Chile, Mexico); Furadantine (Netherlands); Furadantine MC (Belgium); Furadoine (France); Furanpur (Uruguay); Furantoina (Costa Rica, Dominican Republic, El Salvador, Guatemala, Honduras, Nicaragua, Panama); Furobactina (Spain); Infurin (Peru); Nifuran (New Zealand); Nifurantin (Czech Republic); Orafuran (Bulgaria); Urantin (South Africa); Urofuran (Finland); Urotoina (Paraguay)

Drug Class	Antibiotics; Nitrofurans
Indications	UTI
Mechanism	Bactericidal at high concentrations; inhibits protein and cell wall synthesis
Dosage with Qualifiers	UTI—100mg PO bid; alternatively 50-100mg PO qid UTI suppression—50-100mg PO qhs *NOTE: renal dosing.* • **Contraindications**—hypersensitivity to drug or class, CrCl <50ml/h • **Caution**—asthma, anemia, G6PD deficiency
Maternal Considerations	UTI is common during pregnancy, and all pregnant women should be screened. Treatment of asymptomatic bacteriuria and recurrent cystitis during pregnancy reduces the risk of pyelonephritis. **Ampicillin** should not be used because of the high prevalence of resistant *E. coli.* **Nitrofurantoin** is highly soluble in urine. It is safe and effective for the treatment of asymptomatic bacteriuria as well as acute and recurrent UTIs. Resistance rates are <10%. Pyelonephritis occurs in approximately 7% of women despite adequate treatment. Women with recurrent UTI are

candidates for long-term antibiotic prophylaxis. Neither gravidity nor pyelonephritis alters the renal excretion or blood concentration of **nitrofurantoin.** However, labor reduces renal excretion and increases the blood level. Thus, **nitrofurantoin** is a poor selection for therapy during labor. Acute pulmonary reactions to **nitrofurantoin,** presumably immune-mediated, are uncommon but may be life-threatening. Symptoms include fever, chills, cough, pleuritic chest pain, dyspnea, pleural effusion, and pulmonary hemorrhage. The drug should be discontinued and corticosteroids initiated for severe reactions. Irreversible pulmonary fibrosis is also reported. Patients with *G6PD deficiency* may experience hemolytic reactions. It remains unclear how long a woman with asymptomatic bacteriuria should be treated, and there are no randomized studies. Some suggest that short-term administration combined with continued surveillance for recurrent bacteriuria is sufficient.

Side effects include acute pulmonary hypersensitivity, hepatitis, pancreatitis, cholestatic jaundice, N/V, flatulence, peripheral neuropathy, exfoliative dermatitis, erythema multiforme, Stevens-Johnson syndrome, lupus-like syndrome, angioedema, urticaria, rash, agranulocytosis, leukopenia, granulocytopenia, hemolytic anemia, thrombocytopenia, interstitial pneumonitis, and arthralgia.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **nitrofurantoin** crosses the human placenta. There is no evidence **nitrofurantoin** is a human teratogen. Although contraindicated in labor and in infants <1mo, there are no well-documented cases of hemolytic reactions in neonates. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically.

Breastfeeding Safety

The long clinical experience is reassuring, though the literature is conflicting. One study whose subjects received 100mg concluded **nitrofurantoin** is actively transported into human milk, and that a nursing newborn could ingest 6% of the maternal dose. Another study whose subjects received 50mg found a much lower M:P ratio and concluded the likelihood of a nursing newborn ingesting a clinically relevant amount of **nitrofurantoin** was low. Thus, concern remains for breastfeeding women treated therapeutically with **nitrofurantoin** if they have a family history of G6PD deficiency or sensitivity to **nitrofurantoin.**

Drug Interactions

Antacids containing magnesium trisilicate reduce both the rate and extent of **nitrofurantoin** absorption. The mechanism for this interaction probably is adsorption of **nitrofurantoin** onto the surface of magnesium trisilicate.

Uricosuric drugs (e.g., **probenecid, sulfinpyrazone**) inhibit renal tubular secretion of **nitrofurantoin** and may cause **nitrofurantoin** toxicity. Further, the decreased urine concentration reduces its efficacy as a urinary tract antibacterial.

References

Akerele P, Abhulimen F, Okonofua J. J Obstet Gynaecol 2001; 21:141-4.

Ben David S, Einarson T, Ben David Y, et al. Fundam Clin Pharmacol 1995; 9:503-7.

Bint AJ, Hill D. J Antimicrob Chemother 1994; 33(Suppl A):93-7.

Boggess KA, Benedetti TJ, Raghu G. Obstet Gynecol Surv 1996; 51:367-70.

Christensen B. J Antimicrob Chemother 2000; 46(Suppl 1):29-34.

Cunha BA. Obstet Gynecol Surv 1989; 44:399-406.

Czeizel AE, Rockenbauer M, Sorensen HT, Olsen J. Eur J Obstet Gynecol Reprod Biol 2001; 95:119-26.
Delzell JE Jr, Lefevre ML. Am Fam Physician 2000; 61:713-21.
Dwyer PL, O'Reilly M. Curr Opin Obstet Gynecol 2002; 14:537-43.
Gait JE. DICP 1990; 24:1210-3.
Gerk PM, Kuhn RJ, Desai NS, McNamara PJ. Pharmacotherapy 2001; 21:669-75.
Gilstrap LG 3rd, Hankins GD, Snyder RR, Greenberg RT. Compr Ther 1986; 12:38-42.
Hailey FJ, Fort H, Williams JC, Hammers B. J Int Med Res 1983; 11:364-9.
Lenke RR, VanDorsten JP, Schifrin BS. Am J Obstet Gynecol 1983; 146:953-7.
Nicolle LE. Am J Med 2002; 113(Suppl 1A):35S-44S.
Noschel H, Schroder S, Eichhorn KH, Peiker G. Pharmazie 1982; 37:204-5.
Philpot J, Muntoni F, Skellett S, Dubowitz V. Neuromuscul Disord 1995; 5:67-9.
Pons G, Rey E, Richard MO, et al. Dev Pharmacol Ther 1990; 14:148-52.
Prytherch JP, Sutton ML, Denine EP. J Toxicol Environ Health 1984; 13:811-23.
Stamm WE. Am J Med 1984; 76:148-54.
Van Dorsten JP, Lenke RR, Schifrin BS. J Reprod Med 1987; 32:895-900.
Whalley PJ, Cunningham FG. Obstet Gynecol 1977; 49:262-5.

Summary

Pregnancy Category: B
Lactation Category: S (likely)

- **Nitrofurantoin** is a first-line agent for both the treatment of UTI and outpatient prophylaxis.

Nitroglycerin—(Deponit; Glyceryl; Minitran; Mi-Trates; Natirose; Nitrek; Nitro; Nitro-Bid; Nitrocap T.D.; Nitrocine; Nitrocot; Nitrodisc; Nitro-Dur; Nitrogard; Nitroglyn; Nitrol; Nitrolin; Nitrolingual; Nitronal; Nitrong; Nitro-Par; Nitrorex; Nitrospan; Nitrostat; Nitro-Time; NTS; NTG; Transderm-Nitro; Transiderm; Tridil)

International Brand Name—Anglix (Mexico); Cardinit (Mexico); Coro-Nitro (Germany); Deponit (China, Germany, Malaysia, Peru, Philippines); Deponit-5 (Korea, Thailand); Deponit NT (Hong Kong, Israel); Deponit TTS 5 (Israel); Deponit TTS 10 (Israel); Epinitril (France); Gilustenon (Germany); Glytrin Spray (New Zealand, Singapore); Lenitral (France, Hong Kong); Lycinate (Australia); Millsrol (Japan); Minitran (Argentina, Australia, Canada, Costa Rica, El Salvador, Greece, Guatemala, Honduras, Panama, Paraguay, Philippines, Uruguay, Venezuela); Myonit (India); Myovin (India); Niong Retard (Switzerland); Nitradisc (Australia, Brazil, Denmark, Germany, Hong Kong, Indonesia, Mexico, Norway, Peru, Portugal, Spain); Nitradisc Pad (New Zealand); Nitradisc TTS (Greece); Nit-Ret (Czech Republic); Nitriderm TTS (France, Germany); Nitro (Finland); Nitrobaat (Belgium, Netherlands); Nitro-Bid (Australia, Malaysia); Nitrobid (Japan); Nitrobid Oint (New Zealand); Nitrocerin (Greece); Nitrocine (Taiwan); Nitrocontin (Ireland); Nitrocontin Continus (England, India, Ireland); Nitrocor (Italy, Portugal); NitroCor (New Zealand); Nitroderm TTS (Austria, Belgium, Bulgaria, China, Ecuador, Germany, Hong Kong, India, Israel, Italy, Malaysia, New Zealand, Portugal, Spain, Switzerland, Taiwan, Thailand); Nitroderm TTS-5 (Colombia, Costa Rica, Dominican Republic, El Salvador, Guatemala, Honduras, Mexico, Nicaragua, Panama); Nitroderm TTS Ext (Czech Republic); Nitrodisc (Malaysia); Nitrodor (Chile); Nitro-Dur (China, Italy, Norway, Portugal, Spain); Nitro-Dur 10 (Israel); Nitro Dur TTS (Switzerland); Nitrodyl (Greece); Nitrodyl TTS (Greece); Nitro-Gesanit Retard (Germany); Nitrogesic (India); Nitroglin (Germany); Nitroglyn (Sweden); Nitrol (Canada, Philippines); Nitrolingual (Austria, Belgium, China, Denmark, England, Germany, Greece, Hong Kong, Hungary, Ireland, Netherlands, Philippines, Portugal, Sweden, Switzerland); Nitrolingual Spray (Korea, New Zealand, Philippines, Singapore); Nitrolong (Switzerland); Nitro Mack (China); Nitro Mack Retard (Austria, Costa Rica, Czech Republic, Dominican Republic, El Salvador, Germany, Greece, Honduras, Malaysia, Panama, Switzerland); Nitro-Mack Retard (Thailand); Nitromack Retard (Hong Kong, Indonesia, Paraguay); Nitro-M-Bid (Belgium); Nitromex (Denmark, Finland, Norway, Sweden); Nitromint (Hungary, Switzerland); Nitronal Aqueous (Philippines); Nitrong (Belgium, China, Finland, Hungary, Norway, South Africa, Sweden); Nitrong Retard (Austria, Greece); Nitrong-SR (Canada); Nitropen (Japan); Nitro-Pflaster (Germany); Nitroplast (Spain); Nitroprol (Belgium); Nitropront (Finland); Nitroprontan (Argentina); Nitrorectal (Germany); Nitro Retard (Bulgaria, Norway, Sweden); Nitro Rorer (Germany); Nitrostat (Canada, Hong Kong, Philippines, Taiwan); Nitro-Time (China); Nitrozell Retard (Austria, Netherlands); Nysconitrine (Belgium); Percutol (Ireland); Percutol Oint. (England, Ireland); Perlinganit (Korea); Ratiopharm (Germany); Rectogesic (Australia); Suscard (England, Ireland); Sustac (England); Transderm-Nitro (Canada); Transiderm Nitro (Australia, Denmark, Finland, Hungary, Netherlands, Norway, Sweden); Trinipatch (Israel); Trinter (England, Ireland); Vasolator (Japan); Venitrin (Italy)

Drug Class	Vasodilators
Indications	Angina
Mechanism	NO donor, relaxing vascular smooth muscle via cGMP
Dosage with Qualifiers	Angina, acute—0.3-0.6mg SL q5min; max 3 doses within 15min Angina, prophylaxis—0.3-0.6mg SL ×1; take 5-10min before strenuous activity *NOTE: available in 2% cream, tablets, aerosol spray, parenteral, and patch formats; store tablets in original glass container.* • **Contraindications**—hypersensitivity to drug or class, anemia, methemoglobinemia, increased ICP, head trauma, cerebral hemorrhage, recent **sildenafil** • **Caution**—hypotension, hypovolemia, chronic heart failure, acute MI
Maternal Considerations	*Hypertension during pregnancy:* Hypertension remains a significant cause of maternal and fetal morbidity and death. Severe hypertension during pregnancy (BP >170/110mmHg) should be treated immediately to improve both maternal and fetal outcome. An uncontrolled reduction in BP may lead to coma, stroke, MI,

acute renal failure, and death. Treatment of a hypertensive episode during pregnancy further complicates the process because an acute decrease in BP might adversely affect the fetus. Thus, the goal is not just to decrease BP, but to do so with minimal adverse effects while preserving organ function. It is suggested NO donors may have a therapeutic role in preeclampsia. Doppler studies are conflicting. Some investigators report vascular smooth muscle sensitivity to **nitroglycerin** is unaltered by preeclampsia, while others observe that **nitroglycerin** produces a more profound decrease in BP of preeclamptic women compared to normal subjects. **Nitroglycerin** also causes a fall in the resistance indices of the uterine arteries whether administered acutely or chronically. It is unknown whether the decline in resistance is associated with an increase in perfusion. Low-dose prophylactic **nitroglycerin** beginning in the 2nd trimester does not reduce the incidence of preeclampsia or IUGR.

Cervical ripening and tocolysis: The NO-cGMP relaxation pathway is present in the human cervix and uterus and it has been postulated NO may have a physiologic role in uterine quiescence and cervical ripening. High doses of sublingual or IV **nitroglycerin** have been used acutely as a uterine relaxant to assist fetal surgery, fetal extraction at cesarean section, external version, internal intrapartum podalic version of the 2nd twin, manual exploration of the uterus to remove a retained placenta, and replacement of an inverted uterus. Yet placebo-controlled trials demonstrate **nitroglycerin** is no better than placebo for the facilitation of fetal extraction at cesarean section, or for external version. IV **nitroglycerin** currently continues to be used intra- and postoperatively to facilitate uterine relaxation during or after open uterine fetal surgery. Pulmonary edema is the most common complication. The short t/2 (2.5min) of **nitroglycerin** makes long-term therapy difficult, and tolerance is associated with longer acting donors. **Nitroglycerin** has also been used for intrapartum management of fetal distress. In a recent RCT, there was no difference between **nitroglycerin** and **terbutaline** in successful acute intrapartum fetal resuscitation. However, **terbutaline** provided more effective tocolysis with less impact on maternal BP. There are no identifiable placebo-controlled trials of intrauterine resuscitation. While **nitroglycerin** reduces the force necessary to dilate the cervix for a 1st trimester termination, it is less effective than prostaglandins for cervical ripening. **Nitroglycerin** has also proved a poor tocolytic. It does not inhibit uterine contractility in sheep. In laboring women, a 800mcg/dose reduces BP but has no effect on either uterine tone or contractility. Controversy continues regarding the ability of **nitroglycerin** to prevent preterm labor. **Nitroglycerin** is more effective than placebo but similar to a β-agonist or **magnesium sulfate** as a tocolytic agent. Its purported ability to delay labor was gestational age dependent.

Side effects include hypotension, methemoglobinemia, anaphylactic reactions, bradycardia, headache, tolerance/dependence, light-headedness, burning/tingling oral sensation, reflex tachycardia, postural hypotension, dizziness, flushing, and edema.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. When given to women with mild preeclampsia, **nitroglycerin** is associated with a decrease in the resistance in fetoplacental circulation approximately 20-30min after administration. Low levels of **nitroglycerin** are found in the fetus after its use to facilitate an acute obstetric procedure. Sheep studies reveal no adverse fetal effects after maternal administration. There is no effect on fetal carotid blood flow.

Rodent teratogenicity studies are reassuring, but limited by dose and format.

Breastfeeding Safety

There is no published experience in nursing women. It is unknown whether **nitroglycerin** enters human breast milk. However, considering the indication, dosing, and clearance rate, limited **nitroglycerin** use is unlikely to pose a clinically significant risk to the breastfeeding neonate.

Drug Interactions

Ethanol may enhance sensitivity to the hypotensive effects of nitrates.

The vasodilating effects of **nitroglycerin** may be additive with those of other vasodilators. Marked symptomatic orthostatic hypotension has been reported when calcium channel blockers and organic nitrates were used in combination. Dose adjustments of either agent may be necessary.

References

Anumba DO, Ford GA, Boys RJ, Robson SC. Am J Obstet Gynecol 1999; 181:1479-84.

Belfort MA. S Afr Med J 1993; 83:656.

Black RS, Lees C, Thompson C, et al. Obstet Gynecol 1999; 94:572-6.

Buhimschi CS, Buhimschi IA, Malinow AM, Weiner CP. Am J Obstet Gynecol 2002; 187:235-8.

Buhimschi I, Ali M, Jain V. Hum Reprod 1996; 11:1755-66.

Buhimschi I, Yallampalli C, Dong YL, Garfield RE. Am J Obstet Gynecol 1995; 172:1577-84.

Cacciatore B, Halmesmaki E, Kaaja R, et al. Am J Obstet Gynecol 1998; 179:140-5.

Caponas G. Anaesth Intensive Care 2001; 29:163-77.

Chanrachakul B, Herabutya Y, Punyavachira P. Obstet Gynecol 2000; 96:549-53.

Choi JW, Im MW, Pai SH. Ann Clin Lab Sci 2002; 32:257-63.

David M, Nierhaus M, Schauss B, Vetter K. Z Geburtshilfe Neonatol 2001; 205:137-42.

David M, Walka MM, Schmid B, et al. Am J Obstet Gynecol 2000; 182:955-61.

DiFederico EM, Burlingame JM, Kilpatrick SJ, et al. Am J Obstet Gynecol 1998; 179:925-33.

DiFederico EM, Harrison M, Matthay MA. Chest 1996; 109:1114-7.

Dufour P, Vinatier D, Bennani S, et al. J Gynecol Obstet Biol Reprod 1996; 25:617-22.

Dufour P, Vinatier D, Puech F. Arch Gynecol Obstet 1997; 261:1-7.

Ekerhovd E, Brannstrom M, Weijdegard B, Norstrom A. Am J Obstet Gynecol 2000; 183:610-6.

El-Sayed YY, Riley ET, Holbrook RH Jr, et al. Obstet Gynecol 1999; 93:79-83.

Houlihan C, Knuppel RA. Clin Perinatol 1996; 23:91-116.

Kirsten R, Nelson K, Kirsten D, Heintz B. Clin Pharmacokinet 1998; 35:9-36.

Lau LC, Adaikan PG, Arulkumaran S, Ng SC. BJOG 2001; 108:164-8.

Lees C, Campbell S, Jauniaux E, et al. Lancet 1994; 343:1325-6.

Lees C, Valensise H, Black R, et al. Ultrasound Obstet Gynecol 1998; 12:334-8.

Lees CC, Lojacono A, Thompson C, et al. Obstet Gynecol 1999; 94:403-8.

Leszczynska-Gorzelak B, Laskowska M, et al. Ginekol Pol 2002; 73:666-71.

Luzi G, Caserta G, Iammarino G. Ultrasound Obstet Gynecol 1999; 14:101-9.

Mirabile CP Jr, Massmann GA, Figueroa JP. Am J Obstet Gynecol 2000; 183:191-8.
O'Grady JP, Parker RK, Patel SS. J Perinatol 2000; 20:27-33.
Pullen KM, Riley ET, Waller SA, et al. Am J Obstet Gynecol 2007; 197:414.e1-6.
Ramsay B, De Belder A, Campbell S, et al. Eur J Clin Invest 1994; 24:76-8.
Rosen MA, Andreae MH, Cameron AG. Anesth Analg 2003; 96:698-700.
Rowlands S, Trudinger B, Visva-Lingam S. Aust N Z J Obstet Gynaecol 1996; 36:377-81.
Schleussner E, Richter S, Gross W, et al. Z Geburtshilfe Neonatol 2001; 205:189-94.
Skarsgard ED, VanderWall KJ, Morris JA, et al. Am J Obstet Gynecol 1999; 181:440-5.
Smith GN, Brien JF. Obstet Gynecol Surv 1998; 53:559-65.
Smith GN, Walker MC, McGrath MJ. Br J Obstet Gynaecol 1999; 106:736-9.
Vinatier D, Dufour P, Berard J. Int J Gynaecol Obstet 1996; 55:129-34.
Weiner CP, Knowles RG, Nelson SE, Stegink LD. Endocrinology 1994; 135:2473-8.
Weiner CP, Thompson LP. Semin Perinatol 1997; 21:367-80.
Wessen A, Elowsson P, Axemo P. Acta Anaesthesiol Scand 1995; 39:847-9.
Wetzka B, Schafer WR, Stehmans A, et al. Gynecol Endocrinol 2001; 15:34-42.
Yallampalli C, Garfield RE. Am J Obstet Gynecol 1993; 169:1316-20.
Yanny H, Johanson R, Balwin KJ, et al. BJOG 2000; 107:562-4.

Summary

Pregnancy Category: C
Lactation Category: U

- **Nitroglycerin** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.
- In emergent situations, IV **nitroglycerin** may provide short-term uterine relaxation.
- There are superior options for cervical ripening.
- **Nitroglycerin** is a poor agent for tocolysis and does not provide effective prophylaxis for either preterm labor or preeclampsia.

Nitroprusside—(Nipride; Nitropress)

International Brand Name—Nitan (Mexico); Nitroprusiato de sodio-ecar (Colombia)

Drug Class ..... Vasodilators

Indications ..... Hypertension, heart failure

Mechanism ..... NO donor, relaxing vascular smooth muscle via cGMP

Dosage with Qualifiers .....

Hypertension—begin 0.25-0.3mcg/kg/min IV; max 10mcg/kg/min
Heart failure—0.3-10mcg/kg/min IV; max 10mcg/kg/min

NOTE: check serum thiocyanate levels with prolonged usage.

- **Contraindications**—hypersensitivity to drug or class, poor cerebral or coronary perfusion, optic atrophy, tobacco-induced amblyopia
- **Caution**—increased ICP

Maternal Considerations

The metabolism of **nitroprusside** is important to remember. One molecule of **nitroprusside** combines with Hb to produce 1 molecule of cyanmethemoglobin and 4 CN^- ions. Thiosulfate reacts with cyanide to produce thiocyanate. Thiocyanate is eliminated in the urine. Cyanide not otherwise removed binds to cytochromes. Cyanide is much more toxic than methemoglobin or thiocyanate.

Hypertension during pregnancy: Hypertension remains a significant cause of maternal and fetal morbidity and death. Severe hypertension during pregnancy (BP >170/110mmHg) should be treated immediately to improve both maternal and fetal outcome. An uncontrolled reduction in BP may lead to coma, stroke, MI, acute renal failure, and death. Treatment of an acute hypertensive episode during pregnancy further complicates the process because an acute decrease in BP might adversely affect the fetus. Thus, the goal is not just to decrease BP, but to do so with minimal adverse effects while preserving organ function. It has been suggested NO donors could have a therapeutic role in preeclampsia. IV **nitroprusside** is an excellent hypotensive agent with the added advantage of a titratable effect. **Nitroprusside** exerts its relaxant effect by an endothelium-independent mechanism. Pharmacologic studies reveal that *in vitro* vasorelaxation in response to **nitroprusside** is attenuated in vessels obtained from preeclamptic women. Conversely, many severely preeclampsia patients are relatively or absolutely hypovolemic. In these patients, systemic BP may be extremely sensitive to small doses. Therefore, some clinicians begin therapy at lower rates of infusion (e.g., 0.5-0.1mcg/min).

Cervical ripening: The NO-cGMP relaxation pathway is present in the human and cervix uterus. **Nitroprusside** decreases collagen cross-links in the guinea pig cervix. It reduces the force necessary to dilate the cervix for a 1st trimester termination.

Side effects include increased ICP, dizziness, N/V, cyanide or thiocyanate toxicity, bradycardia, reflex tachycardia, ileus, diaphoresis, abdominal pain, headache, muscle twitching, acidosis, and flushing.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **nitroprusside** crosses the human placenta. **Nitroprusside** dilates the fetal vascular bed of the isolated perfused placenta, and its efficacy is unaffected by preeclampsia or IUGR. Fetal cyanide toxicity occurs in sheep after maternal administration. It is reversed by maternal administration of sodium thiosulfate, which unfortunately does not cross the human placenta. Rodent teratogenicity studies have not been performed.

Breastfeeding Safety

There is no published experience in nursing women. It is unknown whether **nitroprusside** enters human breast milk. However, considering the indication, dosing, and clearance rate, limited **nitroprusside** use is unlikely to pose a clinically significant risk to the breastfeeding neonate.

Drug Interactions

The hypotensive effect is augmented by most other hypotensive drugs, including ganglionic blocking agents, negative inotropic agents, and inhaled anesthetics.

References

Boujedaini N, Liu J, Thuillez C, et al. Eur J Pharmacol 2001; 427:143-9.

Chwalisz K, Shao-Qing S, Garfield RE, Beier HM. Hum Reprod 1997; 12:2093-101.

Curry SC, Carlton MW, Raschke RA. Anesth Analg 1997; 84:1121-6.
Ekerhovd E, Weidegard B, Brannstrom M, Norstrom A. Obstet Gynecol 1999; 93:987-94.
Facchinetti F, Piccinini F, Volpe A. Hum Reprod 2000; 15:2224-7.
Fittkow CT, Shi SQ, Bytautiene E, et al. J Perinat Med 2001; 29:535-43.
Graeme KA, Curry SC, Bikin DS, et al. Anesth Analg 1999; 89:1448-52.
Gregg AR, Thompson LP, Herrig JE, Weiner CP. J Vasc Res 1995; 32:106-11.
Keeble JE, Poyser NL. Reproduction 2002; 124:317-22.
Longo M, Jain V, Vedernikov YP, et al. Am J Obstet Gynecol 2001; 184:971-8.
Ong SS, Crocker IP, Warren AY, Baker PN. Hypertens Pregnancy 2002; 21:175-83.
Prisant LM, Carr AA, Hawkins DW. Postgrad Med 1993; 93:92-6, 101-4, 108-10.
Read MA, Giles WB, Leitch IM, et al. Reprod Fertil Dev 1995; 7:1557-61.
Shi L, Shi SQ, Saade GR, et al. Mol Hum Reprod 2000; 6:382-9.
Shoemaker CT, Meyers M. Am J Obstet Gynecol 1984; 149:171-3.
Silver HM. Med Clin North Am 1989; 73:623-38.
Thompson LP, Aguan K, Pinkas G, Weiner CP. Am J Physiol Regul Integr Comp Physiol 2000; 279:R1813-20.
Thompson LP, Weiner CP. Am J Obstet Gynecol 1999; 181:105-11.
Thompson LP, Weiner CP. Pediatr Res 1996; 40:192-7.
Wetzka B, Schafer WR, Stehmans A, et al. Gynecol Endocrinol 2001; 15:34-42.
Xiao D, Pearce WJ, Zhang L. Am J Physiol Heart Circ Physiol 2001; 281:H183-90.
Zhang XQ, Kwek K, Read MA. Placenta 2001; 22:337-46.

Summary

Pregnancy Category: C
Lactation Category: U

- **Nitroprusside** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.
- The prudent use of **nitroprusside** is excellent for the rapid treatment of a hypertensive crisis during pregnancy.
- There are superior options for cervical ripening.

Nizatidine—(Axid)

International Brand Name—Acinon (Japan); Actidine (Korea); Antizid (South Africa); Axadine (Korea); Axid Pulvules (Brazil, Bulgaria, Canada, China, England, Greece, Hong Kong, Hungary, Indonesia, Ireland, Korea, Malaysia, Mexico, Philippines, Poland, Singapore, Venezuela); Calmaxid (Belgium, Switzerland); Cronizat (Italy); Distaxid (Spain); Gastrax (Germany); Jadin (Korea); Nacid (Korea); Naxidine (Netherlands); Nex (Korea); Nizax (Denmark, Finland, Germany, Italy); Nizaxid (France, Korea, Portugal); Panaxid (Belgium); Tazac (Australia, Taiwan); Tinza (Korea); Ulxit (Austria); Zanitidine (Korea); Zanitin (Korea); Zanizal (Italy); Zatidine (Korea); Zinga (England)

Drug Class — Antihistamines, H_2; Gastrointestinals

Indications — GERD, duodenal ulcer

Mechanism — Competitive, reversible peripheral H_2 receptor antagonist

Dosage with Qualifiers

GERD—150mg PO bid
Duodenal ulcer, maintenance—150mg PO qhs

Duodenal ulcer, active—300mg PO qhs

NOTE: renal dosing.

- **Contraindications**—hypersensitivity to drug or class
- **Caution**—renal dysfunction

Maternal Considerations

Gastroesophageal reflux and heartburn are reported by 45-85% of women during pregnancy. There are no adequate reports or well-controlled studies of **nizatidine** in pregnant women. **Nizatidine** should be reserved for patients with severe symptoms. ***Side effects*** include hepatitis, thrombocytopenic purpura, exfoliative dermatitis, rhinitis, headache, N/V, anorexia, dyspepsia, abdominal pain, constipation, increased LFTs, pharyngitis, agitation, confusion, somnolence, insomnia, sinusitis, dry mouth, leukopenia, and anemia.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **nizatidine** crosses the human placenta *in vivo*. It freely crosses the isolated perfused cotyledon. A collaborative study by the European Network of Teratology Information Services of H_2 blockers noted an excess of preterm deliveries in the exposed group. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically.

Breastfeeding Safety

There are no adequate reports or well-controlled studies in nursing women. **Nizatidine** is scantly excreted into human breast milk. On average, <0.1% of the maternal dose is secreted during a 12h interval after either single or multiple doses. This is less than either **cimetidine** or **ranitidine.** Thus, it is unlikely the breastfeeding newborn would ingest a clinically relevant quantity. The relevance of the observation that pups reared by **nizatidine**-treated lactating rats had poor growth is unclear.

Drug Interactions

No clinically relevant interactions identified.

References

Broussard CN, Richter JE. Drug Saf 1998; 19:325-37.
Dicke JM, Johnson RF, Henderson GI, et al. Am J Med Sci 1988; 295:198-206.
Garbis H, Elefant E, Diav-Citrin O, et al. Reprod Toxicol 2005; 19:453-8.
Hagemann TM. J Hum Lact 1998; 14:259-62.
Obermeyer BD, Bergstrom RF, Callaghan JT, et al. Clin Pharmacol Ther 1990; 47:724-30.

Summary

Pregnancy Category: B
Lactation Category: S (likely)

- **Nizatidine** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.
- **Nizatidine** use may be associated with preterm birth.

Norethindrone—(Dianor; Micronor; Norethisterone; Norlutin; Nor-QD; Primulut)

International Brand Name—Aminor (Israel); Menzol (England); Micronor (Australia, Brazil, Canada, England, Ireland); Micro-Novom (South Africa); Micronovum (Austria, Germany, South Africa, Switzerland); Mini-PE (Denmark); Norcolut (Hong Kong, Malaysia, Puerto Rico); Norelut (Indonesia); Norestin (Brazil); Nor-Ethis (Malaysia); Noriday (Australia, England, Malaysia, South Africa); Noriday 28 (New Zealand); Norluten (France); Primolut N (England, Finland, Hong Kong, Ireland, Israel, Korea, Netherlands, Norway, Poland, Puerto Rico, Switzerland, Taiwan); Primolut-N (Korea); Primolut Nor (Belgium, Bulgaria, Czech Republic, Italy, Paraguay, Uruguay); Regamen (Indonesia); Shiton (Taiwan); Steron (Thailand); Styptin 5 (India); Sunolut (Malaysia); Utovlan (England)

Drug Class	Contraceptives; Hormones; Progestins
Indications	Contraception, dysmenorrhea, dysfunctional uterine bleeding, endometriosis, PCOS
Mechanism	Inhibits pituitary gonadotropin release, transforms proliferative to secretory endometrium, thickens cervical mucus
Dosage with Qualifiers	Contraception—1 tab PO qd; take at same time every day Dysmenorrhea—1 tab PO qd Dysfunctional uterine bleeding—1 tab PO qd Endometriosis—1 tab PO qd PCOS—1 tab PO qd *NOTE: available in combination with* ***ethinyl estradiol*** *(35mcg/1mg or 50mcg/1mg).* • **Contraindications**—hypersensitivity to drug or class, pregnancy, breast or hepatic cancer, CAD, abnormal vaginal bleeding, acute hepatic disease • **Caution**—smoking
Maternal Considerations	**Norethindrone** is the progestogen in several popular oral contraceptives. The use of oral contraceptives containing **norethindrone** is causally related to an increased incidence of breakthrough bleeding. A slight increase in the incidence of ectopic pregnancy may occur with **progesterone**-only contraceptives. There is no indication for **norethindrone** during pregnancy and lactation. ***Side effects*** include irregular vaginal bleeding, altered menstrual bleeding, amenorrhea, acne, hirsuitism, weight gain, headache, breast tenderness, N/V, thromboembolism, MI, hypertension, hepatic adenoma, edema, melasma, rash, and dizziness.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. **Norethindrone** likely crosses the human placenta since there are scattered cases of masculinized female fetuses reported. Most consist of clitoral hypertrophy not requiring surgical treatment. 1st trimester exposure is an indication for a detailed anatomic ultrasound between 18 and 22w. **Norethindrone** is not teratogenic in rodents.
Breastfeeding Safety	Small amounts of **norethindrone** pass into the breast milk, resulting in steroid levels of 1-6% that of maternal plasma in the infant. Long-term follow-up studies reveal that progestogen-only contraceptives do not adversely affect breastfeeding and infant development.
Drug Interactions	The effectiveness of progestogen-only pills may be reduced by liver enzyme–inducing drugs such as **phenytoin, carbamazepine,** barbiturates, and **rifampin.**

■ **References**

Beischer NA, Cookson T, Sheedy M, et al. Aust N Z J Obstet Gynaecol 1992; 32:233-8.
Cooke ID, Back DJ, Shroff NE. Contraception 1985; 31:611-21.
Maier WE, Herman JR. Regul Toxicol Pharmacol 2001; 34:53-61.
Shaaban MM. J Steroid Biochem Mol Biol 1991; 40:705-10.
Van Vliet H, Grimes D, Helmerhorst F. Cochrane Database Syst Rev 2006; (3):CD003553.
van Vliet HA, Grimes DA, Helmerhorst FM, et al. Contraception 2002; 65:321-4.
WHO, Task Force for Epidemiological Research on Reproductive Health; Special Programme of Research, Development, and Research Training in Human Reproduction. Contraception 1994; 50:55-68.

■ **Summary**

Pregnancy Category: X
Lactation Category: S

- **Norethindrone** is an effective contraceptive when used as directed.
- There are no indications for its use during pregnancy.

Norfloxacin—(Chibroxin; Floxenor; Norofin; Noroxin; Norxacin; Oroflox)

International Brand Name—Ambigram (Colombia); Amicrobin (Spain); Ampliron (Peru); Anquin (Israel); Apirol (Israel); Baccidal (Japan, Spain, Taiwan); Barazan (Germany); Bexinor (Singapore); B.G.B. Norflox (Thailand); Biofloxin (India); Chibroxin (Brazil, Chile, Costa Rica, Ecuador, El Salvador, Germany, Guatemala, Honduras, Nicaragua, Panama, Peru, Spain, Venezuela); Chibroxine (France); Chibroxol (Netherlands, Switzerland); Effectsal (Singapore); Euroflox (Philippines); Floxacin (Mexico); Floxen (Hong Kong); Fluseminal (Greece); Foxgoria (Singapore); Foxinon (Thailand); Fulgram (Italy); Gonorcin (Thailand); Grenis (Peru); Gyrablock (Israel, Singapore); Hurusfec (Korea); Insensye (Australia); Janacin (Hong Kong, Malaysia, Thailand); Lexinor (Finland, Hong Kong, Korea, Sweden, Thailand); Manoflox (Thailand); M-Flox (Thailand); Myfloxin (Thailand); Negaflox (Bulgaria); N-Flox (Peru); Nolicin (Czech Republic, Hungary, Poland); Noprose (Colombia); Noracin (Brazil); Norbactin (Malaysia, Philippines, South Africa, Thailand); Norbactin Eye Drops (India, South Africa); Norbiotic (Peru); Norflohexal (Germany); Norflox (India); Norflox-AZU (Germany); Norfloxbeta (Germany); Norflox Eye (India); Noritacin (Peru); Normax Eye Ear Drops (India); Norocin (Greece); Noroxin (Canada, Chile, Ecuador, England, Finland, Italy, Mexico, Netherlands, Peru, Portugal, Switzerland, Venezuela); Noroxine (France); Noroxin Oftalmico (Mexico); Noroxin Ophthalmic (Canada); Norpurisine (Korea); Norsol (Argentina); Nufloxib (Australia); Oranor (Mexico); Orsanac (Ecuador); Orsanic (Paraguay); Proxinor (Thailand); Respexil (Brazil); Roxin (Australia); Sefnor (Singapore); Septinor (Philippines); Snoffocin (Thailand); Sofasin (Greece); Tenusin (Philippines); Trizolin (Malaysia); Urekacin (Korea); Urinex (Colombia); Urisold (Greece); Uritracin (Thailand); Urobacid (Indonesia, Philippines, Singapore); Uroctal (Costa Rica, Dominican Republic, El Salvador, Guatemala, Honduras, Hong Kong, Israel, Panama); Uroflox (India, Peru, Republic of Yemen); Uronor (Uruguay); Uroxacin (Argentina); Utiflox (Singapore); UT-in (Slovenia); Utinor (England); Winaflox (Philippines); Xacin (Thailand); Zoroxin (Austria, Belgium, Costa Rica, Denmark, El Salvador, Guatemala, Honduras, Nicaragua, Panama)

■ **Drug Class** — Antibiotics; Ophthalmics; Quinolones

■ **Indications** — Bacterial infections (aerobic gram-positive: *Enterococcus faecalis,* MSSA, *S. saprophyticus, S. pneumoniae, S. pyogenes;* aerobic gram-negative: *Enterobacter cloacae, E. coli, H. influenzae, H. parainfluenzae, Klebsiella pneumoniae, Legionella pneumophila, Moraxella catarrhalis, P. mirabilis, Pseudomonas aeruginosa;* other microorganisms: *Chlamydia pneumoniae, Mycoplasma pneumoniae*), gonorrhea, gastroenteritis, traveler's diarrhea

■ **Mechanism** — Bactericidal—inhibits DNA synthesis

■ **Dosage with Qualifiers**

Bacterial infections—400mg PO bid
Gonorrhea—800mg PO ×1; consult most recent CDC STD guidelines

Gastroenteritis—400mg PO bid ×5d
Traveler's diarrhea—400mg PO bid ×3d

NOTE: renal dosing.

- **Contraindications**—hypersensitivity to drug or class
- **Caution**—renal, hepatic, or pulmonary dysfunction; CV disease; CNS disorder; seizure disorder; diabetes mellitus; G6PD deficiency; myasthenia gravis

Maternal Considerations

There are no adequate reports or well-controlled studies of **norfloxacin** in pregnant women (see **Ciprofloxacin**).
Side effects include photosensitivity, pseudomembranous colitis, vaginitis, seizures, increased ICP, headache, psychosis, N/V, diarrhea, abdominal pain, dyspepsia, dizziness, insomnia, agitation, tendonitis, arthralgia, tendon rupture, restlessness, and elevated LFTs.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **norfloxacin** crosses the human placenta. The limited human experience is reassuring, as 1st trimester use does not appear to be associated with an increased risk of malformations or musculoskeletal problems. Animal studies (rodent, monkey) are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses 6-50× higher than those used clinically.

Breastfeeding Safety

There is no published experience in nursing women. It is unknown whether **norfloxacin** enters human breast milk.

Drug Interactions

Increased **cyclosporine** levels are reported and should be monitored.
Quinolones, including **norfloxacin,** may enhance the effects of oral anticoagulants, including **warfarin** or its derivatives or similar agents.
Use of quinolones, including **norfloxacin,** with **glyburide** (a sulfonylurea agent) has on rare occasions resulted in severe hypoglycemia. Close monitoring of blood glucose is recommended.
Probenecid decreases urinary excretion of **norfloxacin,** potentially increasing serum levels but reducing urine antibacterial efficacy.
Use of **nitrofurantoin** is not recommended since it may antagonize the antibacterial effect of **norfloxacin** in the urinary tract.
Multivitamins or other products containing iron or zinc, antacids, and **sucralfate** should not used with, or within 2h of, **norfloxacin** because they may interfere with absorption of **norfloxacin,** resulting in lower serum and urine levels.
Didanosine chewable/buffered tablets or the pediatric powder for oral solution should not be given concomitantly with, or within 2h of, **norfloxacin** because they interfere with absorption and may result in lower serum and urine levels of **norfloxacin.**
Some quinolones have also been shown to interfere with the metabolism of **caffeine.** This may lead to reduced clearance of **caffeine** and a prolongation of its plasma t/2.

References

Berkovitch M, Pastuszak A, Gazarian M, et al. Obstet Gynecol 1994; 84:535-8.
Gips M, Soback S. J Vet Pharmacol Ther 1999; 22:202-8.
Loebstein R, Addis A, Ho E, et al. Antimicrob Agents Chemother 1998; 42:1336-9.
Mani VR, Vidya KC. J Indian Med Assoc 1997; 95:416-7, 421.

Summary

Pregnancy Category: C
Lactation Category: U

- **Norfloxacin** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.
- There are alternative agents for which there is more experience regarding use during pregnancy and lactation.

Norgestrel—(Norplant; Ovrette)

International Brand Name—LNG-IUS (internationally distributed IUD); Neogest (England)

Drug Class

Contraceptives; Hormones; Progestins

Indications

Contraception, dysmenorrhea, dysfunctional uterine bleeding, endometriosis, PCOS

Mechanism

Inhibits pituitary gonadotropin release, stimulates transformation of the proliferative endometrium into secretory, alters cervical mucus

Dosage with Qualifiers

Contraception—1 tab PO qd; take at same time every day
Dysmenorrhea—1 tab PO qd
Dysfunctional uterine bleeding—1 tab PO qd
Endometriosis—1 tab PO qd
PCOS—1 tab PO qd
Emergency contraception—either 2 tabs immediately, or 1 tab q12-24h for a total of 2 tabs

NOTE: each tab contains 0.75mg; also combined with a variety of estrogens for combination oral contraceptives.

- **Contraindications**—hypersensitivity to drug or class, pregnancy, breast cancer, hepatic cancer, CAD, abnormal vaginal bleeding, acute hepatic disease
- **Caution**—smoking

Maternal Considerations

Norgestrel is a synthetic progestogen that, alone or in combination with estrogen, is used in several popular oral, SR, and local (IUD) forms of contraception. It is pharmacologically similar to **levonorgestrel.** Progestin-only emergency contraception (1 tab PO q12h ×2) is available as a prepackaged product. The **levonorgestrel**-only regimen prevents 85% of unintended pregnancies compared with 57% for the Yuzpe regimen (2 tab each of 50mcg **ethinyl estradiol** and 0.25mg **levonorgestrel**, repeated 12h later). Though the implantable form (Norplant) is effective, patient acceptance is poor with up to 65% reporting menstrual abnormalities; 7.5% discontinue use in less than 4y because of increased bleeding. Other side effects reported include headache (6%), weight gain (3%), mastalgia (1.8%), decreased libido (1.8%), abdominal pain (1.5%), and hypertension (1.2%). Implants are contraindicated in women with a history of seizures. There is no indication for **norgestrel** during pregnancy. Efficacy of the IUD is excellent regardless of parity, with <1 pregnancy per 100 woman-years. Efficacy with immediate postabortal insertion is also good and unaffected by parity. The presence of an IUD does not increase the risk of PID or infertility in either parous or nulliparous women and it may be protective against infection.
Side effects include acne, hirsuitism, weight gain, headache, breast tenderness, N/V, thromboembolism, MI, hypertension, hepatic

adenoma, edema, breakthrough bleeding, altered menstrual bleeding, amenorrhea, melasma, rash, and dizziness.

Fetal Considerations

There are no adequate reports or well-controlled studies of **norgestrel** in human fetuses. *In utero* exposure of male fetuses to progestational agents may double the risk of hypospadias. While there are insufficient data to quantify the risk for the female fetus, some progestational agents may cause mild virilization of the external genitalia. Defects outside the external genitalia are not reported in either humans or rodents. 1st trimester exposure is an indication for a detailed anatomic ultrasound between 18 and 22w.

Breastfeeding Safety

Norgestrel is excreted into maternal milk. Maintaining a time interval between mini-pill intake and breastfeeding results in higher levels in breast milk, thus exposing the newborn to a bolus of drug in a "single-delayed" feed. Long-term follow-up studies reveal that progestogen-only contraceptives do not adversely affect breastfeeding and infant development.

Drug Interactions

Published studies reveal decreased **norgestrel** concentrations in women who require chronic use of **carbamazepine, oxcarbazepine, phenobarbital,** or **phenytoin,** presumably through the induction of microsomal liver enzymes. For women receiving long-term therapy with hepatic enzyme inducers, a different method of contraception should be considered. Women on short-term therapy with hepatic enzyme inducers should consider using a backup method of contraception.
Rifampicin decreases the effectiveness of combination oral contraceptives; its effect on norgestrel concentrations has not been established. Data from clinical trials of Norplant, however, note low serum concentrations and a subsequent pregnancy in one woman using **rifampicin.**
Herbal products containing **St. John's wort** *(Hypericum perforatum)* may induce hepatic enzymes and may reduce the effectiveness of contraceptive steroids.

References

Aisien AO. Afr J Reprod Health 2007; 11:90-7.
Dolan LM, Mulholland M, Price J. J Fam Plann Reprod Health Care 2001; 27:19-21.
Prager S, Darney PD. Contraception 2007; 75(6 Suppl):S12-5.
Schwartz JL. Curr Womens Health Rep 2001; 1:191-5.
Toddywalla VS, Patel SB, Betrabet SS, et al. Contraception 1995; 51:193-5.

Summary

Pregnancy Category: X
Lactation Category: S

- **Norgestrel** is an effective contraceptive when used as directed.
- There are no indications for its use during pregnancy.

Nortriptyline—(Allergron; Lisunim; Pamelor)

International Brand Name—Allegron (Australia, Belgium, England, Ireland, New Zealand); Altilev (Uruguay); Ateben (Argentina); Aventyl (Canada, England, Ireland, Malaysia, South Africa); Kareon (Argentina); Martimil (Spain); Noritren (Denmark, Finland, Italy, Japan, Norway, Sweden); Norline (Thailand); Norpress (New Zealand); Nortrilen (Austria, Belgium, Bulgaria, Czech Republic, Germany, Greece, Hong Kong, Indonesia, Malaysia, Netherlands, Switzerland, Thailand); Nortrix (Portugal); Nortyline (Thailand); Norventyl (Canada); Ortrip (Thailand); Pamelor (Brazil); Paxtibi (Spain); Sensaval (Sweden); Sensival (India, Japan, Korea); Vividyl (Italy)

Drug Class	Antidepressants
Indications	Depression
Mechanism	Unknown (inhibits NE and serotonin reuptake)
Dosage with Qualifiers	Depression—begin 25-50mg PO qhs, tid, or qid, increase q2-3w until desired effect; max 150mg/d • **Contraindications**—hypersensitivity to drug or class, recovery from acute MI, MAOIs <14d • **Caution**—hepatic dysfunction, CAD, suicide risk, thyroid disease, glaucoma, seizure history
Maternal Considerations	Depression is common during and after pregnancy, but typically goes unrecognized. Pregnancy is not a reason *a priori* to discontinue psychotropic drugs. There are no adequate reports or well-controlled studies of **nortriptyline** in pregnant women. Women who experienced one episode of postpartum-onset major depression are at high risk for subsequent recurrence. Unfortunately, **nortriptyline** is no different than placebo as prophylaxis for the prevention of recurrent postpartum depression in a high-risk population. Cigarette smoking during pregnancy is the single largest modifiable risk for pregnancy-related morbidity and death in the US. Although NRT (gum, patch, nasal spray, and inhaler) combined with **bupropion** has the highest rate of success, **nortriptyline** also has a positive impact on smoking cessation rates. **Nortriptyline** is used for the treatment of neuropathic pain, chronic pain, and panic disorder. Its use for these indications may be avoidable during pregnancy. ***Side effects*** include seizures, MI, stroke, thrombocytopenia, agranulocytosis, confusion, disorientation, constipation, tachycardia, dizziness, increased appetite, blurred vision, drowsiness, and dry mouth.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. Maternal and umbilical cord sera were collected at delivery from 10 women taking **nortriptyline.** The F:M ratios of **nortriptyline** and its active metabolite, *cis*-10-hydroxynortriptyline, were 0.68 ± 0.40 and 1.40 ± 2.40, respectively. Fetal exposure may be limited because of its lipophilicity. A case report suggested an association between **nortriptyline** and limb anomalies. There is no other support for this possibility. Rodent teratogenicity studies have yielded conflicting results.
Breastfeeding Safety	**Nortriptyline** is excreted at low concentration into human breast milk. It is estimated the newborn would ingest only 2.5% of the corresponding maternal weight-corrected dose. Not surprisingly, **nortriptyline** levels are typically at or below the level of detection in the nursing newborn. **Nortriptyline** is generally considered a drug of choice for breastfeeding women suffering from depression.

Drug Interactions

Use of **reserpine** with TCAs has been shown to have a "stimulating" effect in some depressed patients.
Close supervision and careful adjustment of the dose is required when used with other anticholinergic drugs and sympathomimetic drugs.
Use with **cimetidine** can produce clinically significant increases in the plasma concentrations of the TCA. The patient should be informed that the response to ethanol may be exaggerated.
Significant hypoglycemia was reported in a type 2 diabetic patient maintained on **chlorpropamide** (250mg/d) after the addition of **nortriptyline** (125mg/d).

References

Bourke GM. Lancet 1974; 1:98.
Heikkinen T, Ekblad U, Laine K. Psychopharmacology 2001; 153:450-4.
Howard LM, Hoffbrand S, Henshaw C, et al. Cochrane Database Syst Rev 2005; (2):CD004363.
Kotlyar M, Hatsukami DK. J Dent Educ 2002; 66:1061-73.
Loughhead AM, Stowe ZN, Newport DJ, et al. Biol Psychiatry 2006; 59:287-90.
McBride WG. Med J Aust 1972; 1:492.
Wisner KL, Perel JM. Am J Psychiatry 1996; 153:1132-7.
Wisner KL, Perel JM, Findling RL, et al. Psychopharmacol Bull 1997; 33:249-51.
Wisner KL, Perel JM, Peindl KS, et al. J Clin Psychiatry 2001; 62:82-6.
Matheson I, Skjaeraasen J. Eur J Clin Pharmacol 1988; 35:217-20.

Summary

Pregnancy Category: D
Lactation Category: S

- Serotonin reuptake inhibitors are first-line agents for the treatment of most depressive and anxiety disorders.
- **Nortriptyline** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.
- **Nortriptyline** is generally considered a drug of choice for breastfeeding women suffering from depression.

Novobiocin—(Albamycin)

International Brand Name—None identified.

Drug Class

Anti-infectives; Dermatologics; Urologics

Indications

Bacterial infections (aerobic gram-positive: *S. aureus;* aerobic gram-negative: *P. mirabilis*)

Mechanism

Unknown

Dosage with Qualifiers

Bacterial infections—250mg PO tid; max 1g q12h

NOTE: ***novobiocin*** *should be used only after other antibiotics with lower toxicity have failed.*

- **Contraindications**—hypersensitivity to drug or class
- **Caution**—unknown

Maternal Considerations

There are no adequate reports or well-controlled studies of **novobiocin** in pregnant women. **Novobiocin** should be used only after other antibiotics with lower toxicity have failed.

Side effects include urticaria, erythematous maculopapular rash, scarlatiniform rash, Stevens-Johnson syndrome, leukopenia, eosinophilia, hemolytic anemia, pancytopenia, agranulocytosis, thrombocytopenia, jaundice, increased LFTs, N/V, and diarrhea.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **novobiocin** crosses the human placenta. Rodent teratogenicity studies have not been performed.

Breastfeeding Safety

There is no published experience in nursing women. It is unknown whether **novobiocin** enters human breast milk. Studies in animals (cows, mice) report **novobiocin** is excreted into breast milk and can be used to treat bovine mastitis.

Drug Interactions

May result in a "pseudojaundice" with yellow discoloration of the skin and plasma. This yellow pigment may interfere with serum bilirubin and icterus index determinations. **Novobiocin** may interfere with the hepatic uptake or biliary excretion of sulfobromophthalein in the bromsulphalein (BSP) test.

References

There are no current relevant references.

Summary

Pregnancy Category: C
Lactation Category: U

- **Novobiocin** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Nystatin—(Barstatin; Bio-Statin; Candex; Candio-Hermal; Korostatin; Mycostatin; Mykinac; Nilstat; Nysert; Nystex; Nystop; O-V Statin; Pedi-Dry; Statin; Vagistat)

International Brand Name—Acronistina (Ecuador); Afunginal (Philippines); Biofanal (Germany); Biofanal Mundgel (Germany); Candida-Lokalicid (Germany); Candio-Hermal (Austria, Germany); Canstat (South Africa); Fongistat (India); Fungatin (Indonesia); Kandistatin (Indonesia); Lystin (Hong Kong, Malaysia, Thailand); Mibesan-S (Mexico); Micad (Paraguay); Micostatin (Argentina, Brazil, Chile, Colombia, Ecuador, Mexico, Peru, Uruguay, Venezuela); Moronal (Germany); Mycastatin (Japan); Mycocide (Taiwan); Mycosantin (China); Mycostatin (Austria, Canada, Denmark, Finland, Greece, Hong Kong, India, Indonesia, Ireland, Italy, Malaysia, New Zealand, Norway, Philippines, Spain, Sweden, Switzerland, Taiwan, Thailand); Mycostatine (France, Korea); Mykoderm (Germany); Nadostine (Taiwan); Nilstat (Argentina, Canada, Taiwan); Nyaderm (Canada); Nymiko (Hong Kong); Nystacid (Finland); Nystan (England); Nystatyna (Poland); Oranyst (Israel); Scanytin (Taiwan)

Drug Class

Antifungals; Dermatologics

Indications

Yeast infections (*Candida* species: *C. albicans*)

Mechanism

Inhibits biosynthesis of ergosterol, and thus the fungal cell wall

Dosage with Qualifiers

Candidiasis, oral—0.5-1 million U PO tid; continue treatment at least 48h after resolution of the symptoms
Candidiasis, cutaneous—apply bid or tid

- **Contraindications**—hypersensitivity to drug or class
- **Caution**—unknown

Maternal Considerations

Candida vaginitis is perhaps the most common female genital tract infection. **Nystatin** is an antifungal antibiotic that is both fungistatic and fungicidal *in vitro* against a wide variety of yeasts and yeastlike fungi. It is a polyene antibiotic obtained from

Streptomyces noursei. The vaginal milieu during pregnancy predisposes to *C. albicans* overgrowth. *In vitro*, **nystatin** is highly effective against 83% of sensitive strains of tested *C. albicans.* There are no adequate reports or well-controlled studies of **nystatin** in pregnant women. It is not clear whether the various imidazole compounds differ in efficacy for mycotic vaginitis. **Nystatin** is thought less effective than **miconazole** for the treatment of vaginal candidiasis during pregnancy, though there are no randomized trials to substantiate this conclusion. There is no significant difference in the cure rates achieved after 7d or 14d of therapy. More patients relapsed after a cure with **nystatin** than with **miconazole.**
Side effects include Stevens-Johnson syndrome, local irritation, N/V, and diarrhea.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **nystatin** crosses the human placenta. 1st trimester use of **nystatin** (and imidazole agents) is unassociated with an increased prevalence of spontaneous abortion or fetal malformation. Congenital candidiasis of the neonate's skin rarely occurs, and **nystatin** is used to treat this infection and avoid septicemia. Rodent teratogenicity studies are limited to a single report where fetal losses were associated with maternal toxicity.

Breastfeeding Safety

There are no adequate reports or well-controlled studies in nursing women. It is unknown whether **nystatin** enters human breast milk. However, considering the indication and dosing, limited **nystatin** use is unlikely to pose a clinically significant risk to the breastfeeding neonate. **Nystatin** is not effective treatment of nipple candidiasis.

Drug Interactions

No clinically relevant interactions identified.

References

Bodley V, Powers D. J Hum Lact 1997; 13:307-11.
Broberg A, Thiringer K. Int J Dermatol 1989; 28:464-5.
Czeizel AE, Kazy Z, Puhó E. Scand J Infect Dis 2003; 35:830-5.
Eliot BW, Howat RC, Mack AE. Br J Obstet Gynaecol 1979; 86:572-7.
Laskus A, Mendling W, Runge K, Schmidt A. Mycoses 1998; 41(Suppl 2):37-40.
Lee CR, McKenzie CA, Nobles A. Am Pharm 1991; NS31:44-6.
Lisiak M, Klyszejko C, Marcinkowski Z, et al. Ginekol Pol 2000; 71:959-63.
Renault F, Roy C, Costil J, Girouin D. Nouv Presse Med 1982; 11:1863-5.
Rosa FW, Baum C, Shaw M. Obstet Gynecol 1987; 69:751-5.
Rudolph N, Tariq AA, Reale MR, et al. Arch Dermatol 1977; 113:1101-3.
Slonitskaia NN, Mikhailets GA. Antibiotiki 1975; 20:45-7.
Weisberg M. Clin Ther 1986; 8:563-7.
Young GL, Jewell D. Cochrane Database Syst Rev 2001; (4):CD000225.

Summary

Pregnancy Category: B
Lactation Category: S

- **Nystatin** is effective for the treatment of candidiasis.
- Topical imidazole agents may be more effective than **nystatin** for treating symptomatic vaginal candidiasis in pregnancy.
- A 7d treatment regimen may be necessary during pregnancy rather than the shorter courses more commonly used in nonpregnant women.

Oatmeal—(Aveeno)

International Brand Name—None identified.

Drug Class	Dermatologics
Indications	Contact dermatitis (e.g., poison ivy/oak)
Mechanism	Forms a moisturizing, colloidal suspension
Dosage with Qualifiers	Contact dermatitis—apply tid or qid prn; may also mix in bath water and soak • **Contraindications**—hypersensitivity to drug or class • **Caution**—unknown
Maternal Considerations	There is no published experience with topical **oatmeal** during pregnancy. ***Side effects*** have not been reported.
Fetal Considerations	There are no adequate reports or well-controlled studies of topical **oatmeal** in human fetuses. Absorption is likely insignificant.
Breastfeeding Safety	There are no adequate reports or well-controlled studies in nursing women. As a traditional food substance, **oatmeal** is unlikely to pose a clinically significant risk to the nursing infant.
Drug Interactions	No clinically relevant interactions identified.
References	There are no current relevant references.
Summary	**Pregnancy Category: A** **Lactation Category: S**

Octreotide acetate—(Sandostatin)

International Brand Name—Sandostatin (Argentina, Brazil, Canada, Chile, Costa Rica, Dominican Republic, Ecuador, El Salvador, Guatemala, Honduras, Nicaragua, Panama, Paraguay, Peru, South Africa, Uruguay, Venezuela); Sandostatina (Italy, Mexico, Portugal); Sandostatina LAR (Colombia, Mexico); Sandostatine (Belgium, France, Netherlands); Sandostatin LAR (Argentina, Brazil, Canada, Chile, Costa Rica, Dominican Republic, El Salvador, Guatemala, Honduras, Korea, Malaysia, Nicaragua, Panama, Peru, Singapore, Taiwan, Thailand, Uruguay)

Drug Class	Antidiarrheals; Endocrine agents; Gastrointestinals
Indications	Secretory diarrhea, carcinoid tumor, acromegaly, esophageal varices
Mechanism	Somatostatin-like activities include inhibition of GH, LH, insulin, glucagon, and VIP
Dosage with Qualifiers	Secretory diarrhea—50-100mcg SC/IV qd to tid; max 1500mcg/d Carcinoid tumor symptoms—50-100mcg SC/IV qd to tid; max 1500mcg/d Carcinoid tumor crisis—50mcg/h IV ×8-24h acutely; 250-500mcg IV ×1, 1-2h preoperatively for prevention Acromegaly—50mcg SC/IV tid; max 1500mcg/d

Esophageal varices—begin 25-50mcg IV ×1 for bleeding, then 25-50mcg/h

- **Contraindications**—hypersensitivity to drug or class
- **Caution**—biliary disease, renal dysfunction, diabetes mellitus

Maternal Considerations

There are no adequate reports or well-controlled studies in pregnant women. **Octreotide** has pharmacologic actions that mimic the natural hormone somatostatin, but is more potent. There are multiple case reports of **octreotide** use during pregnancy without obvious adverse effect, typically for the treatment of acromegaly. Depressed vitamin B_{12} levels and abnormal Schilling tests are observed in some patients, and monitoring of vitamin B_{12} is recommended. **Octreotide** reportedly improves implantation in supraovulated mice. ***Side effects*** include arrhythmias, edema, cholecystitis, cholelithiasis, ascending cholangitis, N/V, diarrhea, steatorrhea, flushing, hyperglycemia, myalgias, arthralgias, and headache.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. It is not known whether **octreotide** crosses the human placenta. It does not affect placental GH production. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically.

Breastfeeding Safety

There are no adequate reports or well-controlled studies in nursing women. **Octreotide** enters human breast milk, but the reported concentrations are unlikely to have a clinically significant effect on the nursing infant.

Drug Interactions

May alter nutrient absorption, and thus impact the absorption of oral drugs.
May decrease blood levels of **cyclosporine** and lead to transplant rejection.
Patients receiving **insulin**, oral hypoglycemic agents, β-blockers, calcium channel blockers, or agents to control fluid and electrolyte balance may require dose adjustments of these agents.
Octreotide increases the availability of **bromocriptine,** possibly by decreasing the metabolic clearance of compounds known to be metabolized by CYP3A4 via the suppression of growth hormones. Since such an effect cannot be excluded for **octreotide,** drugs metabolized mainly by CYP3A4 and that have a low therapeutic index (e.g., **quinidine, terfenadine**) should be avoided or used cautiously.

References

Blackhurst G, Strachan MW, Collie D, et al. Clin Endocrinol 2002; 57:401-4.
Caron P, Buscail L, Beckers A, et al. J Clin Endocrinol Metab 1997; 82:3771-6.
Castronovo FP Jr, Stone H, Ulanski J. Nucl Med Commun 2000; 21:695-9.
Katagiri S, Moon YS, Yuen BH. Hum Reprod 1997; 12:671-6.
Mikhail N. Mayo Clin Proc 2002; 77:297-8.

Summary

Pregnancy Category: B
Lactation Category: S (likely)

- **Octreotide** is considered safe during pregnancy and lactation if the benefit justifies the potential perinatal risk.

Ofloxacin—(Floxin)

International Brand Name—Akilen (Indonesia); Baccidal (Korea); Bactocin (Mexico); Danoflox (Indonesia); Effexin (Korea); Exocin (Ireland); Exocine (France); Flobacin (Italy); Flodemex (Philippines); Flotavid (Indonesia); Flovid (Hong Kong, Malaysia, Philippines); Floxal (Germany); Floxil (Argentina, Mexico); Floxin (Canada); Floxstat (Colombia, Costa Rica, Dominican Republic, Ecuador, El Salvador, Guatemala, Honduras, Mexico, Nicaragua, Panama); Fugacin (Korea); Inoflox (Malaysia, Philippines, Singapore); Kinflocin (Taiwan); Kinoxacin (Korea); Liflox (Indonesia); Loxinter (Indonesia); Marfloxacin (Hong Kong); Medofloxine (Malaysia); Mergexin (Philippines); Novecin (Israel); Nufafloqo (Indonesia); Obide (Korea); Occidal (Thailand); Ocuflox (Australia, Canada, Korea, Mexico); Ofcin (Malaysia, Singapore, Taiwan); Oflin (India); Oflocee (Thailand); Oflocet (France); Oflocin (Italy); Oflodal (Taiwan); Oflodex (Israel); Oflodura (Germany); O-Flox (Thailand); Oflox (Argentina, Brazil, Chile, Colombia, Ecuador, Israel, Peru, Uruguay, Venezuela); Ofloxin (Thailand); Ofus (Hong Kong); Onexacin (Philippines); Operan (Korea); Orocin (Korea); Otonil (Paraguay); Pharflox (Indonesia); Praxin (Korea); Puiritol (Hong Kong); Qinolon (Philippines); Qipro (Indonesia); Quinolon (Thailand); Quotavil (Hong Kong); Rilox (Indonesia); Sinflo (Taiwan); Tabrin (Greece); Tariflox (Indonesia); Tarivid (China, France, Greece, India, Indonesia, Israel, Italy, Japan, Korea, Malaysia, Poland, Singapore, Slovenia, South Africa, Switzerland, Taiwan, Thailand, Turkey); Tarivid Eye Ear (Hong Kong); Tarivid Otic (Malaysia, Singapore); Telbit (Korea); Tructum (Peru); Uro Tarivid (Israel); Viotisone (Thailand); Zanocin (India)

Drug Class ..... Antibiotics; Ophthalmics; Quinolones

Indications ..... Bacterial infection with gram-positive and -negative aerobes, uncomplicated gonorrhea (urethritis, cervicitis, rectal), chlamydial infections, bacterial conjunctivitis, corneal ulcer, otitis externa

Mechanism ..... Bactericidal—inhibits topoisomerase IV and DNA gyrase

Dosage with Qualifiers .....

Bacterial infections—200-400mg PO/IV q12h
Uncomplicated gonorrhea—400mg PO ×1
Bacterial conjunctivitis—1-2gtt q2-4h each eye ×2d, then qid ×5d
Corneal ulcer—1-2gtt q30min each eye ×2d, then q1h ×5d, then qid ×2d
Otitis externa—10gtt bid ×10d

NOTE: renal dosing; available in otic, ophthalmic, and parenteral preparations.

- **Contraindications**—hypersensitivity to drug or class
- **Caution**—hepatic or renal dysfunction, seizure disorder, CNS abnormalities, diabetes mellitus, dehydration, sun exposure

Maternal Considerations ..... There are no adequate reports or well-controlled studies in pregnant women. **Ofloxacin** achieves high tissue penetration. It is not effective prophylaxis for infection after therapeutic abortion; **doxycycline** is preferred. The FDA has added a black box warning covering the potential for tendon rupture.
Side effects include vaginitis, photosensitivity, pseudomembranous colitis, seizures, increased ICP, headache, psychosis, N/V, diarrhea, abdominal pain, dyspepsia, dizziness, insomnia, agitation, tendonitis, arthralgias, and elevated LFTs.

Fetal Considerations ..... There are no adequate reports or well-controlled studies in human fetuses. Less than 4% of maternal **ofloxacin** crosses the isolated perfused human placenta, though clearance is such that potentially therapeutic levels in AF and sera make it a candidate for fetal therapy if otherwise safe. In humans, fluoroquinolones are not associated with an increased risk of malformation. Neither ophthalmic nor otic application results in significant systemic drug levels. In general, rodent studies are reassuring, though some rodent models using otic application revealed minor skeletal abnormalities and IUGR. The administration of very high multiples of the MRHD is associated with fetal toxicity.

Breastfeeding Safety

There are no adequate reports or well-controlled studies in nursing women. **Ofloxacin** achieves an M:P ratio of ≥1 but is consistently lower than **ciprofloxacin.** Serum and milk were obtained from 10 women simultaneously at 2, 4, 6, 9, 12, and 24h after **ofloxacin.** The mean breast milk levels were 2.4, 1.9, 1.3, 0.6, 0.3, and 0.05mcg/ml, respectively. Even with 100% oral absorption, breastfeeding mothers who take **ofloxacin** will expose their infants to **ofloxacin** concentrations below that being studied in the pediatric population.

Drug Interactions

Quinolones form chelates with alkaline earth and transition metal cations. Use of quinolones with antacids containing calcium, magnesium, or aluminum; with **sucralfate;** with divalent or trivalent cations such as iron; with multivitamins containing zinc; or with **didanosine** chewable/buffered tablets or the pediatric powder for oral solution may substantially interfere with the absorption of quinolones, resulting in systemic levels considerably lower than desired. These agents should not be taken within 2h before or after **ofloxacin.**

Cimetidine interferes with the elimination of some quinolones, resulting in significant increases in their t/2 and AUC. The potential interaction between **ofloxacin** and **cimetidine** has not been studied.

Elevated serum levels of **cyclosporine** have been reported with concomitant use of **cyclosporine** with some other quinolones. The potential for interaction between **ofloxacin** and **cyclosporine** has not been studied.

Most quinolones inhibit CYPs, which may lead to a prolonged t/2 for some drugs metabolized by this system (e.g., **cyclosporine**, **theophylline**/methylxanthines, **warfarin**). The extent of this inhibition varies among different quinolones.

Use with NSAIDs may increase the risk of CNS stimulation and convulsive seizures.

Probenecid has been reported to affect renal tubular secretion of other quinolones. Its effect on the elimination of **ofloxacin** has not been studied.

Steady-state **theophylline** levels may increase when used with **ofloxacin. Theophylline** levels should be closely monitored and the dose adjusted as indicated. Adverse reactions (including seizures) may occur with or without an elevation in the serum **theophylline** level.

Some quinolones have been reported to enhance the effects of **warfarin** or its derivatives. The PT or other suitable coagulation test should be monitored closely.

Since disturbances of blood glucose, including hyperglycemia and hypoglycemia, are reported in patients treated with quinolones and an antidiabetic agent, careful monitoring of blood glucose is recommended.

May produce false-positive urine screening results for opiates using commercially available immunoassay kits. Confirmation of positive opiate screens by more specific methods is necessary.

References

Giamarellou H, Kolokythas E, Petrikkos G, et al. Am J Med 1989; 87:49S-51S.

Loebstein R, Addis A, Ho E, et al. Antimicrob Agents Chemother 1998; 42:1336-9.

Nielsen IK, Engdahl, Larsen T. Acta Obstet Gynecol Scand 1993; 72:556-9.

Polachek H, Holcberg G, Sapir G, et al. Eur J Obstet Gynecol Reprod Biol 2005; 122:61-5.

Summary

Pregnancy Category: C
Lactation Category: S (likely)

- **Ofloxacin** should be used during pregnancy if the benefit justifies the potential perinatal risk.
- Though the fetal risk may not be as great as once thought, there are alternative agents during pregnancy for almost all indications.

Olanzapine—(Zyprexa)

International Brand Name—Dozic (Colombia); Oleanz (India); Zelta (Colombia); Zyprexa Zydis (New Zealand)

Drug Class

Antipsychotics

Indications

Bipolar disorder, psychosis

Mechanism

Unknown; high affinity for 5-$HT_{2A/2C}$ and dopamine receptors

Dosage with Qualifiers

Bipolar disorder—begin 5-10mg qd, increasing 5mg/d prn; max 20mg/d
Psychosis—begin 5-10mg qd, increasing 5mg/d prn; max 20mg/d

NOTE: available in an orally disintegrating tablet form.

- **Contraindications**—hypersensitivity to drug or class
- **Caution**—seizure disorder, narrow-angle glaucoma, paralytic ileus, hypotension, hypovolemia, hepatic dysfunction, CV or cerebrovascular disease

Maternal Considerations

Olanzapine is an atypical antipsychotic agent whose clearance is 30% lower in women. However, effectiveness or side effects are unaltered. Patients treated with **olanzapine** for schizophrenia have less akathisia but more weight gain than patients treated with **haloperidol.** Compliance, symptoms, extrapyramidal symptoms, and overall quality of life are similar for the two drugs, but costs are significantly greater with **olanzapine.** While there are no adequate reports or well-controlled studies in pregnant women, the growing body of clinical experience with **olanzapine** during pregnancy is reassuring.
Side effects include hypotension, tachycardia, menstrual irregularities, hyperprolactinemia, tardive dyskinesia, extrapyramidal symptoms, diabetes mellitus, hyperglycemia, somnolence, weight gain, constipation, dry mouth, dyspepsia, rhinitis, fever, and elevated LFTs.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. In one study, the mean F:M ratio was variable but overall quite high (72.1%; standard deviation [SD] = 42.0%); it was only about 33% in a second report. This contrasts with **quetiapine** (mean = 23.8%, SD = 11.0%). There were tendencies toward higher rates of low birth weight (30.8%) and NICU admission (30.8%) among neonates exposed to **olanzapine.** The pregnancy outcomes of women who contacted a teratogen information service after exposure to **olanzapine** appeared normal. As for most psychotropic drugs, monotherapy and the lowest effective quantity given in divided doses to minimize the peaks can minimize the risks. Rodent studies are reassuring, revealing no evidence of teratogenicity despite the use of doses higher than those used clinically. Embryo and fetal toxicities were seen with high doses. There was no effect of intrauterine exposure on postnatal learning.

Breastfeeding Safety

There are no adequate reports or well-controlled studies in nursing women. **Olanzapine** enters human breast milk, though the kinetics remain to be defined.

Drug Interactions

Given the primary CNS effects of **olanzapine,** caution should be used when combining it with other centrally acting drugs and ethanol.
May enhance the effects of certain antihypertensive agents, but may antagonize the effects of **levodopa** and **dopamine** agonists.
Drugs that induce CYP1A2 or glucuronyl transferase enzymes, such as **omeprazole** and **rifampin,** may increase **olanzapine** clearance. Inhibitors of CYP1A2 may likewise inhibit **olanzapine** clearance despite the fact that **olanzapine** is metabolized by multiple enzyme systems.
Activated charcoal (1g) reduced the C_{max} and AUC of oral **olanzapine** by about 60%. As peak **olanzapine** levels are not typically obtained until about 6h after dosing, charcoal may be a useful treatment for overdose.
Carbamazepine (200mg bid) causes an approximately 50% increase in **olanzapine** clearance, likely because **carbamazepine** is a potent inducer of CYP1A2 activity. Higher daily doses of **carbamazepine** may cause an even greater increase in **olanzapine** clearance.
Fluvoxamine is an inhibitor of CYP1A2 and does decrease the clearance of **olanzapine.** This results in a 54% increase in the **olanzapine** C_{max} in female nonsmokers (may be higher in smokers). The mean increase in **olanzapine** AUC was 52%.
A lower dose of **olanzapine** should be considered.

References

Aichhorn W, Yazdi K, Kravolec K, et al. J Psychopharmacol 2008; 22:923-4.
Ernst CL, Goldberg JF. J Clin Psychiatry 2002; 63(Suppl 4):42-55.
Goldstein DJ, Corbin LA, Fung MC. J Clin Psychpharacol 2000; 20:399-400.
Kasper SC, Mattiuz EL, Swanson SP, et al. J Chromatogr B Biomed Sci Appl 1999; 726:203-9.
McKenna K, Koren G, Tetelbaum M, et al. J Clin Psychiatry 2005; 66:444-9.
Newport DJ, Calamaras MR, DeVane CL, et al. Am J Psychiatry 2007; 164:1214-20.
Rosengarten H, Quartermain D. Pharmacol Biochem Behav 2002; 72:575-9.
Rosenheck R, Perlick D, Bingham S, et al. JAMA 2003; 290:2693-702.
Schenker S, Yang Y, Mattiuz E, et al. Clin Exp Pharmacol Physiol 1999; 26:691-7.

Summary

Pregnancy Category: C
Lactation Category: U

- **Olanzapine** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Olmesartan medoxomil—(Benicar)

International Brand Name—Alteis (France); Benicar (Brazil); Olmec (Argentina); Olmetec (England, France, Germany, Hong Kong, Ireland, Israel, Philippines, Singapore); Votum (Germany)

Drug Class

ACEI/A2R-antagonists; Antihypertensives

Indications

Hypertension

Mechanism	Selectively AT-1 receptor antagonist
Dosage with Qualifiers	Hypertension—begin 20-40mg PO qd if monotherapy, lower if on diuretic; max 40mg/d • **Contraindications**—hypersensitivity to drug or class, pregnancy • **Caution**—hepatic or renal dysfunction, CHF, renal artery stenosis, ACE angioedema, hyponatremia, volume depletion
Maternal Considerations	The published experience with **olmesartan** during pregnancy is limited to a case report noting perinatal renal impairment. The lowest effective dose should be used when **olmesartan** is absolutely required during pregnancy for BP control. ***Side effects*** include severe hypotension, angioedema, hyperkalemia, dizziness, fatigue, URI symptoms, back pain, diarrhea, and dyspepsia.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. **Olmesartan** probably crosses the human placenta. Inhibitors of the renin-angiotensin system as a group cross the human placenta. Adverse fetal effects are reported for the class of drugs across gestation and include cranial hypoplasia, anuria, reversible or irreversible renal failure, death, oligohydramnios, prematurity, IUGR, and PDA. The available case report suggets this is true for **olmesartan**. In those rare instances when these inhibitors are necessary, women should be apprised of the potential hazards and serial ultrasound examinations conducted. If oligohydramnios is detected, **olmesartan** should be discontinued unless lifesaving for the mother, and antenatal surveillance initiated. Oligohydramnios may not appear until after irreversible injury. Neonates with *in utero* exposure should be closely observed for hypotension, oliguria, and hyperkalemia.
Breastfeeding Safety	There is no published experience in nursing women. It is unknown whether **olmesartan** enters human breast milk, though it is secreted at low concentration in rat milk.
Drug Interactions	No clinically relevant interactions identified.
References	Celentano C, Prefumo F, diVera E, et al. Pediatr Nephrol 2008; 23:333-4.
Summary	**Pregnancy Category: C** (1st trimester), **D** (2nd and 3rd trimesters) **Lactation Category: U** • **Olmesartan** and other inhibitors of the renin-angiotensin system should be avoided during pregnancy if possible. • Women planning pregnancy should be switched to another class of antihypertensive agent if at all possible prior to conception. • When the mother's disease requires treatment with **olmesartan,** the lowest doses should be used followed by close monitoring of the fetus.

Olopatadine—(Pataday; Patanol)

International Brand Name—Patanol S (many)

Drug Class	Allergy; Antihistamines, H_1; Ophthalmics

Indications	Allergic conjunctivitis
Mechanism	Selective H_1 receptor antagonist, inhibits mast cell release of histamine
Dosage with Qualifiers	Allergic conjunctivitis—1-2gtt each eye bid 6-8h apart • **Contraindications**—hypersensitivity to drug or class • **Caution**—unknown
Maternal Considerations	There is no published experience with **olopatadine** during pregnancy. ***Side effects*** include dry eyes, headache, burning, eyelid edema, keratitis, hyperemia, rhinitis, and sinusitis.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **olopatadine** crosses the human placenta. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically. Very high multiples of the MRHD are associated with fetal toxicity.
Breastfeeding Safety	There is no published experience in nursing women. It is unknown whether **olopatadine** enters human breast milk, though it has been found in rodent milk. However, considering the dose and route, it is unlikely nursing could result in a clinically significant level in the neonate.
Drug Interactions	No clinically relevant interactions identified.
References	No current relevant references are available.
Summary	**Pregnancy Category: C** **Lactation Category: S** (likely) • **Olopatadine** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Olsalazine—(Dipentum)

International Brand Name—None identified.

Drug Class	Gastrointestinals; Inflammatory bowel disease agents; Salicylates
Indications	Ulcerative colitis
Mechanism	Unknown; appears to work directly on the gut
Dosage with Qualifiers	Ulcerative colitis—500mg PO bid • **Contraindications**—hypersensitivity to drug or class, hypersensitivity to salicylates • **Caution**—renal dysfunction
Maternal Considerations	There are no adequate reports or well-controlled studies of **olsalazine** in pregnant women. Limited published experience consists predominantly of case reports and small series. It suggests that **olsalazine** retains efficacy during pregnancy. ***Side effects*** include hepatotoxicity, interstitial nephritis, pancreatitis, bone marrow suppression, N/V, dyspepsia, diarrhea,

	abdominal pain, arthralgias, bloating, anorexia, itching, fatigue, depression, and dizziness.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. Limited quantities of **olsalazine** and its metabolites cross the human placenta. Epidemiological study is reassuring. Rodent studies conducted at multiples of the MRHD revealed IUGR and delayed skeletal and organ maturation.
Breastfeeding Safety	There are no adequate reports or well-controlled studies in nursing women. In a single study, neither **olsalazine** nor its main active metabolite was detected in breast milk up to 48h after ingestion. However, oral administration to lactating rats in doses 5-20× the MRHD reduced growth in the pups.
Drug Interactions	Increased PT has been reported in patients taking concomitant **warfarin.**
References	Christensen LA. Dan Med Bull 2000; 47:20-41. Miller LG, Hopkinson JM, Motil KJ, et al. J Clin Pharmacol 1993; 33:703-6. Rahimi R, Nikfan S, Rezaie A, Abdollahi M. Reprod Toxicol 2008; 25:271-5. Tennenbaum R, Marteau P, Elefant, et al. Gastroenterol Clin Biol 1999; 23:464-9.
Summary	**Pregnancy Category: C** **Lactation Category: S** (possibly) • **Olsalazine** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Omeprazole—(Losec; Omid; Prilosec; Roweprazol)

International Brand Name—Acidex (Ecuador); Aleprozil (Mexico); Antra (Germany, Italy, Switzerland); Audazol (Spain); Azoran (Mexico); Baromezole (Korea); Desec (Thailand); Domer (Mexico); Dudencer (Indonesia); Duogas (Thailand); Epirazole (Israel); Gasec (Malaysia); Gastec (Argentina); Gastop (Peru); Gastracid (Germany); Gastroloc (Germany); H-Etom (Colombia); Hovizol (Philippines); Hyposec (Israel); Inhibitron (Mexico); Inhipump (Indonesia); Logastric (Belgium); Lomac (India); Lopraz (Israel); Losec (Argentina, Austria, Belgium, Brazil, Bulgaria, Canada, Chile, China, Costa Rica, Czech Republic, Denmark, Dominican Republic, El Salvador, England, Finland, Greece, Guatemala, Honduras, Hong Kong, Hungary, Indonesia, Ireland, Italy, Korea, Malaysia, Mexico, Netherlands, New Zealand, Nicaragua, Norway, Panama, Paraguay, Philippines, Poland, Portugal, Spain, Sweden, Taiwan, Thailand, Uruguay, Venezuela); Losec MUPS (Philippines); Madiprazole (Thailand); Maxor (Australia); Medoprazole (South Africa); Medral (Mexico); Meiceral (Thailand); Mepzol (Korea); Miracid (Thailand); Mopral (France, Mexico); Nocid (Thailand); Ocid (India, Singapore); Ogal (Colombia); Olexin (Mexico); Omed (India, Korea, South Africa); Omedar (Israel); Omelon (Taiwan); OMEP (Germany); Omepral (Japan); Omeprazon (Japan); Omepril (Ecuador); Omeq (Korea); Omesec (Malaysia, Singapore); Omez (Thailand); Omezin (Korea); Omezol (Israel, India); Omezole (Singapore, Taiwan); Omezzol (Ecuador); Omisec (Israel); Omizac (Bahrain, India, Republic of Yemen); OMP (China, Korea); Omprazole (Korea); OMZ (Indonesia); Onexal (Colombia); Opal (Peru); Oprax (Peru); Ozoken (Mexico); Parizac (Spain); Penrazole (Singapore); Peptidin (Colombia); Peptilcer (India); Peptizole (Thailand); Pra-Sec (Korea); Prazidec (Mexico); Prazole (Korea); Probitor (Australia, Malaysia); Proceptin (Singapore); Prohibit (Indonesia); Ramezol (Korea); Result (Korea); Risek (Indonesia); Roweprazol (Costa Rica, Dominican Republic, El Salvador, Guatemala, Honduras, Nicaragua, Panama); Severon (Thailand); Stomacer (Indonesia); Stomec (Thailand); Stozole (India); Suifac (Mexico); Ulcozol (Brazil, Colombia, Peru); Ulnor (Germany); Ulsek (Philippines); Ulsen (Mexico); Vulcasid (Mexico); Wonmp (Korea); Xoprin (Peru); Zatrol (Chile); Zefxon (Thailand); Zenpro (Malaysia, Singapore); Zimor (Singapore); Zoltum (France)

Drug Class	Antiulcer; Gastrointestinals; Proton pump inhibitors
Indications	GERD, GI ulcer, erosive esophagitis, *H. pylori* treatment

Mechanism

Inhibits hydrogen-potassium ATPase in the gastric parietal cells

Dosage with Qualifiers

GERD—20-40mg PO before eating qd ×4-8w, then 10mg PO qd; max 80mg/d
GI ulcer (gastric or duodenal)—40mg PO before eating qd ×4-8w
Erosive esophagitis—20-40mg PO before eating qd ×4-8w, max 80mg/d
H. pylori treatment—20mg PO bid ×10d if combined with **amoxicillin** and **clarithromycin**

NOTE: hepatic dosing.

- **Contraindications**—hypersensitivity to drug or class
- **Caution**—hepatic dysfunction, long-term use

Maternal Considerations

Omeprazole is effective treatment for a number of hypersecretory disorders, and effective preoperative prophylaxis (20-40mg PO qd) against aspiration pneumonitis. While there are no adequate reports or well-controlled studies in pregnant women, **omeprazole** appears to retain its efficacy during pregnancy. Though it increases human myometrial contractility in isolated muscle strips, there are no reports of an increased prevalence of preterm delivery. **Omeprazole** is advocated to lower gastric pH prior to cesarean section, but the results of the randomized trials are inconsistent, perhaps reflecting dose and route of delivery. Further, it and similar agents require 20-30min to take effect. Thus, Bicitra (citric acid/sodium citrate solution), perhaps with **metoclopramide** to enhance lower esophageal sphincter tone, remain agents of choice for emergent procedures.
Side effects include headache, diarrhea, hepatic dysfunction, Stevens-Johnson syndrome, and blood dyscrasias.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **omeprazole** crosses the human placenta. Proton pump inhibitors in general, and **omeprazole** specifically, are not associated with an increased risk of malformations. In the ewe, the F:M ratio approximates 0.5 and is strongly related to the rate of maternal clearance. Rodent studies are generally reassuring, revealing no evidence of teratogenicity despite the use of doses higher than those used clinically. However, embryo and fetal toxicity are noted in some models when multiples of the MRHD are used.

Breastfeeding Safety

There are no adequate reports or well-controlled studies in nursing women. **Omeprazole** enters human breast milk, but milk concentrations are less than 10% of the maternal serum level. Thus, the nursing infant is unlikely to ingest a clinically significant amount.

Drug Interactions

May prolong the elimination of **diazepam, warfarin,** and **phenytoin,** all drugs that are metabolized by oxidation in the liver. There have also been clinical reports of interaction with other drugs metabolized via hepatic CYPs (e.g., benzodiazepines, **cyclosporine, disulfiram**). Patients should be monitored to determine if it is necessary to adjust the dose.
Because of its profound and long-lasting inhibition of gastric acid secretion, **omeprazole** may interfere with absorption of drugs where gastric pH is an important determinant of their bioavailability (e.g., **ampicillin,** iron salts, and **ketoconazole**). However, antacids were used in the clinical trials with **omeprazole.**

Use with **clarithromycin** increases the plasma levels of **omeprazole, clarithromycin,** and 14-hydroxy-clarithromycin.

References

Ching MS, Morgan DJ, Mihaly GW, et al. Dev Pharmacol Ther 1986; 9:323-31.
Diav-Citrin O, Arnon J, Shechtman S, et al. Aliment Pharmacol Ther 2005; 21:269-75.
Kallen BA. Eur J Obstet Gynecol Reprod Biol 2001; 96:63-8.
Lin CJ, Huang CL, Hsu HW, Chen TL. Acta Anaesthesiol Sin 1996; 34:179-84.
Marshall JK, Thompson AB, Armstrong D. Can J Gastroenterol 1998; 12:225-7.
Nikfar S, Abdollahi M, Moretti ME, et al. Dig Dis Sci 2002; 47:1526-9.
Ruigomez A, Garcia Rodriguez LA, Cattaruzzi C, et al. Am J Epidemiol 1999; 150:476-81.
Tripathi A, Somwanshi M, Singh B, Bajaj P. Can J Anaesth 1995; 42:797-800.
Yildirim K, Sarioglu Y, Kaya T, et al. Life Sci 2001; 69:435-42.

Summary

Pregnancy Category: C
Lactation Category: S (likely)

- **Omeprazole** should be used during pregnancy only if the benefit justifies the unknown potential perinatal risk.

Ondansetron—(Zofran)

International Brand Name—Bryterol (Colombia); Cedantron (Indonesia); Emeset (China, India, Korea); Modifical (Colombia); Narfoz (Indonesia); Onsia (Thailand); Sakisozin (Japan); Vomceran (Indonesia); Zetron (Thailand); Zofran Zydis (Korea); Zofron (Greece); Zophren (France)

Drug Class

Antiemetics; Serotonin receptor antagonists

Indications

Severe N/V

Mechanism

Selectively inhibits the 5-HT_3 receptors

Dosage with Qualifiers

Severe N/V—*postoperative:* 4mg IM/IV ×1; *post-chemotherapy:* 24mg PO or 32mg IV 30min before initiating chemotherapy; *post–radiation therapy:* begin 8mg PO 1-2h before radiation, continue q8h ×2d

NOTE: renal dosing; also available in orally disintegrating tablets.

- **Contraindications**—hypersensitivity to drug or class
- **Caution**—hepatic dysfunction

Maternal Considerations

Ondansetron is effective for N/V of pregnancy, but the published experience is inadequate to yet consider it first-line therapy. A single IV dose (4mg) given prophylactically significantly reduces the N/V after cesarean delivery, though the same may be accomplished with other less expensive antiemetic agents. Since **ondansetron** (0.1mg/kg IV ×1) significantly reduces the pruritus associated with intrathecal **morphine** or **fentanyl,** some clinicians choose this agent as their antiemetic of choice no matter what the cost; others use less expensive alternative agents. It is no better than **metoclopramide** as prophylaxis for N/V after minor gynecologic surgery, but superior to it for patients undergoing chemotherapy. Recent study indicates that epidural **ondansetron**

is more effective preventing intrathecal **morphine**–associated post–cesarean section pruritus and nausea than IV **ondansetron.** However, it is apparently not effective when given IV for prophylaxis when **fentanyl** is used during labor.
Side effects include bronchospasm, extrapyramidal symptoms, oculogyric crisis, headache, fatigue, constipation, diarrhea, agitation, pruritus, and dizziness.

Fetal Considerations ..... There are no adequate reports or well-controlled studies in human fetuses. It is not known whether **ondansetron** crosses the human placenta. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically.

Breastfeeding Safety ..... There is no published experience in nursing women. It is unknown whether **ondansetron** enters human breast milk. It is detectable in rat milk.

Drug Interactions ..... Clearance of **ondansetron** was significantly increased and blood concentrations decreased in patients treated with potent inducers of CYP3A4 (i.e., **carbamazepine, phenytoin, rifampicin**). However, no dosage adjustment is recommended.

References .....

Abouleish EI, Rashid S, Haque S, et al. Anaesthesia 1999; 54:479-82.
Han DW, Hong SW, Kwon JY, et al. Acta Obstet Gynecol Scand 2007; 86:683-7.
Koren G, Maltepe C. J Obstet Gynaecol 2004; 24:530-3.
Magee LA, Mazzotta P, Koren G. Am J Obstet Gynecol 2002; 185:S256-61.
Monagle J, Barnes R, Goodchild C, Hewitt M. Eur J Anaesthesiol 1997; 14:604-9.
Wells J, Paech MJ, Evans SF. Int J Obstet Anesth 2004; 13:35-9.
Yeh HM, Chen LK, Lin CJ, et al. Anesth Analg 2000; 91:172-5.

Summary .....

Pregnancy Category: B
Lactation Category: U

- **Ondansetron** is a reasonable (though relatively expensive) prophylactic agent for the prevention of postoperative N/V. It is indicated for the "rescue" treatment of postoperative N/V that fails to respond to first-line agents.
- It is superior to most first-line agents for the treatment of N/V associated with chemotherapy.

Oprelvekin—(Neumega)

International Brand Name—Neumega (Argentina, Brazil, Chile, Colombia, Mexico)

Drug Class ..... Hematopoietic agents

Indications ..... Myelosuppressive chemotherapy for nonmyeloid malignancies at high risk of severe thrombocytopenia

Mechanism ..... Directly stimulates hematopoietic stem cells and megakaryocyte progenitor cells

Dosage with Qualifiers ..... Myelosuppressive chemotherapy—50mcg/kg SC qd beginning 6-24h after completing chemotherapy; monitor platelet counts at

time of expected nadir; continue until postnadir platelet count >50,000cells/ml

NOTE: should be used within 3h of reconstitution.

- **Contraindications**—hypersensitivity to drug or class
- **Caution**—CHF, arrhythmia, chronic diuretic therapy, chemotherapy >5d duration, chemotherapy associated with delayed myelosuppression

Maternal Considerations

Oprelvekin is genetically engineered IL-11. There is no published experience with it during pregnancy.
Side effects include fluid retention, weight gain, tachycardia, palpitations, atrial fibrillation, blurred vision, papilledema, transient rash, oral monilia, dyspnea, and pleural effusion.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. IL-11 is an endogenous cytokine with many actions and interactions. **Oprelvekin** is embryocidal in some rodents at doses analogous to those used in humans. IUGR and reduced ossification are also reported.

Breastfeeding Safety

There is no published experience in nursing women. It is unknown whether **oprelvekin** enters human breast milk.

Drug Interactions

No clinically relevant interactions identified.

References

There are no current relevant references.

Summary

Pregnancy Category: C
Lactation Category: U
- **Oprelvekin** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Orlistat—(Xenical)

International Brand Name—Xenical (Hong Kong, Indonesia, Israel, Korea, Philippines, Singapore, Thailand)

Drug Class

Gastrointestinals; Lipase inhibitors

Indications

Obesity

Mechanism

Inhibits gastric and pancreatic lipases

Dosage with Qualifiers

Obesity—120mg PO tid; take during meals with fat

*NOTE: separate **orlistat** from fat-soluble vitamin supplements by at least 2h.*

- **Contraindications**—hypersensitivity to drug or class, cholestasis, chronic malabsorption syndrome
- **Caution**—history of renal stones

Maternal Considerations

Orlistat is a reversible lipase inhibitor for obesity management that acts by inhibiting the absorption of dietary fats. It is also an antiangiogenic agent with a novel mechanism of action: **orlistat** prevents the display of vascular endothelial growth factor (VEGF) receptor (VEGFR2/KDR/Flk1) on the endothelial cell surface.
There is no published experience with it during pregnancy. It has

	been suggested but unproven that **orlistat** might interfere with the absorption of oral contraceptives and thus diminish their efficacy. ***Side effects*** include diarrhea, flatulence, steatorrhea, fecal incontinence, and N/V.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **orlistat** crosses the human placenta. However, the mother absorbs little systemically (peak plasma levels at the limit of detection). Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically. Some dilation of the cerebral ventricles was noted.
Breastfeeding Safety	There is no published experience in nursing women. Considering the maternal systemic level, it is unlikely a clinically relevant concentration of **orlistat** enters human breast milk. It is not known whether the milk components are altered.
Drug Interactions	Preliminary data indicate a reduction in **cyclosporine** levels when **orlistat** is co-administered. A pharmacokinetics study noted a 30% reduction in **β-carotene** absorption. **Orlistat** also inhibited absorption of vitamin E by approximately 60%. In 20 normal-weight female subjects, treatment with **orlistat** (120mg tid ×23d) had no effect on ovulation suppression.
References	Peleg R. Isr Med Assoc J 2000; 2:712. Waterman IJ, Emmison N, Sattar N, Dutta-Roy AK. Placenta 2000; 21:813-23.
Summary	**Pregnancy Category: B** **Lactation Category: S** (likely) • Though there are no clear contraindications for **orlistat** during pregnancy, there are also no indications for a weight loss regimen that would necessitate it.

Orphenadrine—(Banflex; Flexoject; Flexon; Flexor; Marflex; Mio-Rel; Myolin; Myophen; Myotrol; Neocyten; Noradex; Norflex; O'Flex; Orflagen; Orfro; Orphenate; Qualaflex; Tega-Flex)

International Brand Name—Biorfen (England); Biorphen (England); Disipal (Canada, Denmark, England, Norway, Sweden); Distalene (Argentina); Erilax (Korea); Flexen (Peru); Neekxin (Korea); Neexin (Korea); Norflex (Belgium, Canada, Costa Rica, Denmark, Dominican Republic, El Salvador, Guatemala, Honduras, Hong Kong, Kenya, Malaysia, Mauritius, Mexico, Nigeria, Panama, Peru, South Africa, Sweden, Taiwan, Thailand, Uruguay, Venezuela); Opheraxcin (Korea); Opheryl (Korea); Orpherin (Korea); Plenactol (Chile); Prolongatum (Sweden); Slaxin (Korea)

Drug Class	Muscle relaxants
Indications	Muscle spasm
Mechanism	Unknown
Dosage with Qualifiers	Muscle spasm—60-100mg PO bid; also available for injection *NOTE: often combined with **caffeine** and **aspirin.*** • **Contraindications**—hypersensitivity to drug or class, glaucoma, pyloric or duodenal obstruction, myasthenia gravis • **Caution**—CV disease, sulfite allergy, arrhythmia

Maternal Considerations	There is no published experience with **orphenadrine** during pregnancy. ***Side effects*** include drowsiness, N/V, dry mouth, aplastic anemia, light-headedness, and headache.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **orphenadrine** crosses the human placenta. There is some passage across the ovine placenta. Rodent teratogenicity studies have not been conducted.
Breastfeeding Safety	There is no published experience in nursing women. It is unknown whether **orphenadrine** enters human breast milk.
Drug Interactions	No clinically relevant interactions identified.
References	Yoo SD, Axelson JE, Rurak DW. J Chromatogr 1986; 378:385-93.
Summary	**Pregnancy Category: C** **Lactation Category: U** • **Orphenadrine** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Oseltamivir—(Tamiflu)

International Brand Name—Tamiflu (Canada, England, France, Hong Kong, Ireland, Israel, Korea, Philippines, Singapore)

Drug Class	Antivirals
Indications	Influenza A and B virus prophylaxis and treatment
Mechanism	Blocks influenza neuraminidase, altering virus aggregation and release
Dosage with Qualifiers	Influenza A/B prophylaxis—75mg PO qd; initiate at outbreak Influenza A/B treatment—75mg PO bid ×5d beginning within 48h of symptoms *NOTE: renal dosing.* • **Contraindications**—hypersensitivity to drug or class • **Caution**—hepatic dysfunction
Maternal Considerations	There is no published experience with **oseltamivir** during pregnancy. Evidence of evolving viral resistance is emerging. Prophylaxis is not a substitute for vaccination (CDC Immunization Practices Advisory Committee). ***Side effects*** include N/V, bronchitis, insomnia, and vertigo.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. **Oseltamivir** does not apparently cross the human placenta. Even when the isolated cotyledon is perfused at 600-800 times the normal plasma level, the clearance index was only 0.13. Rodent studies are reassuring, revealing no evidence of teratogenicity despite the use of doses higher than those used clinically. Maternal toxicity is noted along with a nonsignificant increase in skeletal abnormalities.
Breastfeeding Safety	There is no published experience in nursing women. It is unknown whether **oseltamivir** enters human breast milk.

Drug Interactions

Information derived from pharmacology and pharmacokinetics studies suggests clinically significant drug interactions are unlikely. Clinically important drug interactions involving competition for renal tubular secretion are unlikely due to the known safety margin for most of these drugs, the elimination characteristics of **oseltamivir** carboxylate (glomerular filtration and anionic tubular secretion), and the excretion capacity of these pathways.
Probenecid increases **oseltamivir** by about 2-fold due to a decrease in active anionic tubular secretion in the kidney. However, no dose adjustments are required because of the safety margin.

References

Worley KC, Roberts SW, Bawdon RE. Infect Dis Obstet Gynecol 2008; 927574.

Summary

Pregnancy Category: C
Lactation Category: U
- **Oseltamivir** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Oxacillin—(Bactocill; Dicloxal OX; Prostaphlin; Staphaloxin; Wydox)

International Brand Name—Bristopen (France); Dicloxal ox (Peru); Ekvacillin (Denmark); Oksin (Bulgaria); Oxacil (Brazil); Penstapho (Belgium, Italy); Prostafilina (Colombia, Ecuador, Venezuela); Prostaphlin (Hungary, Philippines, Taiwan); Stafcil (Philippines); Staficilin-N (Brazil); Stapenor (Austria, Germany); Wydox (Philippines)

Drug Class

Antibiotics; Penicillins

Indications

Bacterial infection, especially with penicillinase-producing *Staphylococcus*

Mechanism

Bactericidal—inhibits cell wall synthesis

Dosage with Qualifiers

Bacterial infection—1-2g IV/IM q4-6h, or 500-1000mg PO q4-6h

NOTE: renal dosing.

- **Contraindications**—hypersensitivity to drug or class
- **Caution**—unknown

Maternal Considerations

Oxacillin is penicillinase-resistant, acid-resistant, semisynthetic penicillin suitable for oral administration. There is a long clinical experience with **oxacillin** during pregnancy.
Side effects include neutropenia, granulocytopenia, eosinophilia, hemolytic anemia, thrombocytopenia, N/V, diarrhea, pseudomembranous colitis, oral lesions, fever, chills, rash, lethargy, urticaria, interstitial nephritis, and elevated LFTs.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. Most penicillin compounds cross the human placenta. There is no evidence **oxacillin** is teratogenic in humans after a long clinical experience. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically. There are a number of interesting studies in rodents suggesting *in utero* exposure alters *in utero* and postnatal immune responses. The implications are unclear.

Breastfeeding Safety

There are no adequate reports or well-controlled studies in nursing women. **Oxacillin** is concentrated in human breast milk

exceeding the typical MIC, making it suitable for the treatment of puerperal mastitis. Unfortunately, many staphylococci are now resistant. Though it is generally considered compatible with breastfeeding, **clindamycin** is a better selection.

Drug Interactions

Tetracyclines and bacteriostatic antibiotics may antagonize the bactericidal effect of penicillin, and their combined use should be avoided.
Blood levels may be prolonged by **probenecid,** which blocks the renal tubular secretion of penicillins.

References

Carneiro LA, Queiroz ML, Merquior VL. J Med Microbiol 2004; 53:761-8.
Czeizel AE, Rockenbauer M, Sorensen HT, Olsen J. Scand J Infect Dis 1999; 31:311-2.
Dostal M, Horka I, Tuma O, Soukupova D. Funct Dev Morphol 1994; 4:67-75.
Peiker G, Schroder S. Pharmazie 1986; 41:793-5.

Summary

Pregnancy Category: B
Lactation Category: S

- **Oxacillin** is an alternative for the treatment of puerperal mastitis.
- There are alternative agents for almost all indications.

Oxaprozin—(Daypro)

International Brand Name—Daypro (Canada); Deflam (South Africa); Duraprox (Chile, Portugal)

Drug Class

Analgesics, non-narcotic; NSAIDs

Indications

Osteoarthritis and rheumatoid arthritis, mild to moderate pain

Mechanism

Inhibits cyclooxygenase and lipoxygenase, leading to reduced prostaglandin synthesis

Dosage with Qualifiers

Osteoarthritis or rheumatoid arthritis—1200mg PO qd with food; max 1800mg/d
Mild to moderate pain—1200mg PO qd

- **Contraindications**—hypersensitivity to drug or class, hypersensitivity to aspirin, aspirin/NSAID-induced asthma
- **Caution**—hypertension, CHF, history of GI bleeding, nasal polyps

Maternal Considerations

Oxaprozin is an NSAID with anti-inflammatory, analgesic, and antipyretic properties. There is no published experience with **oxaprozin** during pregnancy.
Side effects include fluid retention, thrombocytopenia, agranulocytosis, acute renal failure, interstitial nephritis, hepatotoxicity, bronchospasm, N/V, dyspepsia, abdominal pain, headache, dizziness, rash, drowsiness, elevated LFTs, and tinnitus.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **oxaprozin** crosses the human placenta. Other NSAIDs cross the human placenta and are associated with decreased fetal urination and ductal constriction. Malformed fetuses were observed in rabbits but not mice treated

with doses analogous to the human. Pup survival was also reduced.

Breastfeeding Safety

There is no published experience in nursing women. It is unknown whether **oxaprozin** enters human breast milk. It does enter rodent milk.

Drug Interactions

Concurrent use of **aspirin** is not recommended because **oxaprozin** displaces salicylates from plasma protein binding sites and could increase the risk of salicylate toxicity.
Decreases **methotrexate** clearance by >⅓. A lower **methotrexate** dose may be considered.
Alters the pharmacokinetics of **enalapril** [significant decrease in dose-adjusted AUC(0-24) and C_{max}] and its active metabolite enalaprilat [significant increase in dose-adjusted AUC(0-24)]. Adjust dosage carefully.
May reduce the natriuretic effect of **furosemide** and thiazides in some patients secondary to inhibition of renal prostaglandin synthesis. The patient should be observed closely for signs of renal failure during concomitant therapy with NSAIDs.
May elevate plasma **lithium** levels about 15% and a reduce renal **lithium** clearance about 20%, presumably secondary to inhibition of renal prostaglandin synthesis. Patients should be observed carefully for signs of **lithium** toxicity when **lithium** and NSAIDs are administered concurrently.
The effects of **warfarin** and NSAIDs on GI bleeding are synergistic, such that users of both drugs together have a risk of serious GI bleeding higher than that of users of either drug alone.
The total body clearance is reduced by 20% in subjects receiving either **cimetidine** or **ranitidine.** A change of clearance of this magnitude lies within the range of normal variation and is unlikely to produce a clinically detectable difference in the outcome of therapy.
Patients taking β-blockers may experience transient increases in sitting and standing BP after 14d. Routine BP monitoring should be considered in these patients.
False-positive urine immunoassay screening tests for benzodiazepines have been reported due to lack of specificity of the screening tests. False-positive results may be continue for several days after discontinuation of **oxaprozin.**

References

No current relevant references exist.

Summary

Pregnancy Category: C
Lactation Category: U

- **Oxaprozin** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.
- There are alternative agents for which there is more experience regarding use during pregnancy and lactation.

Oxazepam—(Murelax; Serax; Wakezepam)

International Brand Name—Adumbran (Argentina, Austria, Germany, Greece, Portugal, Spain); Alepam (Australia, New Zealand, Taiwan); Alopam (Denmark, Finland, Norway, Sweden); Anastil (Venezuela); Anxiolit (Austria, Greece, Switzerland); Anxiolit Retard (Switzerland); Apo-Oxazepam (Canada); Azutranquil (Germany); Benzotran (New Zealand); Durazepam (Germany); Enidrel (Argentina); Hilong (Japan); Medopam (South Africa); Nesontil (Argentina); Noctazepam (Germany); Noripam (South Africa); Oksazepam (Poland); Opamox (Finland); Oxahexal (Germany); Oxaline (South Africa); Oxapam (Italy); Oxepam (Finland, Italy); Ox-Pam (New Zealand); Praxiten (Argentina, Austria, Greece); Primizum (Japan); Propax (Japan); Psiquiwas (Spain, Taiwan); Purata (South Africa); Quilibrex (Italy); Serefar (Uruguay); Serepax (Australia, Chile, Denmark, Greece, India, New Zealand, Norway, South Africa); Seresta (Belgium, France, Netherlands, Switzerland); Simazepan (Paraguay); Sobile (Spain); Sobril (Norway, Sweden); Tazepam (Bulgaria); Vaben (Israel); Wakazepam (Japan)

Drug Class ..... Anxiolytics; Benzodiazepines

Indications ..... Anxiety, alcohol withdrawal

Mechanism ..... Binds to benzodiazepine receptors, augmenting GABA responses

Dosage with Qualifiers .....

Anxiety, short-term relief—10-30mg PO tid or qid
Alcohol withdrawal—15-30mg PO tid or qid

- **Contraindications**—hypersensitivity to drug or class, psychosis
- **Caution**—unknown

Maternal Considerations .....

There are no adequate reports or well-controlled studies in pregnant women. Alcoholism is an often-unrecognized problem during pregnancy that poses a clear hazard to mother and child. **Oxazepam** has a wide safety range compared to other benzodiazepines. Some also consider **oxazepam** a second-line agent for the treatment of pruritus during pregnancy, despite the lack of study for this indication. It is highly effective for the short-term relief of anxiety. Physical and psychological dependency is a risk with chronic usage.
Side effects include nausea, hepatic dysfunction, jaundice, leukopenia, dizziness, syncope, vertigo, headache, edema, tremor, rash, and lethargy.

Fetal Considerations .....

There are no adequate reports or well-controlled studies in human fetuses. **Oxazepam** crosses the human placenta at a slower rate than **diazepam,** reaching an F:M ratio during the 1st trimester of 0.5 after 4h. The impact of benzodiazepines in human pregnancy appears in general to have been overestimated. Long-term follow-up studies are for the most part reassuring. Fetal exposure can be minimized by qid dosing to reduce peak levels. Subtle behavioral affects of *in utero* **oxazepam** exposure are reported in rodents.

Breastfeeding Safety .....

There are no adequate reports or well-controlled studies in nursing women. **Oxazepam** enters human breast milk in low concentrations unlikely to be clinically significant for the breastfeeding infant.

Drug Interactions ..... No clinically relevant interactions identified.

References .....

Drugs and Pregnancy Study Group. Ann Pharmacother 1994; 28:17-20.
Fiore M, Dell'Omo G, Alleva E, Lipp HP. Psychopharmacology 1995; 122:72-7.
McElhatton PR. Reprod Toxicol 1994; 8:461-75.
Jorgensen NP, Thurmann-Nielsen E, Walstad RA. Acta Obstet Gynecol Scand 1988; 67:493-7.
Wretlind M. Eur J Clin Pharmacol 1987; 33:209-10.

Summary

Pregnancy Category: D
Lactation Category: S (likely)

- **Oxazepam** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.
- Though unnecessary treatment should be avoided, appropriate candidates should not be denied therapy solely because they are pregnant.

Oxcarbazepine—(Trileptal)

International Brand Name—Oxrate (India); Timox (Germany); Trileptal (Austria, Bulgaria, China, Colombia, Denmark, England, Finland, France, Greece, Hong Kong, Indonesia, Ireland, Israel, Korea, Malaysia, Mexico, Netherlands, Peru, Philippines, Switzerland); Trileptin (Israel)

Drug Class

Anticonvulsants

Indications

Seizure disorder

Mechanism

Unknown; blocks voltage-sensitive sodium channels

Dosage with Qualifiers

Seizure disorder—begin at 300mg PO bid, increasing by 300mg/d q3d; max 2400mg/d

NOTE: renal dosing.

- **Contraindications**—hypersensitivity to drug or class
- **Caution**—renal dysfunction

Maternal Considerations

Oxcarbazepine is the 10-keto analogue of **carbamazepine** and thus an enzyme-inducing agent. Either a higher dose oral contraceptive or a second method of contraception is recommended. Planned pregnancy and counseling on the importance of folate supplementation and medication adherence are important. There are no adequate reports or well-controlled studies in pregnant women. Maternal levels do decline with advancing gestation, suggesting the need for a dose adjustment. Vitamin K (10mg qd) is recommended for the last 4w of gestation in women taking enzyme-inducing agents such as **carbamazepine, oxcarbazepine, phenobarbital, phenytoin,** and **topiramate.** ***Side effects*** include hyponatremia, thrombocytopenia, leukopenia, Stevens-Johnson syndrome, toxic epidermal necrolysis, N/V, dyspepsia, abdominal pain, somnolence, dizziness, diplopia, fatigue, nystagmus, acne, alopecia, and elevated LFTs.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. **Oxcarbazepine** crosses the human placenta, reaching an F:M ratio approximating unity with the placenta taking an active role in its metabolism. The frequency of neonatal bleeding complications is not increased, calling into question the necessity of vitamin K supplementation. **Oxcarbazepine** is closely related structurally to **carbamazepine,** which is considered teratogenic in humans. Polytherapy increases the risk. If feasible, the number of agents used during pregnancy should be reduced. Rodent studies performed at doses analogous to the human demonstrate embryo lethality, IUGR, and a variety of malformations (craniofacial, CV, and skeletal).

Breastfeeding Safety

There are no adequate reports or well-controlled studies in nursing women. Though the concentrations of **oxcarbazepine**

and its major metabolites in human breast milk are low, and neonatal concentrations decline despite breastfeeding, periodic monitoring of the infant concentration is suggested by some.

Drug Interactions

May inhibit CYP2C19 and induce CYP3A4/5 with potentially important effects on plasma concentrations of other drugs.
CYP3A4 and CYP3A5 are responsible for the metabolism of dihydropyridine calcium antagonists and oral contraceptives; co-administration of **oxcarbazepine** results in a lower plasma concentration of these drugs.
Several AEDs that are CYP inducers can decrease the plasma concentrations of **oxcarbazepine** and its 10-monohydroxy (MHD) metabolite. Strong inducers of CYPs (i.e., **carbamazepine, phenobarbital, phenytoin**) have been shown to decrease MHD plasma levels by 29-40%.
Carbamazepine decreases the MHD concentration by some 40%.
Phenobarbital increases mean **oxcarbazepine** levels by 14% and decreases MHD levels by 25%.
Phenytoin levels increase up to 40% when **oxcarbazepine** is given at doses above 1200mg/d. Therefore, a decrease in the dose of **phenytoin** may be required.
Influences the plasma concentrations of **ethinyl estradiol** (EE) and levonorgestrel (LNG). The mean AUC values of EE were decreased by 48% in one study and 52% in another study. The mean AUC values of LNG were decreased by 32% in one study and 52% in another study. Thus, use of **oxcarbazepine** with oral contraceptives may render them less effective; a secondary method should be used.
The AUC of **felodipine** was lowered by 28%.
Verapamil decreased the MHD levels by approximately 20%.

References

Bruno MK, Harden CL. Curr Treat Options Neurol 2002; 4:31-40.
Bulau P, Paar WD, von Unruh GE. Eur J Clin Pharmacol 1988; 34:311-3.
Christensen J, Sabers A, Sidenius P. Neurology 2006; 67:1497-9.
Kaaja E, Kaaja R, Matila R, Hiilesmaa V. Neurology 2002; 58:549-53.
Mazzucchelli I, Onat FY, Ozkara C, et al. Epilepsia 2006; 47:504-9.
Myllynen P, Pienimaki P, Jouppila P, Vahakangas K. Epilepsia 2001; 42:1482-5.
Pienimaki P, Lampela E, Hakkola J, et al. Epilepsia 1997; 38:309-16.

Summary

Pregnancy Category: C
Lactation Category: S (likely)

- **Oxcarbazepine** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.
- As for most psychotropic drugs, monotherapy and the lowest effective quantity, given in divided doses to minimize the peaks, can minimize the risks.

Oxiconazole—(Oxistat; Oxizole)

International Brand Name—Derimine (Japan); Myfungar (Czech Republic, Germany, Mexico, Switzerland); Oceral (Austria, Portugal, Switzerland); Oceral GB (Germany); Okinazole (Japan); Oxistat (Argentina, Costa Rica, Dominican Republic, El Salvador, Guatemala, Honduras, Mexico, Nicaragua, Panama); Oxitrat (Brazil); Oxizole (Canada); Sylos Vaginal Tab (Korea)

Drug Class

Antifungals; Dermatologics

Indications	Skin fungal infection due to *Epidermophyton floccosum, T. mentagrophytes, T. rubrum, Malassezia furfur*
Mechanism	Inhibits ergosterol biosynthesis, which is critical for cellular membrane integrity
Dosage with Qualifiers	Skin fungal infection—apply to affected and surrounding area bid *NOTE: available in cream or lotion; for dermatologic use only.* • **Contraindications**—hypersensitivity to drug or class, vaginal or ophthalmologic infections • **Caution**—unknown
Maternal Considerations	There is no published experience with **oxiconazole** during pregnancy. However, <1% of the applied dose is absorbed systemically. ***Side effects*** include skin irritation and itching.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **oxiconazole** crosses the human placenta. However, the maternal systemic concentration is not likely to reach a clinically relevant level. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically.
Breastfeeding Safety	There is no published experience in nursing women. It is unknown whether **oxiconazole** enters human breast milk. Because <1% of the applied dose is absorbed systemically, it is unlikely the breastfeeding newborn would absorb a clinically relevant amount.
Drug Interactions	No clinically relevant interactions identified.
References	There are no current relevant references.
Summary	**Pregnancy Category: B** **Lactation Category: S** • **Oxiconazole** should be used during pregnancy and lactation if the benefit justifies the potential perinatal risk.

Oxtriphylline—(Brondecon; Choledyl; Cholegyl)

International Brand Name—Apo Oxtriphyllin (Canada); Brondecon-PD Elixir (Australia); Cholecyl (Spain); Choledyl (Canada); Choledyl Pediatrico (Costa Rica, El Salvador, Guatemala, Honduras, Nicaragua, Panama); Choledyl Retard (Greece); Choledyl SA (Canada); Euspirax (Germany); Euspirax Forte (Germany); Euspirax Retard (Germany); Theocolin (Japan)

Drug Class	Bronchodilators; Xanthines
Indications	Bronchospasm, asthma, bronchitis, emphysema
Mechanism	Direct smooth muscle relaxation, possibly by phosphodiesterase inhibition
Dosage with Qualifiers	Bronchospasm in otherwise healthy nonsmoking adults—7.8mg/kg PO load, then 4.7mg/kg PO q8h; target range is 10-20mcg/ml *NOTE: check standard reference as dose varies by age and whether or not the patient is already taking **theophylline;** laboratory monitoring is essential to assure appropriate dosing.*

*NOTE: 0.8mg **oxtriphylline** = 0.5mg **theophylline.***

- **Contraindications**—hypersensitivity to drug or class, active peptic ulcer disease, untreated seizure disorder
- **Caution**—arrhythmias

Maternal Considerations

Oxtriphylline is the choline salt of **theophylline.** Its clearance is increased in cigarette smokers, in patients with CHF and hepatic dysfunction, and in those taking a variety of other drugs such as **cimetidine, erythromycin, lithium,** oral contraceptives, and **phenytoin.** There is no published experience with **oxtriphylline** during pregnancy. See **Theophylline.**
Side effects include arrhythmias, palpitations, hypotension, convulsions, N/V, epigastric pain, headaches, restlessness, insomnia, frequent urination, tachypnea, and hyperglycemia.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **oxtriphylline** crosses the human placenta. Rodent studies have not been conducted. See **Theophylline.**

Breastfeeding Safety

There is no published experience in nursing women. While it is unknown whether **oxtriphylline** enters human breast milk, **theophylline** is distributed into breast milk and may cause irritability or other signs of toxicity in nursing infants (see **Theophylline**).

Drug Interactions

See **Theophylline.**

References

There are no current relevant references. See **Theophylline.**

Summary

Pregnancy Category: C
Lactation Category: U

- **Oxtriphylline** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Oxybutynin—(Ditropan)

International Brand Name—Cystonorm (Germany); Cystrin (England, Ireland); Delifon (Colombia); Ditropan (Argentina, Austria, Belgium, Canada, Czech Republic, England, Finland, France, Greece, Hungary, Ireland, Italy, Korea, Poland, Portugal, South Africa, Spain, Switzerland, Taiwan); Ditropan XL (Canada); Diutropin (Thailand); Dridase (Germany, Netherlands); Driptane (Bulgaria, Philippines); Frenurin (Brazil); Gradual (Uruguay); Iliaden (Peru); Lenditro (South Africa); Lyrinel XL (England, Ireland); Mutum CR (Colombia); Nefryl (Mexico); Novitropan (Israel); Odranal (Chile); Oxyb (Germany); Oxyban (Taiwan); Oyrobin (Korea); Reteven (Venezuela); Tavor (Mexico); Tropan (India); Uricont (Israel); Uroflax (Paraguay); Zatur Ge (France)

Drug Class

Anticholinergics; Antispasmodics

Indications

Bladder spasm

Mechanism

Direct antispasmodic effect; inhibits muscarinic effects of ACh

Dosage with Qualifiers

Bladder spasm—5mg PO bid or tid; max 5mg PO qid

- **Contraindications**—hypersensitivity to drug or class, glaucoma, ulcerative colitis, GI obstruction or ileus, myasthenia gravis
- **Caution**—hepatic or renal dysfunction

Maternal Considerations

There is no published experience with **oxybutynin** during pregnancy.

	Side effects include tachycardia, vasodilation, rash, constipation, decreased sweating, dry mouth, drowsiness, hallucinations, restlessness, cycloplegia, and insomnia.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. It is not known whether **oxybutynin** crosses the human placenta. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically.
Breastfeeding Safety	There is no published experience in nursing women. It is unknown whether **oxybutynin** enters human breast milk.
Drug Interactions	Use with other anticholinergic drugs or agents that produce dry mouth, constipation, somnolence (drowsiness), and/or other anticholinergic-like effects may increase the frequency and/or severity of such effects. Anticholinergic agents may alter the absorption of some orally administered drugs due to anticholinergic effects on GI motility. This may be of special concern for drugs with a narrow therapeutic index. **Ketoconazole,** a potent CYP3A4 inhibitor, increases the mean **oxybutynin** plasma concentrations some 2-fold. Other inhibitors of CYP3A4, such as antimycotic agents (e.g., **itraconazole, miconazole**) or macrolide antibiotics (e.g., **clarithromycin, erythromycin**), may have the same or greater effect. Caution should be used.
References	There are no current relevant references.
Summary	**Pregnancy Category: B** **Lactation Category: U** • **Oxybutynin** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Oxychlorosene—(Clorpactin WCS-90)

International Brand Name—None identified.

Drug Class	Anesthetics, topical
Indications	Interstitial cystitis, wound infection
Mechanism	Stabilized organic derivative of hypochlorous acid
Dosage with Qualifiers	Interstitial cystis—bladder instillations with a 0.4% solution in water Wound care—add powder to saline, allow to stand 2-3min before applying to gauze compresses; use tid or qid • **Contraindications—**hypersensitivity to drug or class, site of the infection not exposed to direct contact with the solution, systemic use • **Caution**—unknown
Maternal Considerations	**Oxychlorosene** is used as a topical antiseptic for treating localized infections, particularly when resistant organisms are present. The greatest published experience is for the treatment of interstitial cystitis. However, it has also proved useful for wound

	débridement to promote secondary healing. There are no adequate reports or well-controlled studies of **oxychlorosene** in pregnant women. Any systemic absorption is likely minimal. ***Side effects*** include chemical cystitis.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **oxychlorosene** crosses the human placenta. Any systemic absorption is likely minimal.
Breastfeeding Safety	There are no adequate reports or well-controlled studies in nursing women. It is unknown whether **oxychlorosene** enters human breast milk. Any systemic absorption of hypochlorous acid is likely minimal.
Drug Interactions	No clinically relevant interactions identified.
References	There is no published experience in pregnancy or during lactation.
Summary	**Pregnancy Category: C** **Lactation Category: S** (likely) • **Oxychlorosene** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Oxycodone—(OxyContin [slow release]; Roxicodone [immediate release])

International Brand Name—Codix 5 (Colombia); Endone (Australia); Eubine (France); Eucodalum (Poland); Oxicontin (Colombia); Oxycod (Israel); OxyContin (Argentina, Brazil, Canada, Chile, Denmark, Ecuador, England, Ireland, Israel, Mexico, Paraguay, Peru); Oxycontin CR (Korea); Oxycontin LP (France); Oxygesic (Germany); Oxy IR (Canada); Oxynorm (France); Supeudol (Canada)

Drug Class	Analgesics, narcotic
Indications	Moderate to severe pain
Mechanism	Binds to opiate receptors
Dosage with Qualifiers	Moderate to severe pain—*immediate release:* 5-30mg PO q4h prn; *slow release:* 10mg bid, increase as needed *NOTE: hepatic and renal dosing.* *NOTE: tablets are to be swallowed whole, not broken, chewed, or crushed to release the drug rapidly. A fatal overdose may result.* • **Contraindications**—hypersensitivity to drug or class • **Caution**—history of opiate abuse, hepatic dysfunction, acute abdomen, GI obstruction or ileus
Maternal Considerations	Thirty milligrams (30mg) of **oxycodone** is approximately equal to 10mg **morphine. Oxycodone** is not intended for use as a prn analgesic. Women have, on average, plasma **oxycodone** concentrations up to 25% higher than men on a body-weight-adjusted basis. In one RCT, the **oxycodone-acetaminophen** combination provided superior pain control after cesarean delivery with fewer side effects compared to **morphine** PCA. ***Side effects*** include dependency, hepatotoxicity, seizures, respiratory depression, dizziness, sedation, N/V, pruritus, rash, dysphoria, and constipation.

Fetal Considerations

There are no adequate reports or well-controlled studies of **oxycodone** in human fetuses. Other drugs in its class readily cross the human placenta. **Oxycodone** abuse during pregnancy may be associated with neonatal withdrawal.

Breastfeeding Safety

Oxycodone was detected in the milk of mothers who have taken any dose in a 24h period, with significant correlation between maternal plasma and milk levels (r^2 =.81). The M:P ratio was 3.2:1. Over the next 48h, the relationship between plasma and milk levels was weaker (r^2 =.59). **Oxycodone** levels up to 168ng/ml were detected in breast milk (20% >100ng/ml), though it was detected in only 1/41 infants tested. Maternal **oxycodone** intake up to 72h post–cesarean section poses only minimal risk to the breastfeeding infant as volume of breast milk ingested is low during this period.

Drug Interactions

May enhance the neuromuscular blocking action of skeletal muscle relaxants and produce an increased degree of respiratory depression.
Metabolized in part to **oxymorphone** via CYP2D6. While this pathway may be blocked by a variety of drugs (e.g., certain CV drugs, including **amiodarone** and **quinidine**), such blockade has not yet been shown to be of clinical significance with this agent.
All opioid analgesics should be started at ⅓ to ½ of the usual dose in patients concurrently receiving other CNS depressants, including sedatives or hypnotics, general anesthetics, phenothiazines, centrally acting antiemetics, tranquilizers, and ethanol, because respiratory depression, hypotension, and profound sedation or coma may result.

References

Davis KM, Esposito MA, Meyer BA. Am J Obstet Gynecol 2006; 194:967-71.
Dickson PH, Lind A, Studts P, et al. J Forensic Sci 1994; 39:207-14.
Rao R, Desai NS. J Perinatol 2002; 22:324-5.
Seaton S, Reeves M, McLean S. Aust N Z J Obstet Gynaecol 2007; 47:181-5.

Summary

Pregnancy Category: C
Lactation Category: S (likely)
- **Oxycodone** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.
- There are alternative agents for which there is more experience regarding use during pregnancy and lactation.

Oxymetazoline, nasal—(Afrin, Nasivion, Vicks Sinex, Visine)

International Brand Name—None identified.

Drug Class

Nasal spray

Indications

Nasal congestion

Mechanism

α_2-Adrenergic agonist

Dosage with Qualifiers

Nasal congestion—2-3sprays each nostril bid; max 6sprays per nostril/d

- **Contraindications**—hypersensitivity to drug or class, glaucoma
- **Caution**—preeclampsia, hypertension, hyperthyroidism, diabetes mellitus, eye injury

Maternal Considerations

Allergic rhinitis affects about ⅓ of reproductive-age women. **Oxymetazoline** is available OTC, and the prevalence of its use during pregnancy and lactation are unknown. Chronic abuse may lead to rebound rhinitis. Because there are no adequate reports or well-controlled studies in pregnant women, it should be considered a second-line agent behind 1st generation antihistamines such as **chlorpheniramine. Oxymetazoline** binds to human myometrium, and can *in vitro* cause contraction of both the myometrium and the umbilical artery. Preeclamptic women may experience an acute rise in BP after administration. ***Side effects*** include hypertension, CV collapse, rebound rhinitis, nasal irritation, burning, and sneezing.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. It is suggested that some vasoactive decongestants may be involved in the etiology of gastroschisis, including **oxymetazoline.** It can also constrict the umbilical artery, and is suggested as a cause of a nonreactive NST. However, another study of healthy pregnancies could detect no effect of **oxymetazoline** on fetal Doppler flows in a variety of vessels.

Breastfeeding Safety

There are no adequate reports or well-controlled studies in nursing women. It is unknown whether **oxymetazoline** enters human breast milk. However, considering the dose, route, and frequency, it is unlikely the breastfeeding neonate would absorb clinically relevant quantities.

Drug Interactions

No clinically relevant interactions identified.

References

Adolfsson PI, Dahle LO, Berg G, Svensson SP. Gynecol Obstet Invest 1998; 45:145-50.
Baxi LV, Gindoff PR, Pregenzer GJ, Parras MK. Am J Obstet Gynecol 1985; 153:799-800.
Mazzotta P, Loebstein R, Koren G. Drug Saf 1999; 20:361-75.
Rayburn WF, Anderson JC, Smith CV, et al. Obstet Gynecol 1990; 76:180-2.
Torfs CP, Katz EA, Bateson TF, et al. Teratology 1996; 54:84-92.

Summary

Pregnancy Category: C
Lactation Category: S (likely)
- **Oxymetazoline** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.
- There are alternative agents for which there is more experience regarding use during pregnancy and lactation.

Oxymorphone—(Numorphan, Opana)

International Brand Name—None identified.

Drug Class

Analgesics, narcotic

Indications

Moderate to severe pain, labor analgesia

Mechanism

Binds opiate receptors

Dosage with Qualifiers

Moderate to severe pain—0.5-1.5mg SC/IM q4-6h;
0.5mg IV q4-6h
Labor analgesia—0.5-1mg SC/IM

- **Contraindications**—hypersensitivity to drug or class
- **Caution**—pulmonary, hepatic, or renal dysfunction; head trauma; seizure disorder; history of substance abuse

Maternal Considerations

Oxymorphone was at one time popular for labor analgesia. It provides similar pain relief with less pruritus compared to **morphine** when used with epidural analgesia. **Oxymorphone** is an alternative to **morphine** administered by PCA after cesarean section, but may be associated with an increase in nausea. The level of sedation is similar.
Side effects include abuse or addiction, constipation, hypotension, respiratory depression, sedation, confusion, N/V, dizziness, sweating, nervousness, and hallucinations.

Fetal Considerations

There are no adequate reports or well-controlled studies of **oxymorphone** in human fetuses (see **Morphine**).

Breastfeeding Safety

There is no published experience in nursing women. It is unknown whether **oxymorphone** enters human breast milk. Only limited quantities of **morphine** enter breast milk.

Drug Interactions

Use of other CNS depressants, including sedatives, hypnotics, tranquilizers, general anesthetics, phenothiazines, other opioids, TCAs, MAOIs, and ethanol, may produce additive CNS depressant effects. The dose of one or both agents should be reduced to ½ or ⅓.
Anticholinergics or other medications with anticholinergic activity may result in increased risk of urinary retention and/or severe constipation, which may lead to paralytic ileus.
The incidence of bradycardia may be increased when used with **propofol** for induction of anesthesia.
CNS toxicity (confusion, disorientation, respiratory depression, apnea, seizures) has been reported following **cimetidine;** no clear-cut cause-and-effect relationship was established.
Agonist-antagonist analgesics (e.g., **buprenorphine, butorphanol, nalbuphine, pentazocine**) should not be administered to patients who have received or are receiving a pure opioid agonist analgesic. In this situation, mixed agonist-antagonist analgesics may reduce the analgesic effect and/or may precipitate withdrawal symptoms.

References

Celleno D, Capogna G, Sebastiani M, et al. Reg Anesth 1991; 16:79-83.
Sinatra R, Chung KS, Silverman DG, et al. Anesthesiology 1989; 71:502-7.

Summary

Pregnancy Category: C
Lactation Category: U

- **Oxymorphone** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Oxytetracycline—(Clinmycin; E.P. Mycin; Oxy-Kesso-Tetra; Terramycin; Tija; Uri-Tet)

International Brand Name—Acu-Oxytet (South Africa); Aknin (Switzerland); BTH-S 250 Broncho-Tetra-Holz (Germany); Chemotrex 500 (Indonesia); Corsamycin (Indonesia); Cotet (South Africa); Leydoxycline (Philippines); Macocyn (Germany); Noxebron (Philippines); Oxacycle (Greece); Oxycyclin (Denmark); Oxylag (Puerto Rico); Oxytetral (Denmark, Norway, Sweden); Rorap (South Africa); Terramicina (Costa Rica, Ecuador, El Salvador, Guatemala, Honduras, Nicaragua, Panama, Peru, Spain); Terramycin (Greece, India, Indonesia, Korea, Malaysia, Philippines, Taiwan, Thailand)

Drug Class ..... Antibiotics; Tetracyclines

Indications ..... Bacterial infections with gram-negative and -positive bacteria including *Rickettsia, Mycoplasma pneumoniae, Borrelia recurrentis, H. influenzae* (respiratory infections), *H. ducreyi* (chancroid), *P. pestis* and *P. tularensis, Bartonella bacilliformis, Bacteroides* species, *V. comma* and *V. fetus, E. coli, Enterobacter aerogenes* (formerly *Aerobacter aerogenes*), *Shigella* species, *Mima* species, *Herellea* species, *Klebsiella* species (respiratory and urinary infections), and the agents of psittacosis, ornithosis, lymphogranuloma venereum, and granuloma inguinale.

Mechanism ..... Bacteriostatic

Dosage with Qualifiers ..... Bacterial infections—250-500mg PO bid depending on severity, or 250mg IM qd
Gonorrhea when penicillin is contraindicated—1.5g PO ×1, then 500mg PO qid for a total of 9g
Syphilis when penicillin is contraindicated—500mg PO qid ×10-15d

NOTE: renal dosing; IM formulation contains 2% lidocaine.

- **Contraindications**—hypersensitivity to drug or class
- **Caution**—concomitant anticoagulant or penicillin therapy

Maternal Considerations ..... When penicillin is contraindicated, tetracyclines are alternative drugs for the treatment of *N. gonorrhoeae, T. pallidum* and *T. pertenue* (syphilis and yaws), *Listeria monocytogenes, Clostridium* species, *B. anthracis, Fusobacterium fusiforme* (Vincent's infection), and *Actinomyces* species. There are no adequate reports or well-controlled studies of **oxytetracycline** in pregnant women. Tetracyclines are generally considered contraindicated during pregnancy because of their effect on the fetal teeth.
Side effects include N/V, diarrhea, glossitis, rash, photosensitivity, renal toxicity, urticaria, angioneurotic edema, hemolytic anemia, eosinophilia, thrombocytopenia, and neutropenia.

Fetal Considerations ..... There are no adequate reports or well-controlled studies in human fetuses. **Oxytetracycline** rapidly crosses the placenta and blood-brain barrier. Epidemiologic study links 1st trimester use of **oxytetracycline** with NTDs, cleft palate, and CV malformations. Tetracyclines in general are known to cause tooth discoloration when given in the 2nd half of pregnancy and during the neonatal period. They are incorporated into fetal bones in a reversible fashion. Rodent studies are reassuring, revealing no evidence of teratogenicity despite the use of doses higher than those used clinically. However, **oxytetracycline** produced dose-dependent maternal and embryo toxicity.

Breastfeeding Safety

There is no published experience in nursing women. It is unknown whether **oxytetracycline** enters human breast milk. Other tetracyclines are excreted in breast milk.

Drug Interactions

See **Tetracycline.**

References

Czeizel AE, Rockenbauer M. Eur J Obstet Gynecol Reprod Biol 2000; 88:27-33.
Medveczky E, Puhó E, Czeizel EA. Pharmacoepidemiol Drug Saf 2004; 13:443-55.
Morrissey RE, Tyl RW, Price CJ, et al. Fundam Appl Toxicol 1986; 7:434-43.
Puhó EH, Szunyogh M, Métneki J, Czeizel AE. Cleft Palate Craniofac J 2007; 44:194-202.

Summary

Pregnancy Category: D
Lactation Category: U

- **Oxytetracycline** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.
- There is reason to suspect **oxytetracycline** is a weak teratogen in humans; it should be avoided.
- There are alternative agents for which there is more experience regarding use during pregnancy and lactation.

Oxytocin—(Pitocin; Syntocinon; Xitocin)

International Brand Name—Fetusin (Philippines); NeOxyn (Philippines); Orasthin (Germany); Oxitone (Peru); Oxiton INJ (Korea); Oxytocin S INJ (Indonesia); Partocon INJ (Finland, Sweden); Pitocin (Ecuador); Pitocin INJ (India); Piton S (Indonesia); Piton S INJ (Israel, Netherlands, Taiwan); Solvoxine (Philippines); Synthetic Oxytocin INJ (India); Syntocinon INJ (Austria, Belgium, Bulgaria, Denmark, England, Finland, France, Hong Kong, Indonesia, Ireland, Italy, Malaysia, Netherlands, Philippines, Spain, Sweden, Switzerland, Taiwan); Syntocinon Spray (Austria, Denmark, Norway, Poland, South Africa, Sweden, Switzerland); Tranoxy (Philippines); Utron INJ (Israel); Xitocin (Mexico)

Drug Class

Hormones/hormone modifiers; Oxytocics; Stimulants, uterine

Indications

Labor induction, postpartum bleeding, lactation aid

Mechanism

Binds oxytocin receptors

Dosage with Qualifiers

Labor induction—1-2mIU/min IV; double q20-30min until 8mIU/min, then increase by 1-2mIU/min; max 200mIU/min
Postpartum bleeding—10-40IU/L at a rate titrated to control bleeding
Lactation aid—1-2 sprays per nostril 2-3min before feeding or pumping during 1st week after delivery

NOTE: available for either parenteral use or as a nasal spray.

- **Contraindications**—hypersensitivity to drug or class; nonpolar lie, CPD, fetal distress, placenta previa, vasa previa, umbilical cord prolapse, fetal bradycardia, other contraindications to vaginal delivery
- **Caution**—prior uterine scar, breech presentation

Maternal Considerations

The physiologic role of **oxytocin** in the stimulation and maintenance of human labor remains unclear. Though the search continues for new **oxytocin** receptor antagonists, large trials conducted with one antagonist revealed it was at best no better than many of the tocolytic agents already available. **Oxytocin** is usually effective stimulating rhythmic uterine contractions and is the drug of choice for induction

and augmentation of labor. In some geographic locales, an OCT is still used to assess placental reserve in the at-risk pregnancy. It is unclear whether routine amniotomy enhances the efficacy of **oxytocin.** High-dose **oxytocin** (4.5mIU/min initially, increased by 4.5mIU/min q30min) is associated with significantly shorter labors without demonstrable adverse fetal or neonatal effect compared to a low-dose **oxytocin** (1.5mIU/min initially, increased by 1.5mIU/min q30min) protocol. In VBAC patients, there is a dose-response relationship between the maximum **oxytocin** infusion rate and uterine rupture. Added caution is indicated at the higher doses of **oxytocin** during a VBAC attempt. Low-dose **oxytocin** (1-4mIU/min) is equivalent to **misoprostol** for cervical ripening.
Oxytocin is also important for the management of postpartum bleeding. **Oxytocin** infused at 80mIU/500ml over 30min for the first 30min postpartum reduces the need for additional uterotonic agents after cesarean delivery compared to an infusion of 10mIU/500ml over 30min at cord clamping. While it is often given (10mIU IV) with the delivery of the anterior shoulder, there is no clinical advantage to its administration then compared to after placental delivery for the reduction of 3rd stage hemorrhage. Injection into the umbilical vein after delivery has little impact on the 3rd stage of labor.
Side effects include uterine tetany, arrhythmia, uterine rupture, placental abruption, fetal distress, SIADH, and N/V.

Fetal Considerations

Oxytocin is used only to end pregnancy, and as such poses only labor-associated risks to the fetus. There are no indications for its use in the 1st trimester, and animal teratogen studies have not been conducted. Electronic FHR monitoring is indicated for all antepartal infusions.

Breastfeeding Safety

There are no adequate reports or well-controlled studies in nursing women. Endogenous **oxytocin** is essential for the initiation of lactation, and synthetic **oxytocin** can aid the establishment of a milk reflex.

Drug Interactions

Severe hypertension has been reported when **oxytocin** was given 3-4h following prophylactic administration of a vasoconstrictor in conjunction with caudal block anesthesia.
Cyclopropane anesthesia may modify **oxytocin's** CV effects so as to produce unexpected results such as hypotension. Maternal sinus bradycardia with abnormal AV rhythms has also been noted when used with **cyclopropane.**

References

Cahill AG, Stamilio DM, Odibo AO, et al. Am J Obstet Gynecol 2007; 197:495.e1-5.
Carroli G, Bergel E. Cochrane Database Syst Rev 2001; (4):CD001337.
Choy CM, Lau WC, Tam WH, Yuen PM. BJOG 2002; 109:173-7.
Ferguson JE 2d, Head BH, Frank FH, et al. Am J Obstet Gynecol 2002; 187:273-9; discussion 279-80.
Howarth GR, Botha DJ. Cochrane Database Syst Rev 2001; (3):CD003250.
Jackson KW Jr, Allbert JR, Schemmer G, et al. Am J Obstet Gynecol 2001; 185:873-7.
Merrill DC, Zlatnik FJ. Obstet Gynecol 1999; 94:455-63.
Munn MB, Owen J, Vincent R, et al. Obstet Gynecol 2001; 98:386-90.

Summary

Pregnancy Category: X
Lactation Category: S

- **Oxytocin** is the drug of choice for labor augmentation.
- It remains a first-line agent for induction and the treatment of puerperal hemorrhage.

Paclitaxel—(Onxol; Taxol)

International Brand Name—Anzatax (Australia, Brazil, China, Hong Kong, Malaysia, Philippines, Singapore, Taiwan, Thailand); Asotax (Argentina, Mexico); Biotax (Israel); Bristaxol (Mexico); Britaxol (Chile); Formoxol (Malaysia); Genexol (Korea, Singapore); Ifaxol (Mexico); Intaxel (India, Thailand); Medixel (Israel); Mitotax (Malaysia); Pacxel (Korea); Padexol (Korea); Parexel (Colombia, Ecuador, Paraguay); Paxus (Indonesia); Praxel (Chile, Mexico); Taxocris (Uruguay); Taxol (Argentina, Canada, China, Ecuador, Germany, Hong Kong, Indonesia, Israel, Korea, Malaysia, New Zealand, Philippines, South Africa, Thailand); Taycovit (Peru)

Drug Class	Antineoplastics, antimitotics
Indications	Malignancy, metastatic ovarian or breast cancer, lung (non–small cell) cancer, and HIV-related Kaposi's sarcoma
Mechanism	Inhibits mitosis by promoting assembly and stabilization of microtubules
Dosage with Qualifiers	Metastatic ovarian or breast cancer, lung (non–small cell) cancer, and HIV-related Kaposi's sarcoma—dosing regimens vary • **Contraindications**—hypersensitivity to drug or class, hypersensitivity to **castor oil**, neutropenia • **Caution**—radiation therapy, pregnancy
Maternal Considerations	**Paclitaxel** is a natural product. It is usually combined with **cisplatin** as first-line therapy. There are dozens of women given **paclitaxel** during pregnancy. In one, the median maternal age was 36y (range: 30-42y), and the primary site was ovarian in 5 (four carcinomas and one dysgerminoma) and the breast in 4. **Paclitaxel** began during the 2nd trimester in 4 instances, and during the 3rd trimester in the remaining 5. No malformations were reported, and the offspring seemed healthy with a median follow-up of 16mo (range: 3-36mo). Only one team studied the pharmacokinetics of **paclitaxel** (175mg/m^2 IV over 3 h) during pregnancy. The C_{max} and AUC of **paclitaxel** were decreased compared with nonpregnant patients. The estimated clearance, t/2, and volume of distribution were each within the ranges previously reported for nonpregnant patients. ***Side effects*** include alopecia, neutropenia, leukopenia, thrombocytopenia, N/V, diarrhea, anemia, arthralgia, myalgia, peripheral neuropathy, infection, elevated LFTs, and injection site reactions.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **paclitaxel** crosses the human placenta. However, several case reports note the development of oligohydramnios during **paclitaxel** therapy. Rodent studies reveal embryotoxicity and IUGR, but no teratogenicity.
Breastfeeding Safety	There is no published experience in nursing women. It is unknown whether **paclitaxel** enters human breast milk. It is concentrated in rat milk.
Drug Interactions	Catalyzed by CYP2C8 and CYP3A4. In the absence of formal clinical drug interaction studies, caution should be exercised when administering **paclitaxel** or **paclitaxel** protein-bound particles for injectable suspension with known substrates or inhibitors of CYP2C8 and CYP3A4. Potential interactions between **paclitaxel,** a substrate of CYP3A4, and protease

inhibitors (e.g., **indinavir, nelfinavir, ritonavir, saquinavir**), which are substrates and/or inhibitors of CYP3A4, have not been evaluated in clinical trials.
In a Phase I trial, myelosuppression was more profound when **paclitaxel** was given after **cisplatin** than with the alternate sequence (i.e., **paclitaxel** before **cisplatin**). Pharmacokinetics data from these patients demonstrated a ⅓ decrease in **paclitaxel** clearance.
Some reports suggest that plasma levels of **doxorubicin** (and its active metabolite doxorubicinol) may be increased when **paclitaxel** and **doxorubicin** are used together.

References

Kai S, Kohmura H, Hiraiwa E, et al. J Toxicol Sci 1994; 19(Suppl 1):69-111.
Lycette JL, Dul CL, Munar M, et al. Clin Breast Cancer 2006; 7:342-4.
Mir O, Berveiller P, Ropert S, et al. Ann Oncol 2008; 19:607-13.
Sood AK, Shahin MS, Sorosky JI. Gynecol Oncol 2001; 83:599-600.

Summary

Pregnancy Category: D
Lactation Category: U

- **Paclitaxel** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.
- Initiate therapy after organogenesis if possible.

Pamidronate—(Aredia)

International Brand Name—Aminomux (Argentina, Paraguay, Uruguay, Venezuela); Aredia (Brazil, Canada, Chile, China, Colombia, Hong Kong, Indonesia, Japan, Mexico, Peru, Philippines, Taiwan, Thailand); Aredronet (India); Ostepam (France); Pamisol (Malaysia, Singapore); Panolin (Korea); Panorin (Korea)

Drug Class

Bisphosphonates

Indications

Paget's disease, malignant hypercalcemia, osteolytic lesions

Mechanism

Inhibits osteoclast bone resorption

Dosage with Qualifiers

Paget's disease—30mg IV infused over 4h qd ×3d
Hypercalcemia secondary to malignancy—60-90mg IV infused over 24h ×1; wait 7d between treatments
Osteolytic lesions—90mg IV infused over 4h qmo

- **Contraindications**—hypersensitivity to drug or class
- **Caution**—renal dysfunction

Maternal Considerations

There are no adequate reports or well-controlled studies of **pamidronate** in pregnant women. The published experience consists of several case reports. In one, **pamidronate** was employed in the 3rd trimester to treat hypercalcemia secondary to metastatic breast carcinoma. There was no apparent adverse effect. In another, a woman with metastatic breast cancer was treated at 28w after unsuccessful chemotherapy, deteriorating renal function, frequent contractions, and a calcium level of 17.6mg/dl. **Pamidronate** dramatically decreased both the calcium levels and the frequency of uterine contractions. In six other instances, women with either polyostotic fibrous dysplasia or osteogenesis imperfecta were treated before conception and throughout pregnancy without any apparent adeverse maternal

or fetal effects. In animal studies, **pamidronate** inhibits bone resorption at the recommended dose for hypercalcemia apparently without inhibiting bone formation and mineralization. ***Side effects*** include N/V, dyspepsia, seizures, hypertension, thrombocytopenia, leukopenia, hypokalemia, hypocalcemia, hypomagnesemia, hypophosphatemia, tachycardia, anorexia, fever, confusion, psychosis, pain, and fatigue.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **pamidronate** crosses the human placenta. The limited human experience is reassuring. Indeed, **pamidronate** may represent an ameliorating fetal therapy for congenital osteogenesis imperfecta if there is placental transport. Rodent studies revealed maternal toxicity, presumably associated with hypocalcemia, and fetal skeletal retardation, but no evidence of teratogenicity. The delayed skeletal formation suggests **pamidronate** crosses the rodent placenta.

Breastfeeding Safety

There are no reports or well-controlled studies in nursing women. In a single case report, **pamidronate** was not found in human breast milk after a single IV dose. Women with hereditary hyperphosphatasia, a rare bone disorder characterized by increased bone turnover, may develop symptomatic hypercalcemia during lactation.

Drug Interactions

Caution is recommended when administering with other potentially nephrotoxic drugs.

References

Chan B, Zacharin M. J Clin Endocrinol Metab 2006; 91:2017-20.
Culbert EC, Schfirin BS. Obstet Gynecol 2006; 108:789-91.
Graepel P, Bentley P, Fritz H, et al. Arzneimittelforschung 1992; 42:654-67.
Illidge TM, Hussey M, Godden CW. Clin Oncol (R Coll Radiol) 1996; 8:257-8.
Munns CF, Rauch F, Ward L, Glorieux FH. J Bone Miner Res 2004; 19:1742-5.
Siminoski K, Fitzgerald AA, Flesch G, Gross MS. J Bone Miner Res 2000; 15:2052-5.

Summary

Pregnancy Category: C
Lactation Category: S

- **Pamidronate** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Pancrelipase—(Amylase; Amylase Lipase Protease; Cotazym-S; Creon; Creon 5; Donnazyme; Encron 10; Entolase; Enzymase 16; Festalan; Ilozyme; Ku-Zyme HP; Lipase; Panase; Pancote; Pancrease; Pancreatic Enzyme; Pancreatin 10; Pancrelipase 10000; Pancrelipase Mt 16; Pancrelipase Mt-16; Pancron 10; Panokase; Promylin; Protease; Protilase; Protilase Mt 16; Ultrase; Ultrase Mt; Vio-Moore; Zymase)

International Brand Name—Combizym (New Zealand); Combizym Compositum (New Zealand); Cotazym (Canada); Cotazym-65 B (Canada); Cotazym ECS (New Zealand); Cotazym-S (Australia); Cotazym-S Forte (Australia); Creon (Canada); Krebsilasi (Italy); Pancrease (Belgium, Denmark, Finland, Israel, Italy, Netherlands, Norway, Spain, Sweden); Pancrease HL (England); Pancrease MT (Canada); Pancrease MT 4 (Canada); Pancrease MT 10 (Canada); Pancrease MT 16 (Canada); Pancrex (Italy); Pankrease (South Africa); Panzytrat (New Zealand); Prolipase (Austria, Poland, Switzerland); Ultrase (Canada); Ultrase MT (Canada); Vitazyme (Malaysia)

Drug Class	Digestive enzymes; Gastrointestinals
Indications	Pancreatic insufficiency
Mechanism	Disintegrates into trypsin, amylase, and lipase
Dosage with Qualifiers	Pancreatic insufficiency—1-3tabs PO swallowed quickly with meals depending on preparation *NOTE: do not cut, crush, or chew.* • **Contraindications**—hypersensitivity to drug or class, allergy to pork, acute pancreatitis • **Caution**—unknown
Maternal Considerations	The enzymes in **pancrelipase** act locally in the GI tract, where either they may be digested, or their constituents partially absorbed and subsequently excreted in the urine. Undigested enzymes are excreted in the feces. There is no published experience in pregnancy though it no doubt has been used for the treatment of cystic fibrosis. ***Side effects*** include N/V, diarrhea, stomatitis, oral ulceration, rash, urticaria, hyperuricemia, and perianal irritation.
Fetal Considerations	There are no adequate reports or well-controlled studies of **pancrelipase** in human fetuses. The enzymes are not absorbed in a functional format and pose no risk to the fetus. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically.
Breastfeeding Safety	There is no published experience with **pancrelipase** in nursing women. However, the enzymes are not absorbed systemically and are unlikely to enter human breast milk.
Drug Interactions	Antacids containing calcium carbonate and magnesium hydroxide should not be taken concurrently as the combination may precipitate glycine-conjugated bile acids and form calcium and magnesium fatty acid soaps, causing a decrease in fat absorption and thus an increase in steatorrhea.

References	There are no current relevant references.
Summary	**Pregnancy Category: B** **Lactation Category: S** • **Pancrelipase** should be used during pregnancy and lactation if the benefit justifies the potential perinatal risk.

Pancuronium—(Pavulon)

International Brand Name—Alpax (Israel); Bromurex (Colombia, Mexico); Curon-B (South Africa); Panconium (India); Pancuron (Paraguay); Pancuronio (Colombia); Pavulon (Argentina, Australia, Brazil, Canada, Chile, France, India, Japan, Korea, South Africa, Sweden, Venezuela)

Drug Class	Neuromuscular blockers, nondepolarizing
Indications	Anesthesia, paralysis
Mechanism	Blocks acetylcholine motor end plate receptors
Dosage with Qualifiers	Paralysis—0.04-0.1mg/kg IV Paralysis, fetal—0.03mg/kg fetal IM or IV into the umbilical vein • **Contraindications**—hypersensitivity to drug or class • **Caution**—hypovolemia, hepatic dysfunction
Maternal Considerations	There are no adequate reports or well-controlled studies of **pancuronium** in pregnant women. However, it has a long clinical experience for cesarean delivery. **Pancuronium** is approximately ⅓ less potent than **vecuronium,** though its duration is longer at equipotent doses. As compared to **vecuronium, pancuronium** is also vagolytic with accompanying tachycardia—unwanted in some adults but perhaps desired during fetal transfusion. **Magnesium sulfate** enhances the neuromuscular blockade, and reversal may be incomplete. Neuromuscular blockade is reversed by anticholinesterase agents such as **edrophonium, neostigmine,** and **pyridostigmine.** ***Side effects*** include arrhythmia, hypertension, tachycardia, rash, increased salivation, and pruritus.
Fetal Considerations	There are no adequate reports or well-controlled studies of **pancuronium** in human fetuses. There is minimal transport across the human placenta. **Pancuronium** is often used for fetal paralysis to facilitate intrauterine procedures (0.3-0.6mg IV or IM). Because it increases HR, **pancuronium** blunts the normal decline in cardiac output after fetal intravascular transfusion. Fetal paralysis modestly reduces oxygen consumption.
Breastfeeding Safety	There is no published experience in nursing women. It is unknown whether **pancuronium** enters human breast milk. However, it is unlikely a significant amount would enter the breast milk given once for the described indications.
Drug Interactions	**Succinylcholine** may enhance the neuromuscular blocking effect and increase its duration of action. If **succinylcholine** is used first, the **pancuronium** should be delayed until the patient starts to recover from the **succinylcholine**-induced neuromuscular blockade. If a small dose of **pancuronium** is given at least 3min prior to the administration of **succinylcholine,** in order to reduce

the incidence and intensity of **succinylcholine**-induced fasiculations, it may cause respiratory depression in some patients. Other nondepolarizing neuromuscular blocking agents (e.g., **atracurium,** *d*-**tubocurarine,** gallamine, metocurine, **vecuronium**) behave in a fashion clinically similar to pancuronium. The combinations of **pancuronium**-metocurine and **pancuronium–***d*-**tubocurarine** are significantly more potent than the additive effects of each of the individual drugs given alone, however, the duration of blockade of these combinations is not prolonged.

Use of volatile inhalational anesthetics (e.g., **enflurane**, **isoflurane**, **halothane**) will enhance neuromuscular blockade. Potentiation is most prominent with **enflurane** and **isoflurane.**

Clinical experience and animal experiments suggest caution when giving **pancuronium** to patients receiving chronic TCA therapy who are anesthetized with **halothane** as severe ventricular arrhythmias may result from this combination.

Parenteral/intraperitoneal administration of high doses of certain antibiotics (e.g., aminoglycosides such as **dihydrostreptomycin, gentamicin, kanamycin, neomycin,** and **streptomycin;** tetracyclines; **bacitracin; polymyxin B; colistin;** and **colistimethate**) may intensify or produce neuromuscular block on their own. If these or other newly introduced antibiotics are used preoperatively or in conjunction with **pancuronium,** unexpected prolongation of neuromuscular block should be considered a possibility.

Use of **quinidine** during recovery from use of other muscle relaxants may trigger recurrent paralysis.

Electrolyte imbalance may alter neuromuscular blockade. Depending on the nature of the imbalance, either enhancement or inhibition can be expected. **Magnesium sulfate,** administered for the management of preeclampsia/eclampsia, may enhance the neuromuscular blockade.

References

Dailey PA, Fisher DM, Shnider SM, et al. Anesthesiology 1984; 60:569-74.
Higashi T, Kamo N, Naitou H, Tada K. Masui 1996; 45:96-8.
Wilkening RB, Boyle DW, Meschia G. Am J Physiol 1989; 257:H734-8.

Summary

Pregnancy Category: C
Lactation Category: U

- **Pancuronium** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Pantoprazole—(Protonix; Somac)

International Brand Name—Branzol (Uruguay); Controloc (Bulgaria, Egypt, Hungary, Iran, Israel, Jordan, Malaysia, Poland, Singapore, Thailand); Eupantol (France); Inipomp (France); Pantecta (Costa Rica, Dominican Republic, El Salvador, Guatemala, Honduras, Italy, Nicaragua, Panama); Pantodac (India); Pantodar (Israel); Pantoloc (Austria, Canada, China, Denmark, Hong Kong, Korea, Philippines, Taiwan); Pantop (Argentina); Pantozol (Germany, India, Indonesia, Israel, Mexico, Netherlands); Pepticus (Paraguay); Protium (England, Ireland); Rifun 40 (Germany); Ulcepraz (Philippines); Ziprol (Brazil); Zoltum (Peru); Zurcal (Austria, Chile, Colombia, Ecuador, Mexico, Peru); Zurcale (Belgium); Zurcazol (Greece)

Drug Class

Antiulcer; Gastrointestinals; Proton pump inhibitors

Indications

Erosive esophagitis, hypersecretory conditions

Mechanism

Inhibits gastric parietal cell hydrogen-potassium ATPase

Dosage with Qualifiers

Erosive esophagitis—40mg PO qd or bid ×8w; may repeat course followed by maintenance of 40mg/d
Hypersecretory conditions—begin 40mg PO bid; max 240mg qd

NOTE: do not crush, cut, or chew tablet.

- **Contraindications**—hypersensitivity to drug or class
- **Caution**—long-term use

Maternal Considerations

There are <60 reported cases during pregnancy in the literature. **Pantoprazole** seems effective for the approved indications. ***Side effects*** include headache, diarrhea, pancreatitis, blood dyscrasias, hepatic dysfunction, toxic epidermal necrolysis, and erythema multiforme.

Fetal Considerations

There are no adequate report or well-controlled studies in human fetuses. It is unknown whether **pantoprazole** crosses the human placenta. The limited published experience does not raise an alarm. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically.

Breastfeeding Safety

There is no published experience during lactation. It is unknown whether **pantoprazole** enters human breast milk; it is excreted into rodent milk.

Drug Interactions

Metabolized primarily through CYP2C19 and CYP3A4 isozymes, and subsequently undergoes phase II conjugation. No dose adjustments will be needed with the use of the following: **amoxicillin, antipyrine, caffeine, carbamazepine, cisapride, clarithromycin, diazepam** (and its active metabolite, desmethyldiazepam), **diclofenac, digoxin,** ethanol, **glyburide, levonorgestrel/ethinyl estradiol, metoprolol, metronidazole, midazolam, naproxen, nifedipine, phenytoin, piroxicam,** or **theophylline.**
There are post-marketing reports of increased INR and PT in patients receiving both proton pump inhibitors, including **pantoprazole,** and **warfarin.** Increases in INR and PT may lead to abnormal bleeding and even death. Patients should be monitored closely.
May interfere with absorption of drugs for which gastric pH is an important determinant of bioavailability (e.g., **ampicillin** esters, iron salts, **ketoconazole**) since **pantoprazole** profoundly inhibits gastric acid secretion.

References

Diav-Citrin O, Arnon J, Shechtman S, et al. Aliment Pharmacol Ther 2005; 21:269-75.

Summary

Pregnancy Category: B
Lactation Category: U

- **Pantoprazole** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.
- There are alternative agents for which there is more experience regarding use during pregnancy and lactation.

Pantothenic acid—(Vilantae)

International Brand Name—None identified.

Drug Class	Vitamins/minerals
Indications	Supplementation
Mechanism	Unknown
Dosage with Qualifiers	Supplementation—RDA not established, but 6mg daily is typically suggested • **Contraindications**—hypersensitivity to drug or class • **Caution**—unknown
Maternal Considerations	**Pantothenic acid** (a.k.a. vitamin B_5) is a water-soluble B vitamin. There are no adequate reports or well-controlled studies of **pantothenic acid** in pregnant women. Its level may decline modestly during pregnancy. ***Side effects*** are not reported.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. **Pantothenic acid** is actively transported across the placenta. Epidemiologically, maternal intake of **pantothenic acid** correlates with birth weight, birth length, and head circumference. However, it is not presently known whether maternal supplementation increases the fetal concentration. Supplementation reduces the incidence of NTDs in mice treated with **valproate.**
Breastfeeding Safety	There are no adequate reports or well-controlled studies in nursing women. **Pantothenic acid** enters human breast milk, and the concentration in term milk correlates with maternal serum, dietary intake, and urinary excretion. Maternal serum levels may decline modestly during lactation without supplementation.
Drug Interactions	No clinically relevant interactions identified.
References	Dawson JE, Raymond AM, Winn LM. Toxicol Appl Pharmacol 2006; 211:124-32. Lagiou P, Mucci L, Tamimi R, et al. Eur J Nutr 2005; 44:52-9. Sato M, Shirota M, Nagao T. Teratology 1995; 52:143-8. Song WO, Chan GM, Wyse BW, Hansen RG. Am J Clin Nutr 1984; 40:317-24. Song WO, Wyse BW, Hansen RG. J Am Diet Assoc 1985; 85:192-8.
Summary	**Pregnancy Category: A** **Lactation Category: S** • **Pantothenic acid** is a common component of prenatal vitamins.

Paregoric

International Brand Name—None identified.

Drug Class ..... Antidiarrheals; Narcotics

Indications ..... Diarrhea

Mechanism ..... Binds opioid receptors

Dosage with Qualifiers .....

Diarrhea—5-10ml qd to qid prn loose stools

- **Contraindications**—hypersensitivity to drug or class, hypersensitivity to **morphine,** diarrhea secondary to toxic metal poisoning
- **Caution**—head injury, abdominal pain of unknown origin

Maternal Considerations .....

Paregoric is a mixture of opium powder (anhydrous **morphine,** 0.4mg/mL) and ethanol. Other ingredients include benzoic acid, camphor, and anise oil. Its main actions are to increase intestinal muscular tone and to inhibit normal peristalsis. **Paregoric's** principle medicinal use is to control fulminant diarrhea. It is also an antitussive. **Paregoric** is sometimes confused with **laudanum,** because their chemical names are similar: camphorated tincture of opium (**paregoric**) vs. tincture of opium (**laudanum**). However, **laudanum** contains 10mg/ml of opium, 25× more than **paregoric.** Confusion between the two drugs has led to overdose and deaths. The term "**paregoric**" should always be used instead of "camphorated opium tincture," since the latter may be confused with **laudanum**. There are no adequate reports or well-controlled studies of **paregoric** in pregnant women. It does not delay or inhibit preterm labor. See **Morphine.**
Side effects include hypotension, convulsions, and SVT.

Fetal Considerations .....

There are no adequate reports or well-controlled studies of **paregoric** in human fetuses. Rodent teratogenicity studies have not been conducted, though the large clinical experience is reassuring. **Paregoric** is used postnatally for the treatment of neonatal withdrawal. See **Morphine.**

Breastfeeding Safety .....

There are no adequate reports or well-controlled studies of **paregoric** in nursing women (see **Morphine**).

Drug Interactions .....

See **Morphine.**
The patient should be advised that **morphine** in combination with other narcotic analgesics, general anesthetics, phenothiazines, tranquilizers, sedative-hypnotics, or other CNS depressants (including ethanol) has additive depressant effects and, when combined, the dose of one or both agents should be reduced.

References .....

Levy M, Spino M. Pharmacotherapy 1993; 13:202-11.

Summary .....

Pregnancy Category: B
Lactation Category: S

- **Paregoric** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.
- There are alternative agents for which there is more experience regarding use during pregnancy and lactation.

Paricalcitol—(Zemplar)

International Brand Name—None identified.

Drug Class	Calcium metabolism agents
Indications	Hyperparathyroidism, typically secondary to dialysis
Mechanism	Stimulates intestinal calcium and phosphorus absorption, bone mineralization; reduces PTH
Dosage with Qualifiers	Secondary hyperparathyroidism—0.04-0.1mcg/kg IV 3×/w; max 0.24mcg/kg • **Contraindications**—hypersensitivity to drug or class, vitamin D toxicity, hypercalcemia • **Caution**—unknown
Maternal Considerations	**Paricalcitol** is a synthetic vitamin D analog. There is no published experience in pregnancy. ***Side effects*** include hypercalcemia, N/V, fever, chills, edema, sepsis, light-headedness, pneumonia, GI bleeding, palpitations, and dry mouth.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **paricalcitol** crosses the human placenta. The results of rodent studies are mixed. Sequelae may reflect hypocalcemia rather than the drug.
Breastfeeding Safety	There is no published experience during lactation. It is unknown whether **paricalcitol** enters human breast milk.
Drug Interactions	Partially metabolized by CYP3A, and **ketoconazole** is known to be a strong CYP3A inhibitor. A multiple-dose drug-drug interaction study revealed **ketoconazole** roughly doubled the **paricalcitol** AUC. Care should be taken when using **ketoconazole** and other strong CYP3A inhibitors (e.g., **atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, voriconazole**). A dose adjustment of **paricalcitol** may be required. Drugs that impair intestinal absorption of fat-soluble vitamins, such as **cholestyramine,** may interfere with the absorption of **paricalcitol.** **Digitalis** toxicity is potentiated by hypercalcemia of any cause, so caution should be applied when **digitalis** compounds are prescribed with **paricalcitol.**
References	There are no current relevant references.
Summary	**Pregnancy Category: C** **Lactation Category: U** • **Paricalcitol** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Paromomycin—(Humatin)

International Brand Name—Gabbroral (Belgium, Bulgaria, Indonesia, Italy, South Africa); Humagel (France); Humatin (Austria, Bulgaria, Canada, Ecuador, Germany, Italy, Spain, Switzerland)

Drug Class	Antibiotics; Aminoglycosides; Antiprotozoals
Indications	Intestinal amebiasis, management of hepatic coma
Mechanism	Bactericidal—inhibits protein synthesis by binding the bacterial 30S ribosomal subunit
Dosage with Qualifiers	Intestinal amebiasis—25-35mg/kg/d PO with meals ×5-10d Management (adjunctive) of hepatic coma—4g PO tid ×5-6d • **Contraindications**—hypersensitivity to drug or class, intestinal obstruction • **Caution**—bowel ulcerations
Maternal Considerations	**Paromomycin** closely parallels **neomycin**. It is poorly absorbed orally—nearly 100% is recoverable from the stool. There are no adequate reports or well-controlled studies in pregnant women. A single case report documents the successful treatment of giardiasis. ***Side effects*** include N/V, abdominal cramps, and diarrhea.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **paromomycin** crosses the human placenta. However, it is unlikely the maternal systemic concentration will reach a clinically relevant level.
Breastfeeding Safety	There are no adequate reports or well-controlled studies in nursing women. It is unknown whether **paromomycin** enters human breast milk. However, it is generally considered compatible with breastfeeding because of the poor oral absorption.
Drug Interactions	No clinically relevant interactions identified.
References	Kreutner AK, Del Bene VE, Amstey MS. Am J Obstet Gynecol 1981; 140:895-901.
Summary	**Pregnancy Category: C** **Lactation Category: S** • **Paromomycin** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Paroxetine—(Paxil)

International Brand Name—Aropax 20 (Argentina, Belgium, Brazil, Mexico, Paraguay, South Africa, Uruguay); Aroxat (Chile); Deroxat (France); Divarius (France); Paroxet (Peru); Paxan (Colombia); Paxil (Canada, Costa Rica, Dominican Republic, Ecuador, El Salvador, Guatemala, Honduras, Mexico, Nicaragua, Panama); Paxil CR (Korea); Paxtine (Australia); Paxxet (Israel); Seroxat (Austria, Bulgaria, Colombia, Czech Republic, Denmark, England, Finland, Germany, Hungary, Ireland, Italy, Netherlands, Norway, Peru, Poland, Spain, Sweden); Setine (Taiwan); Tagonis (Germany); XET (India)

Drug Class ..... Antidepressants; SSRIs

Indications ..... Depression, postpartum depression, OCD, panic disorder, anxietal disorders, post-traumatic stress, chronic headache, diabetic neuropathy

Mechanism ..... Selectively inhibits serotonin reuptake

Dosage with Qualifiers .....

Depression—begin 20mg PO qam, increasing by 10mg/d qw; max 60mg/d
OCD—begin 20mg PO qam, increasing by 10mg/d qw; max 60mg/d
Panic disorder—begin 10mg PO qam, increasing by 10mg/d qw; max 60mg/d
Anxietal disorders—begin 20mg PO qam, increasing by 10mg/d qw; max 60mg/d
Post-traumatic stress—begin 20mg PO qam, increasing by 10mg/d qw; max 60mg/d
Chronic headache—begin 10mg PO qam, increasing by 10mg/d qw; max 60mg/d
Diabetic neuropathy—begin 10mg PO qam, increasing by 10mg/d qw; max 60mg/d

NOTE: taper gradually.

- **Contraindications**—hypersensitivity to drug or class, MAOI use within 14d, **thioridazine** use
- **Caution**—abrupt withdrawal, mania, history of seizures, hepatic or renal dysfunction, narrow-angle glaucoma, suicide risk

Maternal Considerations ..... Depression is common during and after pregnancy, but typically goes unrecognized. Pregnancy is not a reason *a priori* to discontinue psychotropic drugs. There are no adequate reports or well-controlled studies of **paroxetine** in pregnant women. About ⅔ of women taking SSRIs during pregnancy for major depression must increase their dose to maintain efficacy. Women should not feel compelled to stop **paroxetine** when they become pregnant if therapy is indeed indicated. If, after receiving appropriate evidence-based information, they decide to stop, it should be tapered gradually to avoid the abrupt discontinuation syndrome. There is growing clinical experience with the use of **paroxetine** for the treatment of postpartum depression. **Paroxetine** is also effective for the treatment of menopause-associated hot flashes. ***Side effects*** include serotonin or withdrawal syndromes, extrapyramidal symptoms, mania, seizures, nausea, diarrhea, headache, somnolence, dizziness, weakness, constipation, tremor, flatulence, anxiety, sweating, decreased libido, blurred vision, appetite changes, and flushing.

Fetal Considerations ..... There are no adequate reports or well-controlled studies in human fetuses. **Paroxetine** crosses the human placenta, achieving a mean F:M ratio approximating 0.5, a value significantly

lower than that observed with **citalopram** and **fluoxetine.**
Neonatal withdrawal symptoms are documented. Epidemiologic studies are somewhat mixed and suggest confounding factors are at play. Some larger studies suggest an increase in CV malformations after 1st trimester exposure to **paroxetine.**
The effect is however small, appears dose-dependent (only above a daily dose of 25mg) and the most recent large epidemiological study found no such association. However, the risks may not be only structural. In one follow-up study, blunted facial-action responses were observed among infants exposed prenatally to SSRIs, whereas both prenatal and postnatal exposure was associated with reduced parasympathetic withdrawal and increased parasympathetic cardiac modulation during recovery after an acute noxious event. Given that postnatal exposure via breast milk is extremely low and altered biobehavioral pain reactivity is not associated with levels of maternal reports of depression, these findings suggest possible sustained neurobehavioral outcomes beyond the newborn period. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically.

Breastfeeding Safety

There are no adequate reports or well-controlled studies in nursing women. **Paroxetine** is excreted into human breast milk with the highest concentrations in the hind milk. However, the levels are variable, and no breastfed child studied to date has had clinically relevant levels detected, suggesting **paroxetine** is a good selection for breastfeeding women.

Drug Interactions

In a controlled study of healthy volunteers, a single dose of **pimozide** (2mg) displayed increases in the **pimozide** AUC of 151% and C_{max} of 62% after **paroxetine** was titrated to 60mg daily compared to **pimozide** alone. Due to the narrow therapeutic index of **pimozide** and its known ability to prolong the QT interval, concomitant use of **pimozide** and **paroxetine** is contraindicated.
Based on the **paroxetine** mechanism of action and the potential for serotonin syndrome (primarily headache, nausea, sweating, and dizziness), caution is advised when using with other drugs or agents that may affect the serotonergic neurotransmitter systems, such as tryptophan, triptans, SSRIs, **linezolid** (an antibiotic that is a reversible nonselective MAOI), **lithium, tramadol,** or **St. John's wort.**
There may be a pharmacodynamic interaction between **paroxetine** and **warfarin** that causes a bleeding diathesis with unaltered PT. Caution is indicated.
Epidemiologic studies of the case-control and cohort design reveal an association between psychotropic drugs that interfere with serotonin reuptake and upper GI bleeding. Thus, patients should be cautioned about the use of such drugs concurrently with **paroxetine.**
Rare post-marketing reports describe patients with weakness, hyperreflexia, and incoordination after the use of a SSRI (e.g., **fluoxetine, fluvoxamine, paroxetine, sertraline**) and **sumatriptan.**
Cimetidine (300mg tid) increased steady-state plasma concentrations of **paroxetine** by approximately 50%. The **paroxetine** dosage should be guided by clinical effect.
Phenobarbital (100mg qd ×14d) reduced the **paroxetine** (30mg ×1) AUC and t/2 by 25% and 38%, respectively compared to **paroxetine** alone. Since **paroxetine** exhibits nonlinear pharmacokinetics, the results of this study may not address the case where the 2 drugs are both being used

chronically. No initial dosage adjustment of **paroxetine** is necessary; any subsequent adjustment should be guided by clinical effect.

Phenytoin (300mg qd ×14d) reduces the **paroxetine** (30mg ×1) AUC and t/2 50% and 35%, respectively, compared to **paroxetine** alone. When a single **phenytoin** dose (300mg PO ×1) was given at **paroxetine** steady state (30mg PO qd ×14d), **phenytoin** AUC was reduced about 12% compared to **phenytoin** administered alone. Since both drugs exhibit nonlinear pharmacokinetics, these studies may not apply where both being used chronically. No initial dosage adjustments are considered necessary when these drugs are co-administered.

Paroxetine is both metabolized by and inhibits CYP2D6. Co-administration with drugs that are metabolized by CYP2D6 (e.g., **amitriptyline, fluoxetine, imipramine, nortriptyline**), phenothiazines, and class 1C antiarrhythmics (e.g., **encainide, flecainide, propafenone**) should be approached with caution. In most patients (>90%), CYP2D6 is saturated early during dosing. In one study, **paroxetine** (20mg qd) increased the **desipramine** (100mg PO ×1) C_{max}, AUC, and t/2 by some 2-, 5-, and 3-fold, respectively. In another study, **paroxetine** (20mg PO ×1) given to patients stabilized on **risperidone** (4-8mg/d) increased the plasma **risperidone** 4-fold, decreased 9-hydroxyrisperidone approximately 10%, and increased the active moiety (the sum of **risperidone** plus 9-hydroxyrisperidone) 1.4-fold. The effect of **paroxetine** on the pharmacokinetics of **atomoxetine** was evaluated when both drugs were at steady state. In healthy but extensive CYP2D6 metabolizers, **paroxetine** (20mg qd) increased **atomoxetine** AUC values 6- to 8-fold and C_{max} 3- to 4-fold. The dose of **atomoxetine** may need to be either reduced or initiated at a lower level when given with **paroxetine.**

At steady state, when CYP2D6 is essentially saturated, **paroxetine** clearance is governed by alternative P450 isozymes that, unlike CYP2D6, show no evidence of saturation. Due to the risk of serious ventricular arrhythmias and sudden death potentially associated with elevated plasma levels, **paroxetine** and **thioridazine** should not be used together.

Caution is indicated in the co-administration of TCAs since **paroxetine** may inhibit TCA metabolism. Plasma TCA concentrations should be monitored, and the dose of TCA reduced, if needed.

Because **paroxetine** is highly bound to plasma protein, use with another drug that is highly protein bound may cause increased free concentrations of the other drug, potentially resulting in adverse events. Conversely, adverse effects could result from displacement of **paroxetine** by other highly bound drugs.

Due to the potential for serotonin syndrome, caution is advised when **paroxetine** is used with **lithium.**

Increases the AUC(0-24), C_{max}, and C_{min} values of **procyclidine** (5mg PO qd) by 35%, 37%, and 67%, respectively. The dose of **procyclidine** should be reduced if anticholinergic effects are seen.

There are reports of elevated **theophylline** levels associated with **paroxetine.** While this interaction has not been formally studied, it is recommended that **theophylline** levels be monitored when these drugs are used together.

Use of **fosamprenavir-ritonavir** with **paroxetine** significantly decreased plasma levels of **paroxetine.** Any dose adjustment should be guided by clinical effect.

References

Bérard A, Ramos E, Rey E, et al. Birth Defects Res B Dev Reprod Toxicol 2007; 80:18-27.

Cole JA, Ephross SA, Cosmatos IS, Walker AM. Pharmacoepidemiol Drug Saf 2007; 16:1075-85.
Hendrick V, Stowe ZN, Altshuler LL, et al. Am J Psychiatry 2003; 160:993-6.
Hostetter A, Stowe ZN, Strader JR Jr, et al. Depress Anxiety 2000; 11:51-7.
Kulin NA, Pastuszak A, Sage SR, et al. JAMA 1998; 279:609-10.
Louik C, Lin AE, Werler MM, et al. N Engl J Med 2007; 356:2675-83.
Misri S, Kim J, Riggs KW, Kostaras X. J Clin Psychiatry 2000; 61:828-32.
Nijhuis IJ, Kok-Van Rooij GW, Bosschaart AN. Arch Dis Child Fetal Neonatal Ed 2001; 84:F77.
Oberlander TF, Grunau RE, Fitzgerald C, et al. Pediatrics 2005; 115:411-25.
O'Brien L, Einarson TR, Sarban M, et al. J Obstet Gynaecol Can 2008; 30:696-701.
Rampono J, Proud S, Hackett LP, et al. Int J Neuropsychopharmacol 2004; 7:329-34.
Rayburn WF, Gonzalez CL, Christensen HD, et al. J Matern Fetal Med 2000; 9:136-41.
Stearns V, Beebe KL, Iyengar M, Dube E. JAMA 2003; 289:2827-34.
Stowe ZN, Cohen LS, Hostetter A, et al. Am J Psychiatry 2000; 157:185-9.

Summary

Pregnancy Category: D
Lactation Category: S (likely)

- **Paroxetine** should be used during pregnancy only if the benefit justifies the potential perinatal risk.
- As there may be a small increase in the prevalence of cardiac malformations after 1st trimester exposure, consideration should be given to a fetal echocardiogram at 20-22w.
- Fetal levels are significantly lower than **citalopram** and **fluoxetine.**

Pegfilgrastim—(Neulasta)

International Brand Name—Neulasta (Australia)

Drug Class

Hematopoietic agents

Indications

Post-chemotherapy neutropenia

Mechanism

Stimulates granulocyte and macrophage proliferation and differentiation

Dosage with Qualifiers

Post-chemotherapy neutropenia—6mg SC ×1 >24h after chemotherapy completed

NOTE: do not give within 14d of next chemotherapy course.

- **Contraindications**—hypersensitivity to drug or class, hypersensitivity to *E. coli* proteins
- **Caution**—myelodysplasia, sickle cell disease, myeloid malignancy

Maternal Considerations

There is no published experience with **pegfilgrastim** in pregnancy. ***Side effects*** include thrombocytopenia, splenic rupture, splenomegaly, ARDS, muscular and skeletal pain, headache,

	abdominal pain, flank pain, elevated LDH or uric acid or alkaline phosphatase, and injection site reaction.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **pegfilgrastim** crosses the human placenta. Rodent studies reveal increased postimplantation resorption and abortion rates and IUGR often at doses in excess of that recommended and in association with maternal toxicity.
Breastfeeding Safety	There is no published experience during lactation. It is unknown whether **pegfilgrastim** enters human breast milk.
Drug Interactions	Drugs such as **lithium** may potentiate the release of neutrophils; patients receiving **lithium** and **pegfilgrastim** require frequent neutrophil counts.
References	There is no published experience in pregnancy or during lactation.
Summary	**Pregnancy Category: C** **Lactation Category: U** • **Pegfilgrastim** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Peginterferon alfa-2b—(PEG-Intron, Rebetol, Roferon-A)

International Brand Name—None identified.

Drug Class	Antivirals; Immunomodulators
Indications	HCV infection
Mechanism	Inhibits viral replication via multiple antiviral, antiproliferative, and immunomodulatory effects
Dosage with Qualifiers	Chronic HCV infection—1mg/kg/w SC ×1y *NOTE: anemia and neutropenia dosing; restricted access in US.* • **Contraindications**—hypersensitivity to drug or class, autoimmune hepatitis, decompensated hepatic disease • **Caution**—myelosuppression, diabetes mellitus, psychiatric disorders, thyroid disease, colitis, cardiac or pulmonary disease, ophthalmologic disorders
Maternal Considerations	Interferons bind to specific cell surface membrane receptors to initiate a complex sequence of intracellular events. Alfa interferons, including **peginterferon alfa-2b,** may cause or aggravate fatal or life-threatening neuropsychiatric, autoimmune, ischemic, and infectious disorders. Patients should be monitored closely with periodic clinical and laboratory evaluations. Therapy should be discontinued in women with persistently severe or worsening signs or symptoms. In many, but not all, instances, these disorders resolve after discontinuation. There is no published experience with **peginterferon alfa-2b** in pregnancy. Irregular menstrual cycles occurred in cynomolgus monkeys treated SC with doses in multiples of the MRHD. ***Side effects*** include psychosis, suicidal ideation, anemia, neutropenia, thrombocytopenia, thyroid dysfunction,

	cardiomyopathy, arrhythmias, MI, pancreatitis, retinal thrombosis, retinal hemorrhage, headache, N/V, fatigue, rigors, fever, depression, abdominal pain, diarrhea, and injection site reactions.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **peginterferon alfa-2b** crosses the human placenta. High doses of native interferon alfa-2b were associated with abortion in cynomolgus monkeys.
Breastfeeding Safety	There is no published experience during lactation. It is unknown whether **peginterferon alfa-2b** enters human breast milk. Unlike HIV, breastfeeding is not considered a risk for the newborns of HCV-infected women.
Drug Interactions	No clinically relevant interactions identified.
References	There is no published experience in pregnancy or during lactation.
Summary	**Pregnancy Category: C** **Lactation Category: U** • **Peginterferon alfa-2b** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Pemirolast ophthalmic—(Alamast)

International Brand Name—Alegysal (China, Indonesia, Korea, Philippines, Taiwan); Pemirox (Hong Kong, Thailand)

Drug Class	Allergy; Mast cell stabilizers; Ophthalmics
Indications	Allergic conjunctivitis
Mechanism	Inhibits mast cell degranulation
Dosage with Qualifiers	Allergic conjunctivitis—1-2gtt each eye qid for max 4w • **Contraindications**—hypersensitivity to drug or class • **Caution**—unknown
Maternal Considerations	There is no published experience with **pemirolast** in pregnancy. ***Side effects*** include headache, dry eyes, burning or other ocular discomfort, and respiratory symptoms.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **pemirolast** crosses the human placenta. However, considering the dose and route, it is unlikely the maternal systemic concentration would achieve a clinically relevant level. Rodent teratogenicity studies revealed skeletal abnormalities following the systemic administration of doses 20,000× or more above the MRHD.
Breastfeeding Safety	There is no published experience during lactation. It is unknown whether **pemirolast** enters human breast milk. However, considering the dose and route, it is unlikely the breastfed neonate will ingest clinically relevant amounts. It is concentrated in rodent milk.

Drug Interactions	No clinically relevant interactions identified.
References	There are no current relevant references.
Summary	**Pregnancy Category: C** **Lactation Category: S** (likely) • **Pemirolast** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Pemoline—(Cylert)

International Brand Name—Betanamin (Japan); Ceractiv (Chile); Cylert (Chile, Israel); Hyperilex (Germany); Tradon (Germany)

Drug Class	Anorexiants; CNS stimulants
Indications	ADHD, narcolepsy
Mechanism	Stimulates CNS by unknown mechanisms
Dosage with Qualifiers	ADHD—begin 37.5mg PO qam, increasing by 18.75mg qw; max 112.5mg/d Narcolepsy—25-100mg PO bid *NOTE: check ALT at baseline and q2w.* • **Contraindications**—hypersensitivity to drug or class, hepatic dysfunction, Tourette's syndrome, dependency • **Caution**—seizure disorder, renal dysfunction
Maternal Considerations	**Pemoline** has a pharmacologic activity similar to other known CNS stimulants; however, it has minimal sympathomimetic effects. There are no adequate reports or well-controlled studies in pregnant women. It has been used to treat narcolepsy during pregnancy. ***Side effects*** include seizures, aplastic anemia, ototoxicity, N/V, abdominal pain, headache, rash, insomnia, drowsiness, irritability, Tourette's syndrome, dyskinesia, and elevated LFTs.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **pemoline** crosses the human placenta. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically.
Breastfeeding Safety	There is no published experience in nursing women. It is unknown whether **pemoline** enters human breast milk.
Drug Interactions	Decreased seizure threshold is reported in patients also receiving AEDs.
References	Hoover-Stevens S, Kovacevic-Ristanovic R. Clin Neuropharmacol 2000; 23:175-81.
Summary	**Pregnancy Category: B** **Lactation Category: U** • **Pemoline** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Penbutolol—(Levatol)

International Brand Name—Betapresin (Mexico); Betapressin (Austria, Germany, Japan, Korea, Netherlands)

Drug Class	Adrenergic antagonists; Antihypertensives; β-blockers
Indications	Hypertension
Mechanism	Nonspecific β-adrenergic receptor antagonist
Dosage with Qualifiers	Hypertension—begin 20mg PO qd; max 80mg PO qd *NOTE: avoid abrupt discontinuation.* • **Contraindications**—hypersensitivity to drug or class, AV block, sinus bradycardia, cardiac insufficiency • **Caution**—COPD, diabetes mellitus
Maternal Considerations	Hypertensive disorders complicate 5-10% of pregnancies and are a leading cause of maternal and perinatal morbidity and death. There are no adequate reports or well-controlled studies of **penbutolol** in pregnant women. The free fraction of **penbutolol** increases during pregnancy because of altered protein binding. ***Side effects*** include N/V, diarrhea, abdominal pain, dyspepsia, headache, dizziness, fatigue, URI, CHF, asthenia, insomnia, and sweating.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **penbutolol** crosses the human placenta. Other β-blockers are associated with IUGR and fetal/neonatal bradycardia. The former is dose-dependent and appears to reflect an excessive drop in maternal cardiac output. Other neonatal sequelae associated with β blockade include hypoglycemia and hyperbilirubinemia. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically. Fetal toxicity was noted.
Breastfeeding Safety	There is no published experience in nursing women. It is unknown whether **penbutolol** enters human breast milk.
Drug Interactions	Increases the number of errors in eye-hand psychomotor function testing when combined with ethanol. Increases the volume of distribution of **lidocaine,** which may necessitate higher loading doses of **lidocaine.** Synergistic hypotensive effects, bradycardia, and arrhythmias are reported in some patients also receiving β-adrenergic blocking agents. Generally, **penbutolol** should not be used in patients receiving catecholamine-depleting drugs.
References	Aquirre C, Rodriguez-Sasiain JM, Navajas P, Calvo R. Eur J Drug Metab Pharmacokinet 1988; 13:23-6.
Summary	**Pregnancy Category: C** **Lactation Category: U** • **Penbutolol** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk. • There are alternative agents for which there is more experience regarding use during pregnancy and lactation.

Penciclovir topical—(Denavir)

International Brand Name—Vectavir (Costa Rica, Dominican Republic, El Salvador, Germany, Guatemala, Honduras, Israel, Nicaragua, Panama, South Africa)

Drug Class	Antivirals; Dermatologics
Indications	Herpes labialis
Mechanism	Inhibits DNA polymerase
Dosage with Qualifiers	Herpes labialis—apply q2h ×4d • **Contraindications**—hypersensitivity to drug or class • **Caution**—immune deficiency
Maternal Considerations	There is no published experience with **penciclovir** in pregnancy. There is little systemic absorption after topical application. ***Side effects*** include headache, pruritus, taste changes, and erythema.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **penciclovir** crosses the human placenta; it does apparently cross the rodent placenta. However, considering the dose and route, it is unlikely the maternal systemic concentration will reach clinically relevant levels. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically.
Breastfeeding Safety	There is no published experience in nursing women. It is unknown whether **penciclovir** enters human breast milk. However, considering the dose and route, it is unlikely the breastfed neonate would ingest clinically relevant amounts. One report suggests it rapidly is excreted into and then cleared from rodent breast milk.
Drug Interactions	No clinically relevant interactions identified.
References	Choi WS, Im GJ, Kim DK, et al. Drug Metab Dispos 2001; 29:945-9.
Summary	**Pregnancy Category: B** **Lactation Category: S** (likely) • **Penciclovir** should be used during pregnancy only if the benefit justifies the potential perinatal risk.

Penicillamine—(Cuprimine; Depen; Mercaptyl)

International Brand Name—Adaleen (Mexico); Artamin (Austria, Korea, Malaysia); Atamir (Denmark); Cuprenil (Bulgaria, Hungary); Cuprimine (Canada, Malaysia, Netherlands, Norway, Sweden, Taiwan, Thailand); Cuprimune (Argentina, Brazil); Cupripen (Spain, Uruguay); Depen (Canada); Distamine (England, Ireland, Netherlands, Switzerland); D-Penil (Peru); Kelatin (Belgium, Netherlands); Kelatine (Portugal); Metalcaptase (Germany, Japan); Pendramine (England); Penicilamina (Chile); Penicillamine (South Africa); Sufortanon (Spain)

Drug Class	Antirheumatics; Cystine-depleting agents
Indications	Wilson's disease, cystinuria, rheumatoid arthritis, heavy-metal poisoning
Mechanism	Unknown for arthritis; chelates copper
Dosage with Qualifiers	Wilson's disease—250-500mg PO tid or qid 30min before meals Cystinuria—250-1000mg PO qid 30min before meals Rheumatoid arthritis (unresponsive to conventional agents)—250mg PO bid or tid 30min before meals; requires 3-6mo for max effect Heavy-metal poisoning—125-600mg PO tid 30min before meals • **Contraindications**—hypersensitivity to drug or class, gold salt, antimalarial or immunosuppressant use, history of **penicillamine**-related anemia • **Caution**—renal dysfunction, penicillin allergy
Maternal Considerations	There are no adequate reports or well-controlled studies in pregnant women. **Penicillamine** is contraindicated during pregnancy except for the treatment of Wilson's disease and some cases of cystinuria. The published experience is limited to case reports and small series. Recurrent abortions are common in women with untreated Wilson's disease. Successful pregnancies and uneventful full-term delivery may occur with treatment and in presymptomatic patients. Pregnancy does not seem to have adverse effect on the clinical course of Wilson's disease. Zinc, which induces intestinal cell metallothionein that binds copper and prevents its transfer into blood, may be a suitable adjunct or alternative therapy. ***Side effects*** include thrombocytopenia, aplastic anemia, agranulocytosis, pancreatitis, exfoliative dermatitis, myasthenia gravis, SLE-like syndrome, rash, pruritus, N/V, dyspepsia, proteinuria, glossitis, taste changes, stomatitis, and hirsutism.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. **Penicillamine** apparently crosses the human placenta, since congenital cutis laxa and associated defects such as micrognathia, contractures, and CNS abnormalities are reported in neonates of treated women. Teratogenicity has otherwise not been reported in women receiving low-dose **penicillamine** and zinc sulfate. **Penicillamine** is teratogenic in rodents at doses 6× the MRHD. Adverse effects include skeletal deformities, cleft palate, and embryotoxicity.
Breastfeeding Safety	There is no published experience in nursing women. It is unknown whether **penicillamine** enters human breast milk.
Drug Interactions	No clinically relevant interactions identified.
References	Brewer GJ, Johnson VD, Dick RD, et al. Hepatology 2000; 31:364-70.

Furman B, Bashiri A, Wiznitzer A, et al. Eur J Obstet Gynecol Reprod Biol 2001; 96:232-4.
Martinez-Frias ML, Rodriguez-Pinilla E, Bermejo E, Blanco M. Am J Med Genet 1998; 76:274-5.
Pinter R, Hogge WA, McPherson E. Am J Med Genet A 2004; 128A:294-8.
Sinha S, Taly AB, Prashanth LK, et al. J Neurol Sci 2004; 217:37-40.

Summary

Pregnancy Category: D
Lactation Category: U

- **Penicillamine** should be used during pregnancy only if the benefit justifies the potential perinatal risk.
- It is probably best to avoid breastfeeding.

Penicillin G, aqueous

Drug Class

Antibiotics; Penicillins

Indications

Systemic infection (moderate to severe), anthrax, syphilis

Mechanism

Bactericidal—inhibits cell wall mucopeptide synthesis

Dosage with Qualifiers

Systemic infection (moderate to severe)—4 million U IM/IV q4h
Anthrax—*oral, GI, or inhalational:* 4 million U IV q4h as part of a multidrug regimen ×60d; *cutaneous:* 4 million U IV q4h ×7-10d, then switch to PO for 60d
Neurosyphilis—18-24 million U qd IV ×10-14d

NOTE: renal dosing.
*NOTE: Bicillin combines **penicillin G** and **benzathine penicillin G.***

- **Contraindications**—hypersensitivity to drug or class
- **Caution**—renal dysfunction, cephalosporin allergy, seizure disorder

Maternal Considerations

Penicillin G is typically given parenterally because it is unstable in gastric hydrochloric acid. Because it is given IV, higher tissue concentrations are achieved than with **penicillin VK** (phenoxymethylpenicillin). There is a long clinical experience with **penicillin G** during pregnancy that is reassuring. Vaginal GBS colony counts fall rapidly after intrapartum **penicillin G,** which explains in part the effectiveness of chemoprophylaxis. It is as effective as **cephalothin** for the prevention of post–cesarean section infection.
Side effects include thrombocytopenia, seizures, Stevens-Johnson syndrome, hemolytic anemia, neutropenia, interstitial nephritis, N/V, abdominal pain, diarrhea, rash, fever, and thrombophlebitis.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. Most penicillins cross the human placenta to some extent. **Penicillin G** is efficiently transferred across the horse placenta. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically.

Breastfeeding Safety

There are no adequate reports or well-controlled studies in nursing women. Only trace amounts of **penicillin G** enter human

breast milk. It is generally considered compatible with breastfeeding.

Drug Interactions

Tetracycline, a bacteriostatic antibiotic, may antagonize the bactericidal effect of penicillin, and use of these drugs together should be avoided.
Use with **probenecid** increases and prolongs serum penicillin levels by decreasing the apparent volume of distribution and slowing the rate of excretion by competitively inhibiting renal tubular secretion of penicillin.

References

Matsuda S. Biol Res Pregnancy Perinatol 1984; 5:57-60.
McNanley AR, Glantz JC, Hardy DJ, Vicino D. Am J Obstet Gynecol 2007; 197:583.e1-4.
Murchie TA, Macpherson ML, LeBlanc MM, et al. Equine Vet J 2006; 38:520-5.
Rudge MV, Atallah AN, Peraçoli JC, et al. Acta Obstet Gynecol Scand 2006; 85:945-8.

Summary

Pregnancy Category: B
Lactation Category: S

- **Penicillin G** has been used for decades during pregnancy and lactation.
- Though there is little objective study, it is generally considered safe for listed indications.
- Penicillin resistance is a growing disadvantage.

Penicillin G, benzathine—(Bicillin LA; Pen-Di-Ben; Permapen)

International Brand Name—Benzacillin (Korea); Benzanil Simple (Mexico); Benzetacil (Brazil, Ecuador, Mexico, Spain); Benzetacil A.P. (Mexico); Benzetacil L.A. (Argentina, Colombia, Ecuador, Paraguay, Peru, Uruguay, Venezuela); Benzilfan (Mexico); Bicillin L-A (New Zealand); Bicillin LA 1.2 (South Africa); Bicillin LA 2.4 (South Africa); Cepacilina (Spain); Diaminocillina (Italy); Durabiotic (Israel); Extencilline (France); Lentopenil (Mexico); Lutecilina (Colombia); Penadur (Switzerland); Penadur L-A (Thailand); Penadur L.A. (Belgium, Greece, Switzerland); Penadur - LA (Puerto Rico); Penadur LA (Hong Kong, Indonesia, Israel, Malaysia, Philippines, South Africa); Pencom (India); Pen Di Ben (Argentina); Pen-Di-Ben (Dominican Republic, El Salvador, Guatemala, Honduras, Nicaragua, Panama); Penidural (Netherlands); Penidure LA 6 (India); Penidure LA 12 (India); Penidure LA 24 (India); Penilente (South Africa); Penilente - LA (South Africa); Penretard (Brazil); Retarpen (Austria, Costa Rica, Dominican Republic, Ecuador, El Salvador, Guatemala, Honduras, Israel, Malaysia, Nicaragua, Panama, Singapore); Tardocillin 1200 (Germany); Wycillina A P (Italy); Zalpen (Philippines)

Drug Class

Antibiotics; Penicillins

Indications

Syphilis, group A streptococcus infection

Mechanism

Bactericidal—inhibits cell wall mucopeptide synthesis

Dosage with Qualifiers

Syphilis (primary, secondary or early latent)—2.4 million U IM ×1 if <1y duration, qw ×3 if >1y duration (late latent, unknown duration, tertiary)
Group A streptococcus infection—1.2 million U IM ×1

*NOTE: Bicillin combines **penicillin G** and **benzathine penicillin G.***

- **Contraindications**—hypersensitivity to drug or class
- **Caution**—renal dysfunction, cephalosporin allergy, seizure disorder

Maternal Considerations

Benzathine penicillin G is slowly absorbed after IM injection and subsequently hydrolysed to benzylpenicillin. It is the drug of choice when prolonged low concentrations of benzylpenicillin are required, allowing for prolonged antibiotic action over 2-4w. There are no adequate reports or well-controlled studies in pregnant women. **Benzathine penicillin G** remains the drug of choice for syphilis during pregnancy. However, it should be noted that Bicillin C-R (contains 1.2 million U of **benzathine penicillin G** and 1.2 million units of **procaine penicillin G**) is not recommended for treating syphilis because it contains only half the recommended dose of **benzathine penicillin G.** Medication errors have occurred, and as a result changes in product packaging were made; specifically, the statement "Not for the Treatment of Syphilis" has been added in red text to both the Bicillin CR and Billin CR 900/300 syringe labels. There is some concern **benzathine penicillin G** may not prevent neurosyphilis, but the overall risk appears low. Partner notification is mandatory to prevent the spread of the disease. About 40% of patients experience a Jarisch-Herxheimer reaction; treated women should be warned of the possibility and monitored closely for the first 48h. **Benzathine penicillin G-penicillin G** suspension (Bicillin L-A) 2.4 million U IM is insufficient as sole therapy for group B streptococcal prophylaxis.

Side effects include thrombocytopenia, seizures, rash, Stevens-Johnson syndrome, fever, hemolytic anemia, neutropenia, interstitial nephritis, N/V, abdominal pain, diarrhea, and thrombophlebitis.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. Most penicillins cross the human placenta to some extent. The currently recommended dose of **benzathine penicillin G** is effective for preventing congenital syphilis in most settings, although some additional study regarding dose modification is needed. **Azithromycin** and **ceftriaxone** are potential alternatives for penicillin-allergic women, but there is insufficient data on efficacy, which limits their use in pregnancy. Rodent studies of **benzathine penicillin G** are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically.

Breastfeeding Safety

There are no adequate reports or well-controlled studies in nursing women. Only trace amounts of **benzathine penicillin G** enter human breast milk. It is generally considered compatible with breastfeeding.

Drug Interactions

Tetracycline, a bacteriostatic antibiotic, may antagonize the bactericidal effect of penicillin, and use of these drugs together should be avoided.

Use with **probenecid** increases and prolongs serum penicillin levels by decreasing the apparent volume of distribution and slowing the rate of excretion by competitively inhibiting renal tubular secretion of penicillin.

References

Matsuda S. Biol Res Pregnancy Perinatol 1984; 5:57-60.

Myles TD, Elam G, Park-Hwang E, Nguyen T. Obstet Gynecol 1998; 92:859-64.

Pinette MG, Thayer K, Wax JR, et al. J Matern Fetal Neonatal Med 2005; 17:333-5.

Sheffield JS, Sanchez PJ, Morris G, et al. Am J Obstet Gynecol 2002; 186:569-73.

Watson-Jones D, Gumodoka B, Weiss H, et al. J Infect Dis 2002; 186:948-57.

Wendel Jr GD, Sheffield JS, Hollier LM, et al. Clin Infect Dis 2002; 35(Suppl 2):S200-9.

Summary

Pregnancy Category: B
Lactation Category: S

- **Benzathine penicillin G** has been used for decades during pregnancy and lactation.
- Though there is little objective study, it is generally considered safe for listed indications.
- It remains the drug of choice for the treatment of syphilis.

Penicillin G, procaine—(Crysticillin AS; Duracillin AS; Pfizerpen AS; Provaine Penicillin; Wycillin)

International Brand Name—Aqucilina (Spain); Farmaproina (Spain); Fradicilina 600 (Spain); Kemopen (Indonesia); Novocillin (South Africa); Penicil (Mexico); Procapen (Finland); Procillin (South Africa)

Drug Class

Antibiotics; Penicillins

Indications

Systemic infection (moderate to severe), pneumococcal pneumonia, gonorrhea, syphilis

Mechanism

Bactericidal—inhibits cell wall mucopeptide synthesis

Dosage with Qualifiers

Systemic infection (moderate to severe)—0.6-1.2 million U IM qd
Pneumococcal pneumonia—0.6-1.2 million U IM qd
Uncomplicated gonorrhea—4.8 million U IM ×1 30min after 1g **probenecid** PO
Neurosyphilis (alternative to aqueous penicillin)—2.4 million U IM qd plus **probenecid** 500mg PO qid, each ×10-14d

- **Contraindications**—hypersensitivity to drug or class, IV injection
- **Caution**—renal dysfunction, cephalosporin allergy, seizure disorder

Maternal Considerations

Procaine penicillin G is a combination of benzylpenicillin with the local anaesthetic agent **procaine.** It is slowly absorbed after IM administration and hydrolysed to benzylpenicillin and thus used to achieve prolonged but low concentrations of benzylpenicillin. The combination seeks to reduce the pain and discomfort associated with a large IM injection of penicillin. There are no adequate reports or well-controlled studies in pregnant women. **Procaine penicillin G** may be used in place of **benzathine penicillin G** for the treatment of syphilis, but has no medical advantage.
Side effects include thrombocytopenia, seizures, rash, Stevens-Johnson syndrome, Jarisch-Herxheimer reaction, myocardial depression, hemolytic anemia, neutropenia, interstitial nephritis, N/V, abdominal pain, diarrhea, fever, sterile abscess, vasodilation, and thrombophlebitis.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. Most penicillins cross the human placenta to some extent. **Procaine penicillin G** should behave the same as **benzathine penicillin G.** The large clinical experience is reassuring, as are the rodent studies, which reveal no evidence of

teratogenicity or IUGR despite the use of doses higher than those used clinically.

Breastfeeding Safety

There are no adequate reports or well-controlled studies in nursing women. Only trace amounts of **procaine penicillin G** enter human breast milk. It is generally considered compatible with breastfeeding.

Drug Interactions

Use with bacteriostatic antibiotics (e.g., **erythromycin**, **tetracycline**) may reduce the bactericidal effects of penicillins by slowing the rate of bacterial growth. There are few clinical situations in which the concurrent use of "static" and "cidal" antibiotics are indicated. In those circumstances, using adequate doses and beginning the penicillin therapy first should minimize the risks.
Penicillin blood levels may be prolonged by use with **probenecid,** which blocks the renal tubular secretion of **penicillin**.
Displacement from plasma protein binding sites will elevate the free **penicillin** levels.

References

Matsuda S. Biol Res Pregnancy Perinatol 1984; 5:57-60.
Paryani SG, Vaughn AJ, Crosby M, Lawrence S. J Pediatr 1994; 125:471-5.

Summary

Pregnancy Category: B
Lactation Category: S

- **Procaine penicillin G** has been used for decades during pregnancy and lactation.
- Though there is little objective study, it is generally considered safe for listed indications.
- Penicillin resistance is a growing disadvantage.

Penicillin VK—(Pen-Vee K; Veetids)

International Brand Name—Abbocillin VK (Australia); Anapenil (Mexico); Apo-Pen-VK (Canada); Arcasin (Germany); Beapen (Malaysia); Cilacil (Argentina); Cliacil (Argentina); Crystapen V (India); Distaquaine V-K (England); DuraPenicillin (Germany); Fenocin (Indonesia); Fenoxcillin (China, Denmark); Fenoxypen (Norway, Sweden); Isocillin (Germany); Kavipen (Mexico); Len V.K. (South Africa); L.P.V. (Australia); Megacilina Oral (Peru); Megacillin Oral (China, Germany); Milcopen (Finland); Nadopen-V (Canada); Newcillin (Japan); Novopen-VK (Canada); Novo-VK (South Africa); Oracilin (Brazil); Oracillin VK (South Africa); Orvek (Israel); Ospen (China, France, Malaysia, Singapore, Uruguay, Venezuela); Ospen 250 (Austria); Penbeta (Germany); Penoral (Argentina); Penoxil (Malaysia); Pentacillin (Philippines); Pentid (Argentina); Pentranex (Philippines); Pen V (Hong Kong); Pen Vee K (Colombia); Pen-Vi-K (Mexico); Primcillin (Denmark); Rafapen V-K (Israel); Robicillin VK (Israel); Rocilin (Denmark); Servipen-V (Thailand); Trepopen VK (Philippines); V-Cil-K (Ireland, Puerto Rico, South Africa); Vepicombin (Denmark); V-Kal-K (Japan); V-Pen (Israel); V-Penicillin Kalium (Japan)

Drug Class

Antibiotics; Penicillins

Indications

Group A streptococcus infection, pneumococcal pneumonia or rheumatic fever prophylaxis

Mechanism

Bactericidal—inhibits cell wall mucopeptide synthesis

Dosage with Qualifiers

Group A streptococcus infection—250-500mg PO q6-8h ×10d
Pneumococcal pneumonia prophylaxis—250mg PO bid
Rheumatic fever prophylaxis—250mg PO bid

NOTE: to be taken 1h before or 2h after meals.

- **Contraindications**—hypersensitivity to drug or class
- **Caution**—renal dysfunction, cephalosporin allergy, seizure disorder, PKU

Maternal Considerations	**Penicillin VK** is the orally active form of penicillin. It is less active than benzylpenicillin and is only appropriate in circumstances where high tissue concentrations are not required. There are no adequate reports or well-controlled studies in pregnant women. However, there is a long clinical experience that is reassuring. ***Side effects*** include thrombocytopenia, seizures, rash, Stevens-Johnson syndrome, hemolytic anemia, neutropenia, interstitial nephritis, N/V, abdominal pain, diarrhea, pseudomembranous colitis, and fever.
Fetal Considerations	There are no adequate reports or well-controlled studies of **penicillin VK** in human fetuses. Most penicillins cross the human placenta to some extent. The large clinical experience is reassuring, as are the rodent studies, which reveal no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically.
Breastfeeding Safety	There are no adequate reports or well-controlled studies in nursing women. Only trace amounts of **penicillin VK** enter human breast milk. It is generally considered compatible with breastfeeding.
Drug Interactions	Use with bacteriostatic antibiotics (e.g., **erythromycin, tetracycline**) may reduce the bactericidal effects of penicillins by slowing the rate of bacterial growth. There are few clinical situations in which the concurrent use of "static" and "cidal" antibiotics are indicated. In those circumstances, using adequate doses and beginning the penicillin therapy first should minimize the risks. **Penicillin** blood levels may be prolonged by use with **probenecid,** which blocks the renal tubular secretion of **penicillin**. Displacement from plasma protein binding sites will elevate the free **penicillin** levels.
References	Dencker BB, Larsen H, Jensen ES, et al. Clin Microbiol Infect 2002; 8:196-201. Matsuda S. Biol Res Pregnancy Perinatol 1984; 5:57-60.
Summary	**Pregnancy Category: B** **Lactation Category: S** • **Penicillin VK** has been used for decades during pregnancy and lactation. • Though there is little objective study, it is generally considered safe for listed indications. • Penicillin resistance is a growing disadvantage.

Pentamidine—(Nebupent; Pentam 300)

International Brand Name—Benambex (Japan); Pentacarinat (Argentina, Bulgaria, Canada, Czech Republic, France, Hungary, Ireland, Israel, New Zealand, Peru, Poland, Puerto Rico, Slovenia, South Africa, Thailand, Turkey)

Drug Class	Antiprotozoals
Indications	PCP prophylaxis and treatment
Mechanism	Unknown

Dosage with Qualifiers

PCP prophylaxis—300mg NEB q4wk
PCP treatment—4mg/kg IV/IM qd ×14-21d

- **Contraindications**—hypersensitivity to drug or class
- **Caution**—hepatic or renal dysfunction, hypertension, hypotension, leukopenia, hypoglycemia

Maternal Considerations

There are no adequate reports or well-controlled studies of **pentamidine** in pregnant women. Withholding appropriate PCP prophylaxis can adversely affect maternal and fetal outcomes. PCP during pregnancy may have a more aggressive course with increased morbidity and death. Maternal and fetal outcomes are poor. Treatment with **sulfamethoxazole-trimethoprim** may improve outcome compared to other therapies. Aerosolized **pentamidine** does not appear to pose a significant risk to pregnant health care workers.
Side effects include renal failure, leukopenia, thrombocytopenia, hypoglycemia, Stevens-Johnson syndrome, bronchospasm, fatigue, nausea, dyspepsia, decreased appetite, fever, rash, cough, and dizziness.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. There are no published human reports of concern, and human placental transport of **pentamidine** across the isolated cotyledon is limited. **Pentamidine** crosses the rodent placenta and penetrates all fetal compartments. Rodent studies are in general reassuring, revealing embryotoxicity but no teratogenicity or IUGR.

Breastfeeding Safety

There is no published experience in nursing women. It is unknown whether **pentamidine** enters human breast milk. Breastfeeding is contraindicated in HIV-infected nursing women where formula is available to reduce the risk of neonatal transmission.

Drug Interactions

No clinically relevant interactions identified.

References

Ahmad H, Mehta NJ, Manikal VM, et al. Chest 2001; 120:666-71.
Fortunato SJ, Bawdon RE. Am J Obstet Gynecol 1989; 160:759-61.
Harstad TW, Little BB, Bawdon RE, et al. Am J Obstet Gynecol 1990; 163:912-6.
Ito S, Koren G. Chest 1994; 106:1460-2.
Little BB, Harstad TH, Bawdon RE, et al. Am J Obstet Gynecol 1991; 164:927-30.

Summary

Pregnancy Category: C
Lactation Category: NS

- **Pentamidine** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.
- Withholding appropriate PCP prophylaxis can adversely affect maternal and fetal outcomes.

Pentazocine—(Talwin)

International Brand Name—Peltazon (Japan); Pentagin (Japan); Rafazocine X (Israel); Sosegon (Japan); Talwin (Canada)

Drug Class

Analgesics, narcotic; Narcotic agonist-antagonists

Indications

Moderate to severe pain, obstetric analgesia, anesthesia adjunct

Mechanism

Binds opiate receptors, producing both agonist and antagonist effects

Dosage with Qualifiers

Moderate to severe pain—30mg IM/IV/SC q3-4h prn; max 60mg/dose
Obstetric analgesia—20mg IV (or 30mg IM) q2-4h prn
Anesthesia adjunct—20mg IV (or 30mg IM) q2-4h prn

NOTE: SC injections may cause severe tissue damage and are best avoided.
NOTE: may be combined with ***naloxone*** *or* ***acetaminophen.***

- **Contraindications**—hypersensitivity to drug or class
- **Caution**—opiate dependence; head injury; hepatic, renal, or pulmonary dysfunction; post MI

Maternal Considerations

Pentazocine is a potent analgesic; 30-45mg is equianalgesic to **morphine** 10mg and **meperidine** 75-100mg. There are no adequate reports or well-controlled studies in pregnant women. **Pentazocine** is a poor choice for labor analgesia because of greater maternal respiratory depression than the alternatives. Some patients receiving narcotics, including **methadone,** experience withdrawal symptoms since **pentazocine** is a weak narcotic antagonist.
Side effects include addiction, respiratory depression, hypotension, seizures, granulocytopenia, N/V, dizziness, euphoria, hallucinations, sedation, headache, constipation, blurred vision, miosis, tremor, irritability, facial edema, flushing, and pruritus.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. **Pentazocine** crosses the human placenta. The addictive combination of **pentazocine** and **tripelennamine** (T's and blues) remains popular in some locales. Infants of women who use T's and blues throughout pregnancy have interactive deficits and withdrawal similar to **methadone**-addicted newborns. In general, rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically. A single study in hamsters suggested an increased risk of CNS malformations.

Breastfeeding Safety

There is no published experience in nursing women. While it is unknown whether **pentazocine** enters human breast milk, the clinical experience is reassuring.

Drug Interactions

Ethanol should be avoided because of the potential for increased CNS depressant effects.

References

Chasnoff IJ, Hatcher R, Burns WJ, Schnoll SH. Dev Pharmacol Ther 1983; 6:162-9.
Geber WF, Schramm LC. Am J Obstet Gynecol 1975; 123:705-13.
Wahab SA, Askalani AH, Amar RA, et al. Int J Gynaecol Obstet 1988; 26:75-80.

Summary

Pregnancy Category: C
Lactation Category: U

- **Pentazocine** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.
- There are less addictive but equally effective analgesics available for most indications.

Pentobarbital—(Carbrital; Nembutal)

International Brand Name—Dormital (Uruguay); Embutal (Argentina); Medinox Mono (Germany); Mintal (Japan); Sombutol (Finland)

Drug Class	Anticonvulsants; Anxiolytics; Barbiturates; Sedatives
Indications	Sedation, insomnia, barbiturate coma
Mechanism	Depresses the sensory and motor cortex and alters cerebellar function
Dosage with Qualifiers	Sedation—20-40mg PO bid to qid Insomnia—100mg PO qhs prn for short-term therapy Barbiturate coma—load with 5mg/kg over 30min, then 1-3mg/kg/h IV; systemic arterial BP must be supported (e.g., inotropic support) • **Contraindications**—hypersensitivity to drug or class, decreased respiratory function, porphyria • **Caution**—hepatic dysfunction, history of substance abuse, suicidal ideation
Maternal Considerations	Barbiturates produce CNS mood alteration ranging from excitation to sedation to hypnosis and deep coma. As a sleep aid, barbiturates are of limited value beyond the short term as they lose effectiveness after 1-2w. There are superior agents that have less effect on the sleep cycle. There are no adequate reports or well-controlled studies of **pentobarbital** in pregnant women. Hypnotic doses do not impair uterine activity during labor. ***Side effects*** include addiction, respiratory depression, Stevens-Johnson syndrome, SLE, angioedema, confusion, agitation, hyperkinesias, ataxia, CNS depression, hallucinations, dizziness, apnea, bradycardia, hypotension, syncope, N/V, constipation, and headache.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. **Pentobarbital** rapidly crosses the human placenta. The highest concentrations are found in placenta, liver, and brain. Its administration during labor can cause neonatal respiratory depression. Preterm infants are particularly susceptible, and resuscitation equipment should be available. Chronic use during the 3rd trimester can yield addicted neonates who have an extended withdrawal syndrome. Retrospective, case-control studies suggest a connection between barbiturates and an increased risk of fetal abnormalities. However, there are no such reports specifically for **pentobarbital,** and the rodent studies are reassuring. There is a single study suggesting a reduction in fertility.
Breastfeeding Safety	There are no adequate reports or well-controlled studies in nursing women. Only small amounts of **pentobarbital** enter human breast milk, and it is generally considered compatible with breastfeeding.
Drug Interactions	Most reports of clinically significant drug interactions with barbiturates involve **phenobarbital.** However, the application of these data to other barbiturates may be valid. Barbiturates may induce liver microsomal enzymes, increasing the metabolism and decreasing the anticoagulant response to oral anticoagulants (e.g., acenocoumarol, **dicumarol,** phenprocoumon,

warfarin). Anticoagulant dose adjustments may be necessary if barbiturates are added or withdrawn.
Barbiturates enhance the metabolism of exogenous corticosteroids probably through the induction of liver microsomal enzymes. A dose adjustment may be required if barbiturates are added or withdrawn.
Phenobarbital may interfere with the oral absorption of **griseofulvin.** The effect of decreased blood levels of **griseofulvin** on therapeutic response has not been established. It is preferable to avoid their use together.
Phenobarbital may shorten the t/2 of **doxycycline** for as long as 2w after barbiturate dicontinuation, probably through the induction of liver microsomal enzymes that metabolize **doxycycline.** The clinical response to **doxycycline** should be monitored closely if the two drugs are used together.
The effect of barbiturates on **phenytoin** metabolism appears variable. Some note an accelerating effect, while others report no effect. Because the effect is unpredictable, **phenytoin** and barbiturate blood levels should be monitored more frequently if used together.
Valproate and **valproic acid** appear to decrease barbiturate metabolism; thus, barbiturate blood levels should be monitored and dose adjustments made as appropriate.
Use with other CNS depressants, including other sedatives or hypnotics, antihistamines, tranquilizers, or ethanol, may produce additive depressant effects.
MAOIs prolong the effects of barbiturates probably by inhibiting the metabolism of the barbiturate.
Pretreatment with or concurrent use of **phenobarbital** may decrease the effect of **estradiol** by increasing its metabolism. There are reports of women treated with AEDs (e.g., **phenobarbital**) becoming pregnant while taking oral contraceptives. An alternate contraceptive method should be suggested.

References

Ito T, Ingalls TH. Arch Environ Health 1981; 36:316-20.

Summary

Pregnancy Category: D
Lactation Category: S

- **Pentobarbital** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.
- For all but coma, there are other agents with superior safety profiles during pregnancy.

Pentosan polysulfate sodium—(Elmiron)

International Brand Name—None identified.

Drug Class — Genitourinary

Indications — Interstitial cystitis

Mechanism — Unknown

Dosage with Qualifiers — Interstitial cystitis—100mg PO tid 1h before or 2h after meals

- **Contraindications**—hypersensitivity to drug or class
- **Caution**—hepatic or splenic disorders

Maternal Considerations	There is no published experience with **pentosan polysulfate** in pregnancy. ***Side effects*** include hepatotoxicity, diarrhea, N/V, headache, dyspepsia, abdominal pain, dizziness, depression, alopecia, and elevated LFTs.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. **Pentosan polysulfate** does not appear to cross the human placenta and should pose little risk during pregnancy.
Breastfeeding Safety	There are no published studies in nursing women. It is unknown whether **pentosan polysulfate** enters human breast milk.
Drug Interactions	No clinically relevant interactions identified.
References	Forestier F, Fischer AM, Daffos F, et al. Thromb Haemost 1986; 56:247-9.
Summary	**Pregnancy Category: B** **Lactation Category: U** • **Pentosan polysulfate** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Pentostatin—(Nipent)

International Brand Name—Coforin (Japan); Nipent (Canada, England, France, Germany, Italy, Netherlands, Portugal)

Drug Class	Antineoplastics, antimetabolite
Indications	Hairy cell leukemia
Mechanism	Inhibits adenosine deaminase
Dosage with Qualifiers	Hairy cell leukemia—4mg/m^2 IV qw • **Contraindications**—hypersensitivity to drug or class, concomitant **fludarabine** use • **Caution**—active infection, renal dysfunction
Maternal Considerations	There is no published experience with **pentostatin** during pregnancy. ***Side effects*** include N/V, arrhythmia, hemorrhage, leukopenia, thrombocytopenia, fatigue, anorexia, diarrhea, headache, rash, bronchitis, fever, chills, hematuria, and somnolence.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **pentostatin** crosses the human placenta. The developing mouse allantois is quite sensitive to **pentostatin,** and interference with allantois development leads to embryo lethality. Late exposure in rodent pregnancy is associated with neural tube, craniofacial, and limb defects.
Breastfeeding Safety	There is no published experience during lactation. It is unknown whether **pentostatin** enters human breast milk.
Drug Interactions	Enhances the antiviral effects of **vidarabine.** Combined use may result in an increase in adverse reactions associated with each drug.

Use with **fludarabine** is not recommended as it may be associated with an increased risk of fatal pulmonary toxicity.

References

Airhart MJ, Robbins CM, Knudsen TB, et al. Teratology 1993; 47:17-27.
Airhart MJ, Robbins CM, Knudsen TB, et al. Teratology 1996; 53:361-73.

Summary

Pregnancy Category: D
Lactation Category: U

- **Pentostatin** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Pentoxifylline—(Ebisanin; Sipental; Techlon; Trental)

International Brand Name—Agapurin (Singapore, Thailand); Artal (Finland); Azupentat (Germany); Carpental S.R. (Korea); Cental (Taiwan); Ceretal (Taiwan); C-Vex (Philippines); Elorgan (Spain); Erytral (Indonesia); Fixoten (Mexico); Flexital (Philippines); Harin (Korea); Harine (Korea); Hemovas (Spain); Ipentol (Taiwan); Kentadin (Mexico); Oxopurin 400 SR (Israel); Penphylline (Taiwan); Pentong (Hong Kong); Pentox (Philippines); Pentoxi (Switzerland); Pentoxifilin (Colombia); Pentoxine (Israel); Perencal (Korea); Perental (Korea); Peridane (Mexico); Pexal (Puerto Rico); Pexol (Peru); Platof (Indonesia); Tarontal (Greece, Indonesia); Torental (Belgium, France); Trenfyl (Indonesia); Trenlin (Hong Kong); Trenlin SR (Singapore); Trental (New Zealand, South Africa); Trepal-400 (Thailand); Vazofen (Philippines)

Drug Class

Hematolgics; Xanthine derivatives

Indications

Claudication

Mechanism

Decreases blood viscosity, improves RBC membrane flexibility

Dosage with Qualifiers

Claudication—400mg PO tid with meals

- **Contraindications**—hypersensitivity to drug or class, methylxanthine intolerance
- **Caution**—recent retinal or cerebral hemorrhage

Maternal Considerations

Pentoxifylline and its metabolites improve the flow properties of blood by decreasing viscosity. It also inhibits TNF-α–induced complement C3 synthesis. **Pentoxifylline** is used with **tocopherol** to treat IVF patients with a thin endometrium. It also enhances sperm motility prior to IVF or IUI. It has even been used in a preliminary study to treat endometriosis related infertility. In rodents, long-term use is associated with the development of mammary fibroadenomas. There are no adequate reports or well-controlled studies during pregnancy. Clearance is unaltered by pregnancy.
Side effects include arrhythmia, angina, N/V, diarrhea, dyspepsia, dizziness, headache, insomnia, blurred vision, drowsiness, and agitation.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **pentoxifylline** crosses the human placenta. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically. Embryotoxicity was noted.

Breastfeeding Safety

There are no adequate reports or well-controlled studies in nursing women. **Pentoxifylline** enters human breast milk, achieving near unity with maternal plasma. It is perhaps wise to

avoid **pentoxifylline** while breastfeeding because of its association with mammary fibroadenomas in rodents.

Drug Interactions

While a causal relationship is not established, there are reports of bleeding and/or prolonged PT in patients treated with **pentoxifylline** with and without anticoagulants or platelet aggregation inhibitors. Patients on **warfarin** should undergo more frequent monitoring of PTs, while patients with other risk factors complicated by hemorrhage (e.g., recent surgery, peptic ulcer) should have periodic tests for bleeding.
Pentoxifylline may increase **theophylline** and the risk of **theophylline** toxicity in some patients. Monitor closely for signs of toxicity and adjust the **theophylline** dose as appropriate.

References

Boiko SS, Zherdev VP, Vikhliaeva EM, Supriaga OM. Eksp Klin Farmakol 1992; 55:52-5.
Creus M, Fabregues F, Carmona F, et al. Hum Reprod 2008; 23:1910-6.
Griveau JF, Lobel B, Laurent MC, et al. Reprod Biomed Online 2006; 12:14-8.
Hoie EB, McGuire TR, Leuschen PM, Zach TL. Biol Pharm Bull 2004; 27:1670-3.
Ledee-Bataille N, Olivennes F, Lefaix JL, et al. Hum Reprod 2002; 17:1249-53.
Terriou P, Hans E, Giorgetti C, et al. J Assist Reprod Genet 2000; 17:194-9.
Witter FR, Smith RV. Am J Obstet Gynecol 1985; 151:1094-7.

Summary

Pregnancy Category: C
Lactation Category: NS (possibly)
- **Pentoxifylline** should be used during pregnancy only if the benefit justifies the potential perinatal risk.
- There is no published experience during pregnancy except in infertility patients.

Pergolide mesylate—(Permax; Withdrawn from the US.)

International Brand Name—Celance (Argentina, Brazil, Chile, China, Costa Rica, Dominican Republic, El Salvador, England, France, Guatemala, Guyana, Hong Kong, Ireland, Japan, Korea, Nicaragua, Panama, Peru, Philippines, Taiwan, Thailand); Nopar (Italy); Parkotil (Germany); Pergolide (Israel); Permax (Austria, Belgium, Bulgaria, Canada, Czech Republic, Denmark, Finland, Hungary, Mexico, Netherlands, Poland, Portugal, South Africa); Pharken (Spain)

Drug Class

Antiparkinson agents; Dopaminergics; Ergot alkaloids

Indications

Parkinsonism

Mechanism

Dopamine receptor (D_1 and D_2) agonist

Dosage with Qualifiers

Parkinsonism—0.05mg qd ×2d when used as an adjunct with **levodopa** or **carbidopa;** increase by 0.1mg/d q3d ×12d, then 0.25mg q3d ×12d, then adjust; max dose 5mg/d

- **Contraindications**—hypersensitivity to drug or class
- **Caution**—unknown

Maternal Considerations

Pergolide is effective primary treatment for pituitary macroprolactinomas. It is 10-1000× more potent a dopamine

agonist than **bromocriptine.** There are no adequate reports or well-controlled studies in pregnant women.
Side effects include ventricular arrhythmia, MI, cardiac valve damage, hypotension, N/V, dyskinesia, rhinitis, confusion, dizziness, somnolence, hallucinations, diarrhea, dyspepsia, tremor, syncope, and anemia.

Fetal Considerations ..... There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **pergolide** crosses the human placenta. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically.

Breastfeeding Safety ..... There is no published experience in nursing women. It is unknown whether **pergolide** enters human breast milk. The pharmacologic action of **pergolide** suggests it may interfere with lactation, and thus should be avoided at least until the milk reflex is well established.

Drug Interactions ..... Should not be used with dopamine antagonists, such as the neuroleptics (phenothiazines, butyrophenones, thioxanthenes) or **metoclopramide,** as these agents may diminish the effectiveness of **pergolide.**
Caution is indicated when used with drugs known to affect protein binding.

References ..... Orrego JJ, Chandler WF, Barkan AL. Pituitary 2000; 3:251-6.

Summary .....

Pregnancy Category: B
Lactation Category: U

- **Pergolide** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Perindopril erbumine—(Aceon)

International Brand Name—Acertil (China, Hong Kong, Korea, Taiwan); Coverene (Argentina); Coversum (Austria, Germany, Switzerland); Coversyl (Belgium, Brazil, Canada, Chile, Colombia, Costa Rica, Denmark, Dominican Republic, Ecuador, El Salvador, England, France, Greece, Guatemala, Honduras, India, Ireland, Italy, Japan, Kuwait, Malaysia, Mexico, Netherlands, Nicaragua, Panama, Paraguay, Philippines, Portugal, South Africa, Spain, Thailand, United Arab Emirates, Venezuela); Perinace (Malaysia); Prexum (Indonesia)

Drug Class ..... ACEI/A2R-antagonists; Antihypertensives

Indications ..... Hypertension, CHF

Mechanism ..... ACE inhibitor

Dosage with Qualifiers .....

Hypertension—begin 4mg PO qd; max 16mg/d
CHF—begin 2mg PO qd

NOTE: renal dosing; lower dose if on a diuretic.

- **Contraindications**—hypersensitivity to drug or class, history of ACEI-induced or idiopathic angioedema
- **Caution**—renal dysfunction, renal artery stenosis, severe CHF, collagen vascular disease, volume depletion, hyponatremia, pregnancy

Maternal Considerations

There is no published experience with **perindopril** during pregnancy. The lowest dose effective should be used when it is required during pregnancy for BP control.
Side effects include fetal or neonatal death, angioedema, hypotension, renal failure, hyperkalemia, neutropenia, agranulocytosis, pancreatitis, cough, N/V, musculoskeletal pains, dizziness, fatigue, and elevated BUN/Cr.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **perindopril** crosses the human placenta. It does cross the rabbit placenta.
Other renin-angiotensin system inhibitors cross the human placenta, and contrary to initially beliefs, may cause fetal cranial hypoplasia, anuria, reversible or irreversible renal failure, death, oligohydramnios, prematurity, IUGR, and PDA beginning with a 1st trimester exposure. There is no reason to expect **perindopril** is different.

Breastfeeding Safety

There is no published experience in nursing women. It is unknown whether **perindopril** enters human breast milk.

Drug Interactions

Patients on diuretics, especially those started recently, may occasionally experience an excessive reduction of BP after initiation of **perindopril** therapy. Hypotension can be minimized by either discontinuing the diuretic or increasing salt intake prior to initiation of **perindopril.** If diuretics cannot be interrupted, close medical supervision should be provided with the first dose of **perindopril,** for at least 2h, and until BP has stabilized for another hour.
Bioavailability is reduced by diuretics; this is also associated with a decrease in plasma ACE inhibition.
May increase serum potassium because of its potential to decrease aldosterone production. Use of potassium-sparing diuretics (e.g., **amiloride, spironolactone, triamterene**), potassium supplements, or other drugs capable of increasing serum potassium (e.g., **cyclosporine, heparin, indomethacin**) can increase the risk of hyperkalemia. They should be used cautiously and the serum potassium monitored frequently.
Increased serum **lithium** and symptoms of **lithium** toxicity are reported. Caution coupled to frequent monitoring of serum **lithium** levels is recommended. Use of a diuretic may further increase the risk of **lithium** toxicity.
Animal data suggest the possibility of an interaction with **gentamicin.** Use caution if both drugs must be used together.

References

Moulin B, Morin JP, Seurin-Toutain P, et al. Int J Tissue React 1990; 12:309-17.

Summary

Pregnancy Category: C (1st trimester), **D** (2nd and 3rd trimesters)
Lactation Category: U

- **Perindopril** and other inhibitors of the renin-angiotensin system are potentially teratogenic throughout pregnancy and should be avoided whenever possible.
- There are alternative agents for which there is more experience regarding use during pregnancy and lactation.
- When the mother's disease requires treatment with **perindopril,** the lowest dose should be used and coupled with close monitoring of the fetus.

Permethrin topical—(Acticin; Elimite; Nix)

International Brand Name—Assy (Argentina); Destolit (Peru); Dronol (Paraguay); Expar Shampoo (Israel); Gamabenceno Plus (Colombia); Gamaderm (Colombia); Infectopedicul (Germany); Klinits (Chile); Loxazol (Netherlands, Switzerland); Lyclear (England, Ireland, South Africa); Lyclear Creme Rinse (Israel); Lyclear Dermal Cream (Israel); Lyclear Scabies Cream (Australia); Mite-X (Israel); Nedax Plus (Brazil); New-Nok (Israel); Nix (Denmark, Finland, France, Italy, Norway, Sweden); Nix Cream (Puerto Rico); Nix Creme Rinse (Canada); Nix Dermal Cream (Canada, Puerto Rico); Nok (Israel); Novo-Herklin 2000 (Mexico); Permicren (Uruguay); Permite (India); Piopel (Honduras, Nicaragua); Pyrifoam (Australia, Philippines); Quellada Creme Rinse (Australia); Quellada Head Lice (New Zealand); Quellada-P (New Zealand); Scabmite (Indonesia); Zehu-Ze (Israel)

Drug Class	Antiparasitics; Dermatologics; Scabicides/pediculicides
Indications	Scabies
Mechanism	Disrupts nerve cell sodium channel currents in parasite
Dosage with Qualifiers	Scabies—massage into skin from head to toe, allow to remain 8-14h before bathing • **Contraindications**—hypersensitivity to drug or class • **Caution**—unknown
Maternal Considerations	**Permethrin** is rapidly metabolized to inactive metabolites that are excreted primarily in the urine. Although the amount of **permethrin** absorbed after a single application has not been precisely determined, preliminary study suggests it is less than 2% of the amount applied. There are no adequate reports or well-controlled studies in pregnant women. **Permethrin** improves maternal outcome when used as part of a broad strategy such as insecticide-incorporating nets. ***Side effects*** include burning, numbness, tingling, pruritus, and erythema.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **permethrin** crosses the human placenta. However, recent large case series are reassuring. It is unlikely the maternal systemic concentration reaches a clinically relevant level. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically.
Breastfeeding Safety	There are no adequate reports or well-controlled studies in nursing women. **Permethrin** enters human breast milk, but the kinetics remain to be elucidated. Considering the route and frequency of use, it is unlikely a maternal clinically relevant systemic concentration will be reached and sustained.
Drug Interactions	No clinically relevant interactions identified.
References	Bouwman H, Sereda B, Meinhardt HM. Environ Pollut 2006; 144:902-17. Imamura L, Hasegawa H, Kurashina K, et al. Arch Toxicol 2002; 76:392-7. Judge MR, Kobza-Black A. Br J Dermatol 1995; 132:116-9. Mytton OT, McGready R, Lee SJ, et al. BJOG 2007; 114:582-7.
Summary	**Pregnancy Category: B** **Lactation Category: S** (likely) • **Permethrin** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk. • A long clinical experience is reassuring.

Perphenazine—(Trilifan; Trilafon)

International Brand Name—APO-Perphenazine (Canada, Malaysia); Decentan (Austria, Germany, Spain); Fentazin (England, Ireland); F-Mon (Japan); Leptopsique (Mexico); Peratsin (Finland); Pernamed (Thailand); Pernazine (Thailand); Perphenan (Israel); Perzine-P (Thailand); Porazine (Thailand); Trilafon (Canada, Denmark, Indonesia, Italy, Japan, Netherlands, Norway, Philippines, South Africa, Sweden, Switzerland); Trilifan Retard (France); Trimin (Korea); Triomin (Taiwan)

Drug Class ..... Antiemetics; Antipsychotics; Antivertigo agents; Phenothiazines

Indications ..... Psychosis, severe N/V

Mechanism ..... Unknown; antagonizes D_2 receptors

Dosage with Qualifiers .....

Psychosis—8-16mg PO bid to qid; max 64mg/d
Severe N/V—begin 5mg IM/PO (avoid IV); max 24mg/d

- **Contraindications**—hypersensitivity to drug or class, CNS depression, blood dyscrasias, bone marrow depression, hepatic disease, coma, subcortical damage
- **Caution**—unknown

Maternal Considerations .....

Perphenazine is commonly combined with **amitriptyline** (Triavil, Etrafon) in the US. It increases circulating prolactin levels in both humans and rodents. There are no adequate reports or well-controlled studies in pregnant women.
Some phenothiazines have been associated with a prolongation of the QT interval.
Side effects include cardiac arrest, tachycardia, seizures, hepatotoxicity, hemolytic anemia, agranulocytosis, thrombocytopenia, neuroleptic malignant syndrome, extrapyramidal effects, tardive dyskinesia, sedation, drowsiness, dry mouth, blurred vision, N/V, rash, and anorexia.

Fetal Considerations .....

There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **perphenazine** crosses the human placenta. However, peroxidative bioactivation of **perphenazine** by human placental peroxidase occurs and may be one mechanism of the reported toxicity of other phenothiazines. Postnatal behavioral abnormalities are suggested. Rodent teratogenicity studies apparently have not been conducted.

Breastfeeding Safety .....

There are no adequate reports or well-controlled studies in nursing women. **Perphenazine** enters human breast milk. In one woman, the maternal levels were 2.1 and 3.2mcg/L after 16 and 24mg/d, and the M:P ratios were 1.1 and 0.7. The estimated dose to the infant ranged between 0.3 and 0.45mcg/kg/d, or <0.5% of the weight-adjusted maternal dose.

Drug Interactions .....

Some 10% of the Caucasian population have reduced activity of CYP2D6, so-called "poor metabolizers." Poor metabolizers have higher plasma concentrations of antipsychotic drugs at usual doses, which may correlate with emergence of side effects. In one study of elderly patients suffering dementia treated with **perphenazine,** poor metabolizers had significantly greater side effects during the first 10d of treatment than the extensive metabolizers, after which the groups tended to converge. Prospective phenotyping of elderly patients prior to antipsychotic treatment may identify those at risk for adverse events.
Use of other drugs that inhibit CYP2D6 may acutely increase plasma concentrations of antipsychotics. Among these are TCAs

and SSRIs (e.g., **fluoxetine, paroxetine, sertraline**).
Close monitoring is essential and dose reduction may become necessary.

References

Handal M, Matheson I, Bechensteen AG, Lindemann R. Tidsskr Nor Laegeforen 1995; 115:2539-40.
Olesen OV, Bartels U, Poulsen JH. Am J Psychiatry 1990; 147:1378-9.
Yang X, Kulkarni AP. Teratog Carcinog Mutagen 1997; 17:139-51.

Summary

Pregnancy Category: C
Lactation Category: U

- **Perphenazine** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.
- There are alternative agents for which there is more experience regarding use during pregnancy and lactation.

Phenacemide—(Phenurone)

International Brand Name—Phenuron (Japan)

Drug Class

Anticonvulsants

Indications

Seizures

Mechanism

Unknown; elevates seizure threshold

Dosage with Qualifiers

Seizures (complex partial resistant to other drugs)—begin 500mg PO tid ×7d before adjusting; usual dose 2-3g/d

NOTE: measure hepatic transaminases and obtain CBC before and periodically during therapy; the total number of each cell type/mm^3 is a better index of a possible blood dyscrasia than the percentage of cells. Marked depression of the blood count is an indication for withdrawal.

- **Contraindications**—hypersensitivity to drug or class, blood dyscrasias
- **Caution**—personality disorder, suicidal ideation, hepatic dysfunction, allergy

Maternal Considerations

There are no adequate reports or well-controlled studies in pregnant women. Mouse studies reveal synergy when **phenacemide** is administered with either **mephenytoin, phenobarbital,** or trimethadione.
Side effects include personality changes, hepatotoxicity, nephritis, aplastic anemia, death, neutropenia, loss of interest, depression, aggressiveness, sore throat, fever, malaise, blood dyscrasia, anorexia, weight loss, rash, Stevens-Johnson syndrome, fatigue, fever, muscle pain, elevated creatinine, and palpitations.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **phenacemide** crosses the human placenta. While it is difficult to separate the possible teratogenic effects from those of anticonvulsant agents used concurrently, limited rodent study suggests **phenacemide** is a teratogen.

Breastfeeding Safety

There is no published experience in nursing women. It is unknown whether **phenacemide** enters human breast milk.

Drug Interactions ····· Extreme caution is essential when used with any other AED known to cause similar toxic effects.
Considerable caution is indicated when used with ethotoin since paranoid symptoms have been reported.

References ····· Fabro S, Shull G, Brown NA. Teratog Carcinog Mutagen 1982; 2:61-76.

Summary ····· **Pregnancy Category: D**
Lactation Category: U
- **Phenacemide** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.
- There are alternative agents with a superior safety profile for which there is more experience regarding use during pregnancy and lactation.

Phenazopyridine—(Azo-Standard; Eridium; Geridium; Phenazodine; Pyridiate; Pyridium; Ro-Pyridine; Urodine; Urodol; Uropyridine; Viridium)

International Brand Name—Anazo (Thailand); Azo Cefasabal (Peru); Azomir (Philippines); Azopiridin (Peru); Cistalgina (Argentina); Nalixone (Mexico); Phenazo (Canada); Phendiridine (Thailand); Pirimir (Mexico); Pyridium (Brazil, Canada, Chile, Ecuador, Hong Kong, India, Indonesia, Peru, Uruguay, Venezuela); Pyronium (Belgium); Sedural (Israel); Tiotal (Paraguay); Urogen (Taiwan); Urogesic (Singapore); Urohman (Japan); Uroprin (Taiwan); Uropyridin (Japan); Uroxacin (Colombia)

Drug Class ····· Analgesics, non-narcotic; GU agents

Indications ····· Dysuria

Mechanism ····· Unknown

Dosage with Qualifiers ····· Dysuria—100-200mg PO tid pc ×2d

NOTE: turns urine red/orange; may be combined with ***sulfamethoxazole*** *(Azo-Gantanol) or* ***sulfisoxazole*** *(Azo-Gantrisin; Azo-Sulfisoxazole; Azo-Truxazole; Sul-Azo).*

- **Contraindications**—hypersensitivity to drug or class, renal insufficiency, uremia, hepatitis, glomerulonephritis, pyelonephritis during pregnancy
- **Caution**—unknown

Maternal Considerations ····· **Phenazopyridine** has a topical analgesic effect on urinary tract mucosa, helping to relieve pain, burning, urgency, and frequency. There are no adequate reports or well-controlled studies in pregnant women.
Side effects include anemia, headache, N/V, dyspepsia, pruritus, and stained contact lenses.

Fetal Considerations ····· There are no adequate reports or well-controlled studies in human fetuses. **Phenazopyridine** does not apparently cross the human placenta to any significant degree. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically.

Breastfeeding Safety ····· There are no adequate reports or well-controlled studies in nursing women. It is unknown whether **phenazopyridine** enters

	human breast milk. However, it is generally considered compatible with breastfeeding based on long clinical experience.
Drug Interactions	No clinically relevant interactions identified.
References	Meyer BA, Gonik B, Creasy RK. Am J Perinatol 1991; 8:297-9.
Summary	**Pregnancy Category: B** **Lactation Category: S** • **Phenazopyridine** has been used for decades during pregnancy and lactation. • Though there is little objective study, it is generally considered safe for listed indications.

Phendimetrazine—(Adipost; Anorex; Appecon; Bontril; Cam-Metrazine; Dital; Melfiat; Metra; Obalan; Obezine; P.D.M.; Phenazine; Phendiet; Phendimetrazine Bitartrate; Plegine; Prelu-2; PT 105; Statobex; X-Trozine)

International Brand Name—Furing (Korea); Obesan-X (South Africa)

Drug Class	Anorexiants; CNS stimulants
Indications	Obesity
Mechanism	CNS stimulant
Dosage with Qualifiers	Obesity—35mg PO bid or tid; individualize to the lowest effective dose *NOTE: for short-term use only coupled to calorie restriction; tolerance occurs within weeks.* • **Contraindications**—hypersensitivity to drug or class, substance abuse, advanced arteriosclerosis, symptomatic CV disease, moderate or severe hypertension, hyperthyroidism, glaucoma, ingestion of other CNS stimulants, agitation • **Caution**—mild hypertension, diabetes mellitus
Maternal Considerations	**Phendimetrazine** is a phenylalkylamine sympathomimetic with pharmacologic activity similar to **amphetamine.** Obese adult patients given dietary instruction and treated with "anorectic" drugs lost a fraction of a pound more during short-term trials compared to those treated with placebo and diet. Addiction is a risk. There is no published experience with **phendimetrazine** in pregnancy, and no indications for its use. ***Side effects*** include restlessness, insomnia, agitation, flushing, tremor, sweating, dizziness, headache, psychosis, blurred vision, tachycardia, hypertension, dry mouth, nausea, diarrhea, constipation, stomach pain, urinary frequency, dysuria, and libido change.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **phendimetrazine** crosses the human placenta. Similar compounds do. Rodent teratogenicity studies have apparently not been performed.

Breastfeeding Safety	There are no published studies in nursing women. It is unknown whether **phendimetrazine** enters human breast milk.
Drug Interactions	May result in a hypertensive crisis when used within 14d of an MAOI. Caution is indicated if used with other CNS depressants as the combination may be additive.
References	There is no published experience in pregnancy or during lactation.
Summary	**Pregnancy Category: C** **Lactation Category: U** • There are no indications for the use of **phendimetrazine** during pregnancy and lactation. • **Phendimetrazine** is of limited value for the treatment of obesity in nonpregnant women.

Phenelzine—(Nardil)

International Brand Name—Nardelzine (Belgium, Spain); Nardil (Australia, Canada, England, Ireland)

Drug Class	Antidepressants; MAOIs
Indications	Depression, bulimia
Mechanism	Inhibits MAO
Dosage with Qualifiers	Depression—15mg PO tid; response may take at least 4w Bulimia—begin 15mg PO tid; max 30mg PO tid *NOTE: wait >4w after stopping an SSRI before initiating.* • **Contraindications**—hypersensitivity to drug or class, CHF, hypertension, pheochromocytoma, hepatic disease, general anesthesia or **cocaine** use within 10d, **bupropion** use • **Caution**—unknown
Maternal Considerations	Depression is common during and after pregnancy, but typically goes unrecognized. Pregnancy is not a reason *a priori* to discontinue psychotropic drugs. **Phenelzine** is often effective in treating depression characterized as atypical, nonendogenous, or neurotic. These patients frequently have anxiety and depression mixed with phobic or hypochondriacal features. There are no adequate reports or well-controlled studies of **phenelzine** in pregnant women. Most publications consist of case reports or small series. Many drugs interact with MAOIs. Well-documented and potentially fatal interactions between MAOIs and opioids, notably **meperidine,** require that labor analgesia be well planned in advance. Pressor agents should be avoided as even indirect-acting drugs can produce severe hypertension. ***Side effects*** include hypertensive crisis, intracranial hemorrhage, seizures, hypermetabolic syndrome, hypomania, respiratory or CNS depression, coma, leukopenia, SLE-like syndrome, headache, dizziness, weakness, tremor, constipation, dry mouth, dyspepsia, elevated LFTs, weight gain, orthostatic hypotension, hyperreflexia, nystagmus, and edema.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **phenelzine** crosses the

human placenta. As for most psychotropic drugs, monotherapy and the smallest effective quantity given in divided doses may reduce risk by minimizing the systemic peaks. Rodent teratogenicity studies have apparently not been performed.

Breastfeeding Safety — There is no published experience in nursing women. It is unknown whether **phenelzine** enters human breast milk.

Drug Interactions — Nonselective MAOIs may cause serious, sometimes fatal, reactions if combined with serotonergic agents (e.g., **citalopram, dexfenfluramine, fluoxetine, fluvoxamine, paroxetine, sertraline, venlafaxine**), so co-administration should be avoided.

References

Gracious BL, Wisner KL. Depress Anxiety 1997; 6:124-8.
Pavy TJ, Kliffer AP, Douglas MJ. Can J Anaesth 1995; 42:618-20.

Summary

Pregnancy Category: C
Lactation Category: U

- **Phenelzine** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Phenobarbital—(Barbita; Dormiral; Luminaletten; Luminal Sodium; Phenobarbital Sodium; Phenobarbitone; Sedofen; Solfoton)

International Brand Name—Alepsal (Mexico); Andral (Philippines); Atrofen (Dominican Republic); Barbilettae (Finland); Barbiphenyl (Finland); Dormital (Paraguay); Fenemal (Denmark, Norway); Fenemal NM Pharma (Sweden); Fenobarbital (Ecuador, Peru); Gardenal (Belgium, Czech Republic, France, Greece, India, South Africa, Spain, Uruguay, Venezuela); Gardenale (Italy); Lethyl (South Africa); Linasen (Japan); Luminal (Argentina, Germany, India, Korea, Philippines, Spain); Luminale (Italy); Luminaletas (Argentina, Spain); Luminaletten (Germany); Luminalettes (Belgium); Luminalum (Poland); Menobarb (Thailand); Phenobal (Japan); Phenotal (Thailand); Sevenal (Hungary); Uni-Feno (Hong Kong)

Drug Class — Anticonvulsants; Barbiturates; Preanesthetics; Sedatives/hypnotics

Indications — Seizure disorder, status epilepticus, sedation

Mechanism — Nonselective CNS depressant of the sensory cortex and motor activity, alters cerebellar function

Dosage with Qualifiers

Seizure disorder—load with 15-20mg/kg IV, then 60mg PO bid or tid
Status epilepticus—10-20mg/kg IV ×1; may repeat if necessary
Sedation—10-40mg PO/IM/IV tid

*NOTE: avoid abrupt withdrawal; may be combined with **phenytoin, belladonna,** or ergotrate.*

- **Contraindications**—hypersensitivity to drug or class, history of porphyria, hepatic or respiratory dysfunction
- **Caution**—uremia, depression or suicidal ideation

Maternal Considerations — Less time is spent in REM during barbiturate-induced sleep compared to normal sleep. Abrupt cessation may trigger increased dreaming, nightmares, and/or insomnia. Barbiturates provide little analgesia at subanesthetic doses; in fact, they may increase the reaction to painful stimuli. There are no adequate reports or well-controlled studies of **phenobarbital** in pregnant women. Several investigations indicate clearance is increased and

that periodic dose adjustment may be necessary. All adjustments should be guided by clinical symptoms. In addition, **phenobarbital** impacts the a number of liver CYPs.
Phenobarbital is not effective for the treatment of cholestasis of pregnancy. Planned pregnancy and counseling before conception are crucial. It is important to discuss folic acid supplementation, medication adherence, the risk of teratogenicity, and the importance of prenatal care.
Side effects include respiratory depression, habituation, erythema multiforme, Stevens-Johnson syndrome, hepatitis, angioedema, megaloblastic anemia, blood dyscrasias, TTP, drowsiness, lethargy, N/V, rash, urticaria, pain, thrombophlebitis, swelling, and necrosis.

Fetal Considerations

There are no adequate reports or well-controlled studies of **phenobarbital** in human fetuses. Barbiturates readily cross the human placental barrier and are distributed throughout fetal tissues, with highest concentration found in the placenta, fetal liver, and brain. The F:M ratio approximates unity. Withdrawal symptoms can occur in neonates exposed to barbiturates throughout the 3rd trimester. Case-control studies disagree on whether there is a relationship between barbiturate use and a higher than expected incidence of birth defects (oral clefting and cardiac malformations). Otherwise healthy women attempting suicide with barbiturates did not experience an increase in adverse pregnancy outcomes. Antenatal **phenobarbital** exposure does not affect the neurodevelopmental outcome of preterm infants at 18-22mo of age. It also does not reduce the risk of neonatal IVH.

Breastfeeding Safety

Phenobarbital enters human breast milk, and the magnitude is altered by polypharmacy especially early in breastfeeding. Breastfeeding is controversial because of the potential for slow elimination by some neonates. Infant sedation is possible, and the infant should be observed closely. Serum monitoring may be advisable if **phenobarbital** is continued during breastfeeding.

Drug Interactions

Lowers the plasma levels of oral anticoagulants (e.g., acenocoumarol, **dicumarol,** and phenprocoumon, **warfarin**) by increasing their metabolism and resulting in a lower PT. Patients stabilized on anticoagulant therapy may require adjustment if barbiturates are added or withdrawn.
Barbiturates appear to enhance the metabolism of exogenous corticosteroids through the induction of liver microsomal enzymes. Patients stabilized on corticosteroid therapy may require a dose adjustment if barbiturates are added or withdrawn.
May interfere with the absorption of orally administered **griseofulvin,** thus decreasing its blood level. The effect of the decreased blood level on therapeutic response has not been established. It is preferable to avoid co-administration.
Shortens the t/2 of **doxycycline** for as long as 2w after the barbiturate therapy has ended, probably through the induction of liver microsomal enzymes that metabolize the antibiotic.
The effect of barbiturates on **phenytoin** metabolism is variable; **phenytoin** and barbiturate blood levels should be monitored frequently.
Valproate and **valproic acid** appear to decrease barbiturate metabolism; thus, barbiturate levels should be monitored and the dose adjusted as indicated.
Use of other CNS depressants, including other sedatives or hypnotics, antihistamines, tranquilizers, or ethanol, may produce additive depressant effects.
MAOIs inhibit the metabolism of and can prolong the effects of barbiturates.

May decrease the effect of **estradiol** by increasing its metabolism. There are reports of patients treated with AEDs (e.g., **phenobarbital**) who became pregnant using oral contraceptives. An alternate contraceptive method should be considered.

References

Arpino C, Brescianini S, Robert E, et al. Epilepsia 2000; 41:1436-43.
Bar-Oz B, Nulman I, Koren G, Ito S. Paediatr Drugs 2000; 2:113-26.
Crowther CA, Henderson-Smart DJ. Cochrane Database Syst Rev 2001; (2):CD000164.
Dessens AB, Cohen-Kettenis PT, Mellenbergh GJ, et al. Teratology 2001; 64:181-8.
Ejiri N, Katayama K, Doi K. Exp Mol Pathol 2005; 78:150-5.
Gomita Y, Furuno K, Araki Y, et al. Am J Ther 1995; 2:968-71.
Jenkins JK, Boothby LA. Ann Pharmacother 2002; 36:1462-5.
Kuhnz W, Koch S, Helge H, Nau H. Dev Pharmacol Ther 1988; 11:147-54.
Shankaran S, Papile LA, Wright LL, et al. Am J Obstet Gynecol 2002; 187:171-7.
Timmermann G, Czeizel AE, Banhidy F, Acs N. Toxicol Ind Health 2008; 24:109-19.

Summary

Pregnancy Category: D
Lactation Category: S (likely)

- **Phenobarbital** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Phenoxybenzamine—(Dibenzyline)

International Brand Name—Dibenyline (Belgium, Czech Republic, England, Hong Kong, Ireland, Netherlands, South Africa, Taiwan); Dibenzyran (Austria, Bulgaria, Germany); Fenoxene (India)

Drug Class

Adrenergic antagonists; α-Blockers; Antihypertensives

Indications

Pheochromocytoma

Mechanism

Nonspecific α-antagonist

Dosage with Qualifiers

Pheochromocytoma—begin 10mg PO bid, increasing by 10mg qod until target BP achieved

- **Contraindications**—hypersensitivity to drug or class
- **Caution**—renal dysfunction, CAD

Maternal Considerations

Phenoxybenzamine is a long-acting, α-receptor antagonist that creates a "chemical sympathectomy." It increases blood flow to the skin, mucosa, and abdominal organs, and lowers both supine and erect BP. It has no effect on the parasympathetic system. There are no adequate reports or well-controlled studies in pregnant women. Though there are numerous case reports confirming its efficacy for pheochromocytoma during pregnancy, it does not reverse the acute decrease in maternal cardiac output associated with a hypertensive episode.
Side effects include hypotension, CHF, reflex tachycardia, nasal congestion, miosis, dyspepsia, and fatigue.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. **Phenoxybenzamine** crosses the human placenta and is concentrated in the fetal plasma, achieving an F:M ratio of 3:1. Appropriate rodent studies apparently have not been conducted.

Breastfeeding Safety ..... There is no published experience in nursing women. It is unknown whether **phenoxybenzamine** enters human breast milk.

Drug Interactions ..... May interact with agents that stimulate both α- and β-adrenergic receptors (i.e., **epinephrine**) to produce an exaggerated hypotensive response and tachycardia.
Blocks the hyperthermia associated with levarterenol, and the hypothermia associated with **reserpine.**

References .....
Combs CA, Easterling TR, Schmucker BC, Benedetti TJ. Obstet Gynecol 1989; 74:439-41.
Dugas G, Fuller J, Singh S, Watson J. Can J Anaesth 2004; 51:134-8.
Lyons CW, Colmorgen GH. Obstet Gynecol 1988; 72:450-1.
Martinez Brocca MA, Acosta Delgado D, Quijada D, et al. Gynecol Endocrinol 2001; 15:439-42.
Santeiro ML, Stromquist C, Wyble L. Ann Pharmacother 1996; 30:1249-51.

Summary .....
Pregnancy Category: C
Lactation Category: U
- **Phenoxybenzamine** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Phensuximide—(Milontin)

International Brand Name—None identified.

Drug Class ..... Anorexiants; Anticonvulsants

Indications ..... Absence (petit mal) seizures

Mechanism ..... Unknown

Dosage with Qualifiers ..... Absence (petit mal) seizures—0.5-1g PO bid or tid

NOTE: avoid abrupt withdrawal.

- **Contraindications**—hypersensitivity to drug or class
- **Caution**—hepatic or renal dysfunction, SLE

Maternal Considerations ..... **Phensuximide** suppresses the paroxysmal, 3cycles/sec spike-and-wave activity associated with the lapse of consciousness common in absence (petit mal) seizures. There is no published experience with **phensuximide** during pregnancy. Consideration may be given to stopping **phensuximide** if the severity and frequency of seizures are such they do not pose a serious threat to the patient. However, even minor seizures pose some hazard to the embryo and fetus.
Side effects include pruritus, severe blood dyscrasias, granulocytopenia, transient leukopenia, pancytopenia with or without bone marrow suppression, sore throat, fever, evaluated LFTs, muscle weakness, N/V, anorexia, drowsiness, dizziness, ataxia, headache, dreamlike state, lethargy, skin eruptions, erythema multiforme, Stevens-Johnson syndrome, erythematous rashes, and alopecia.

Fetal Considerations ..... There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **phensuximide** crosses the human placenta. It is difficult to separate the impact of **phensuximide** from other agents used concurrently and the potential impact of

the seizures. The sole published estimate is that the risk is similar to **ethosuximide.** Limited rodent studies are reassuring.

Breastfeeding Safety — There is no published experience in nursing women. It is unknown whether **phensuximide** enters human breast milk.

Drug Interactions — May interact with other AEDs necessitating periodic serum level.

References

Fabro S, Shull G, Brown NA. Teratog Carcinog Mutagen 1982; 2:61-76.

Summary

Pregnancy Category: D
Lactation Category: U

- **Phensuximide** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.
- **Ethosuximide** is probably the drug of first choice in absence seizures.

Phentermine—(Adipex-P; Dapex-37.5; Fastin; Obe-Nix; Oby-Cap; Oby-Trim; Ona-Mast; Panbesyl; Phentercot; Phentride; T-Diet; Teramine; Tora; Umi-Pex 30; Zantryl)

International Brand Name—Minobese-Forte (South Africa); Panbesy (Hong Kong, Malaysia, Thailand); Panbesyl Nyscaps (Belgium); Redusa (Hong Kong); Umine (New Zealand)

Drug Class — Anorexiants; CNS stimulants

Indications — Obesity

Mechanism — Sympathomimetic

Dosage with Qualifiers

Obesity—8mg PO tid

- **Contraindications**—hypersensitivity to drug or class, severe hypertension, symptomatic cardiovascular disease, MAOI use <14d, glaucoma, agitated states, history of substance abuse
- **Caution**—unknown

Maternal Considerations

Phentermine is a sympathomimetic similar to **amphetamine.** It is indicated only for short-term monotherapy, and the associated weight loss is typically modest. Tachyphylaxis and tolerance occur with **phentermine** and all related drugs. Serious regurgitant disease of the aortic, mitral, and tricuspid valves occurs in patients taking a combination of **phentermine** and **fenfluramine.** The latter was withdrawn from the US market, but it is not definitive which drug was at fault. There are no adequate reports or well-controlled studies of **phentermine** in pregnant women, and there is probably no indication for its use during either pregnancy or lactation. In one case-control study, the rate of gestational diabetes was significantly greater in the women who took **phentermine** and **fenfluramine** during the 1st trimester. In the guinea pig, **mephentermine** reduces uterine blood flow. **Mephentermine** appears as effective as **ephedrine** for the the treatment of hypotension associated with subarachnoid block. ***Side effects*** include hypertension, insomnia, palpitations, dry mouth, headache, dizziness, excitation, constipation, diarrhea, and urticaria.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **phentermine** crosses the human placenta. Similar agents do cross. There was no significant increase in pregnancy wastage or major malformations in almost 100 women who took **phentermine** and **fenfluramine** during pregnancy. Rodent teratogenicity studies have not been performed. A decrease in serotonergic axons in the hippocampus and mitral valve thickening was observed postnatally in pups of rats exposed to the combination antenatally.

Breastfeeding Safety

There is no published experience in nursing women. It is unknown whether **phentermine** enters human breast milk.

Drug Interactions

Use with ethanol may result in an adverse drug interaction.

References

Bratter J, Gessner IH, Rowland NE. Eur J Pharmacol 1999; 369:R1-3.
Chestnut DH, Ostman LG, Weiner CP, et al. Anesthesiology 1988; 68:363-6.
Jones KL, Johnson KA, Dick LM, et al. Teratology 2002; 65:125-30.
Kansal A, Mohta M, Sethi AK, et al. Anaesthesia 2005; 60:28-34.

Summary

Pregnancy Category: C
Lactation Category: U

- There are no indications for **phentermine** during pregnancy and lactation.

Phentolamine—(Regitine)

International Brand Name—Regitin (Czech Republic, Denmark, Germany, Hungary, Switzerland); Regitina (Peru); Rogitine (England, Ireland); Z-Max (Mexico, Peru)

Drug Class

Adrenergic antagonists; α-Blocker; Antihypertensives

Indications

Pheochromocytoma (preoperation), hypertensive crisis, extravasation necrosis

Mechanism

α-Adrenergic antagonist

Dosage with Qualifiers

Pheochromocytoma (preoperation)—5mg IM/IV 1-2h preoperatively; may repeat as necessary
Hypertensive crisis—5mg IV/IM
Extravasation necrosis—5-10mg/10ml NaCl injected into affected area

- **Contraindications**—hypersensitivity to drug or class, MI, CAD
- **Caution**—peptic ulcer disease

Maternal Considerations

Phentolamine is a short-acting α-antagonist with direct iono- and chronotropic actions. There are no adequate reports or well-controlled studies in pregnant women. There are a number of case reports documenting efficacy for the noted indications. Rodent studies suggest **phentolamine** reduces uterine contractility postpartum, but there is no clinical evidence of such activity in women.
Side effects include MI, stroke, hypotension, arrhythmia, tachycardia, peptic ulceration, weakness, dizziness, flushing, N/V, diarrhea, abdominal pain, and nasal congestion.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **phentolamine** crosses the human placenta. Rodent studies are reassuring for the most part. Only in the mouse was there evidence of IUGR and skeletal delay after the maternal dose exceeded 25× the MRHD.

Breastfeeding Safety

There is no published experience in nursing women. It is unknown whether **phentolamine** enters human breast milk.

Drug Interactions

No clinically relevant interactions identified.

References

O'Halloran T, McGreal G, McDwermott E, O'Higgins N. Ir Med J 2001; 94:200-3.
Takahashi K, Sai Y, Nosaka S. Eur J Anaesthesiol 1998; 15:364-6.
Zupko I, Gaspar R, Kovacs L, Falkay G. Life Sci 1997; 61:PL159-63.

Summary

Pregnancy Category: C
Lactation Category: U

- **Phentolamine** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Phenylephrine—(Ah-Chew D; Ak-Dilate; Dilatair; Efrin; Fenilefrina; I-Phrine; Minims; Mydfrin; Neo-Synephrine; Neofrin; Ocu-Phrin; Phenylephrine HCl; Pupiletto-Forte; Ricobid-D; Spectro-Dilate; Spectro-Nephrine; Storz-Fen)

International Brand Name—Af-Taf (Israel); Albalon Relief (New Zealand); Drosin (India); Efrin-10 (Israel); Efrisel (Indonesia); Isopto Frin (Belgium, Czech Republic, Ecuador, Malaysia); Metaoxedrin (Denmark, Norway, Sweden); Minims Phenylephrine HCL 10% (South Africa); Minims Phenylephrine Hydrochloride (England); Nefrin-Ofteno (Costa Rica, Dominican Republic, El Salvador, Guatemala, Honduras, Nicaragua, Panama); Neo-Synephrine Ophthalmic Viscous 10% (Australia); Neosynephrine (Belgium, Sweden); Neosynephrine 10% Chibret (France); Neosynephrine Faure 10% (France); Neosynephrin-POS (Korea); Oftan-Metaoksedrin (Finland); Optistin (Italy); Phenylephrine (Netherlands); Prefrin (Austria, Ecuador, Greece, Hong Kong, Indonesia, New Zealand, South Africa, Thailand); Pupiletto Forte (India); Vistafrin (Spain); Vistosan (Germany)

Drug Class

Adrenergic agonists; α-Agonist; Inotropes; Pressors; Sympathomimetics

Indications

Shock, nasal congestion, hypotension after neuraxial anesthesia

Mechanism

α-Adrenergic agonist

Dosage with Qualifiers

Shock—40-180mcg/min infusion, or 50mcg IV bolus
Nasal congestion—2-3gtt per nostril q4h; do not exceed 0.25% for more than 3d
Hypotension, spinal or epidural—50-100mcg IV bolus for aggressive support of arterial BP at cesarean delivery

NOTE: frequently combined with a large range of preparations for symptom relief and with topical anesthetics to prolong their duration of action; available in ophthalmic solutions.

- **Contraindications**—hypersensitivity to drug or class, hypertension, ventricular tachycardia
- **Caution**—diabetes mellitus, thyroid disease

Maternal Considerations

Allergic rhinitis affects about ⅓ of reproductive-age women. More than 170 OTC preparations contain a sympathomimetic agent as their active ingredient. **Phenylephrine** should be considered a second-line agent behind 1st- and 2nd-generation antihistamines. It is popular for the prevention of hypotension following neuraxial anesthesia during cesarean delivery especially when **ephedrine** might be contraindicated (e.g., maternal cardiac disease). There was no difference in the rostral spread of spinal hyperbaric **bupivacaine** with prophylactic **phenylephrine** than with **ephedrine.** However, there may be an unexplained increased incidence of fetal acidosis with **ephedrine.** Further, there is evidence that longer spinal-delivery intervals increased the risk of fetal acidosis developing with **ephedrine,** but not **phenylephrine.** No prophylactic technique seems to completely eliminate the need for treatment.
Side effects include arrhythmia, MI, asthma exacerbation, hypertension, palpitations, headache, PVCs, tissue necrosis, and excitability.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **phenylephrine** crosses the human placenta. **Pseudoephedrine** is associated with intestinal atresias, but the same has yet to be reported for **phenylephrine.** The combination of **pseudoephedrine, phenylephrine,** and **phenylpropanolamine** (Triaminic) may be associated with distal limb reduction.

Breastfeeding Safety

There is no published experience in breastfeeding women. It is unknown whether **phenylephrine** enters human breast milk. However, considering the frequency of use, dose, and route, it seems unlikely the breastfed neonate would ingest a clinically relevant amount.

Drug Interactions

Use with an MAOI within 21d may be associated with exaggerated adrenergic effects. The pressor response may also be potentiated by TCAs.

References

Ayorinde BT, Buczkowski P, Brown J, et al. Br J Anaesth 2001; 86:372-6.
Cooper DW, Gibb SC, Meek T, et al. Br J Anaesth 2007; 98:649-56.
Cyna AM, Andrew M, Emmett RS, et al. Cochrane Database Syst Rev 2006; (4):CD002251.
Gilbert-Barness E, Drut RM. Vet Hum Toxicol 2000; 42:168-71.
Langesaeter E, Rosseland LA, Stubhaug A. Anesthesiology 2008; 109:856-63.
Lee A, Ngan Kee WD, Gin T. Anesth Analg 2002; 94:920-6.
Mazzotta P, Loebstein R, Koren G. Drug Saf 1999; 20:361-75.
Saravanan S, Kocarev M, Wilson RC, et al. Br J Anaesth 2006; 96:95-9.
Thomas DG, Robson SC, Redfern N, et al. Br J Anaesth 1996; 76:61-5.
Werler MM, Sheehan JE, Mitchell AA. Am J Epidemiol 2002; 155:26-31.

Summary

Pregnancy Category: C
Lactation Category: S (likely)

- **Phenylephrine** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.
- A 1st- or 2nd-generation antihistamine is preferred for the symptomatic relief of nasal congestion.

Phenylpropanolamine—(Kleer; Propan; Rhindecon)

International Brand Name—None identified.

Drug Class	Adrenergic agonists; Decongestants
Indications	Nasal decongestant
Mechanism	Sympathomimetic amine
Dosage with Qualifiers	Nasal congestion—75mg PO q12h prn (XR tabs); alternatively, 25mg PO q4h (immediate release) *NOTE: previously included in a range of OTC preparations, the FDA ordered removal of **phenylpropanolamine** from the US market because of the associated risk of stroke.* *NOTE: may be contained in combination with other agents in OTC products marketed outside the US.* • **Contraindications**—severe hypersensitivity to drug or class, severe hypertension, severe CAD, concurrent MAOI use • **Caution**—hypertension, diabetes mellitus, ischemic heart disease, increased intraocular pressure, hyperthyroidism, hyperreactivity to **ephedrine**
Maternal Considerations	More than 170 OTC preparations contain a sympathomimetic agent as their active ingredient. An estimated 5 billion doses of **phenylpropanolamine** are taken each year. There are no adequate reports or well-controlled studies in pregnant women. The authors of one small RCT concluded that 50mg bid may be an effective and safe treatment in pregnancy rhinitis. Ventricular arrhythmia during pregnancy and intracranial hemorrhage postpartum are reported. The FDA required the removal of **phenylpropanolamine** in 2005 because of an increased risk of stroke. The agency estimated that it caused 200-500 strokes annually among 18-49y-old users. ***Side effects*** include tachycardia, palpitations, headache, dizziness, N/V, fear, anxiety, weakness, pallor, insomnia, hallucinations, CNS depression, stroke, arrhythmia, and CV collapse.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **phenylpropanolamine** crosses the human placenta. Epidemiologic studies are reassuring. Rodent reproduction and teratogenicity studies have not been conducted. **Pseudoephedrine** is associated with intestinal atresias, but similar data for **phenylpropanolamine** are not available. The combination of **pseudoephedrine, phenylephrine,** and **phenylpropanolamine** (Triaminic) is associated with distal limb reduction. Other epidemiologic evidence suggests a relationship between 1st trimester use and gastroschisis.
Breastfeeding Safety	There are no adequate reports or well-controlled studies in nursing women. It is unknown whether **phenylpropanolamine** enters human breast milk.
Drug Interactions	MAOIs may enhance the BP effects. May reduce the effects of antihypertensive drugs.
References	Gilbert-Barness E, Drut RM. Vet Hum Toxicol 2000; 42:168-71. Källén BA, Olausson PO. Am J Obstet Gynecol 2006; 194:480-5. Maher LM, Peterson PL, Dela-Cruz C. Neurology 1987; 37:1686.

Onuigbo M, Alikhan M. South Med J 1998; 91:1153-5.
Toll K, Graf P. Rhinology 2006; 44:274-7.
Werler MM, Sheehan JE, Mitchell AA. Am J Epidemiol 2002; 155:26-31.
Werler MM, Sheehan JE, Mitchell AA. Epidemiology 2003;14:349-54.

Summary

Pregnancy Category: C
Lactation Category: U

- **Phenylpropanolamine** is being withdrawn from the US market, though the magnitude of risk is unclear.
- A 1st- or 2nd-generation antihistamine is preferred for the symptomatic relief of nasal congestion.

Phenytoin—(Aladdin; Aleviatin; Dantoin; Decatona; Dilantin; Ditoin; Ditomed; Epilantin-E; Eptoin; Hidantoina; Hydantol; Neosidantoina; Phenilep; Zentropil)

International Brand Name—Antisacer (Poland); Difhydan (Denmark); Di-Hydan (France); Dilantin (Canada, France, India, Israel, Malaysia, Philippines, Taiwan, Thailand); Dintoina (Italy); Diphantoine (Netherlands); Epamin (Ecuador, Mexico); Epanutin (Sweden); Epilan-D (Austria); Fenantoin (Sweden); Fenytoin (Denmark); Hydantin (Finland); Lehydan (Sweden); Nuctane (Mexico); Phenhydan (Austria, Germany, Switzerland)

Drug Class

Anticonvulsants; Hydantoins

Indications

Seizure disorder, status epilepticus

Mechanism

Regulates motor cortex neuronal voltage-dependent sodium and calcium channels

Dosage with Qualifiers

Seizure disorder—load with 400mg, 300mg, and 300mg PO 2-4h apart, then 300-400mg PO qd (or divided bid); alternatively, 10-20mg/kg IV ×1, then 4-6mg/kg IV qd
Status epilepticus—15-20mg/kg IV q30min prn; max 1500mg/d

NOTE: therapeutic level 10-20mcg/ml; recommend continuous ECG during load and not to exceed 50mg/min IV; avoid abrupt withdrawal; available in oral and parenteral forms.

- **Contraindications**—hypersensitivity to drug or class, SA or AV block (IV), sinus bradycardia (IV), Adams-Stokes syndrome (IV)
- **Caution**—hepatic or renal dysfunction, hypotension, CV disease, diabetes mellitus, porphyria, thyroid disease, alcohol use

Maternal Considerations

Phenytoin is a 1st-generation, enzyme-inducing anticonvulsant. Stable **phenytoin** serum levels are achieved in most, though there is wide variability with equivalent doses. Patients with unusually low levels may be either noncompliant or hypermetabolizers. Unusually high levels can result from hepatic disease, congenital enzyme deficiency, or other drugs that interfere with metabolism. Clearance is increased during pregnancy, with concentrations declining to half of prepregnancy if the dose is not adjusted. Dose adjustments should be based on clinical symptoms, and not solely serum drug concentrations. **Phenytoin** is highly protein-bound,

and unbound drug levels are less affected than total concentrations. **Phenytoin** may impair the effect of **corticosteroids, coumadin, digitoxin, doxycycline, estrogens, furosemide,** oral contraceptives, **quinidine, rifampin, theophylline,** and vitamin D. Drug interactions between enzyme-inducing anticonvulsants such as **phenytoin** and contraceptives are well-documented. Either a higher dose oral contraceptive or a second contraceptive method is recommended. Planned pregnancy and counseling before conception is crucial, and should include information on the risk of teratogenicity, need for folate supplementation, and the importance of prenatal care.

Side effects include fibrillation (IV), hypotension (IV), CV collapse (IV), hepatotoxicity, hepatitis, gingival hyperplasia, thrombocytopenia, leukopenia, agranulocytosis, pancytopenia, megaloblastic anemia, exfoliative dermatitis, periarteritis nodosa, Stevens-Johnson syndrome, toxic epidermal necrolysis, tissue necrosis (IV), hypersensitivity syndrome, lymphoma, SLE, osteomalacia, N/V, rash, nystagmus, ataxia, slurred speech, dizziness, confusion, somnolence, constipation, headache, insomnia, tremor, hyperglycemia, and coarse facies.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. **Phenytoin** crosses the human placenta apparently by passive diffusion. The risk of major malformations in the offspring of women receiving AEDs is double the general population. Risk factors include dose and polytherapy. **Phenytoin** is specifically associated with congenital heart defects and cleft palate. There is evidence that a **phenytoin**-induced embryonic arrhythmia is one mechanism of teratogenicity. The arrhythmia reflects the ability of **phenytoin** to inhibit current in a specific potassium channel (I_{Kr}), and may cause embryonic ischemia-reperfusion injury with the generation of reactive oxygen species. Exposure to **phenytoin** *in utero* can lead to psychomotor delay. Either midface or digit hypoplasia correlates with neurodevelopmental compromise. *In vitro,* **phenytoin** causes neuronal cell death. **Carbamazepine** and **topiramate** alone did not induce neuronal death, but both drugs exacerbate **phenytoin**-induced cell death. In contrast, co-treatment with **levetiracetam** and **carbamazepine** does not enhance cell death in the developing brain. Thus, it may be possible to avoid proapoptotic effects, even in polytherapy, by choosing appropriate drugs. Prior reports of an increased risk of neonatal intracranial hemorrhage after *in utero* **phenytoin** exposure due to vitamin K deficiency have not been substantiated. As with most psychotropic drugs, the risks may be minimized by monotherapy and the smallest effective quantity given in divided doses to minimize the serum peaks.

Breastfeeding Safety

There are no adequate reports or well-controlled studies in nursing women. The transfer of **phenytoin** into human breast milk appears relatively low, and it is generally considered safe for breastfeeding.

Drug Interactions

Many drugs may increase or decrease **phenytoin** levels. Serum level measurements are especially helpful when possible drug interactions are suspected.

Drugs that may increase serum levels include **amiodarone, chloramphenicol, chlordiazepoxide, diazepam, dicumarol, disulfiram,** estrogens, ethanol, H_2 antagonists, **halothane, isoniazide, methylphenidate,** phenothiazines, phenylbutazone, salicylates, succinimides, sulfonamides, **tolbutamide,** and **trazodone.**

Drugs that may decrease serum levels include **carbamazepine,** chronic ethanol abuse, **reserpine,** and **sucralfate.**
Moban brand of **molindone** contains calcium that interfere with the absorption of **phenytoin.** Ingestion times of **phenytoin** and antacid preparations containing calcium should be staggered in patients with low serum **phenytoin** levels.
Drugs that may either increase or decrease serum levels include **phenobarbital, valproate,** and **valproic acid.** Similarly, the effect of **phenytoin** on **phenobarbital, valproate,** and **valproic acid** levels is unpredictable.
Impairs the efficacy of corticosteroids, coumarin anticoagulants, **digitoxin, doxycycline,** estrogens, **furosemide,** oral contraceptives, **quinidine, rifampin, theophylline,** and vitamin D.

References

Azarbayjani F, Danielsson BR. Epilepsia 2002; 43:457-68.
Beghi E, Annegers JF, The Collaborative Group for the Pregnancy Registries in Epilepsy. Epilepsia 2001; 42:1422-5.
Choulika S, Grabowski E, Holmes LB. Am J Obstet Gynecol 2004; 190:882-3.
Crawford P. CNS Drugs 2002; 16:263-72.
Holmes LB, Coull BA, Dorfman J, Rosenberger PB. J Pediatr 2005; 146:118-22.
Kaaja E, Kaaja R, Matila R, Hiilesmaa V. Neurology 2002; 58:549-53.
Kim J, Kondratyev A, Gale K. J Pharmacol Exp Ther 2007; 323:165-73.
Leppik IE, Rask CA. Semin Neurol 1988; 8:240-6.
McAuley JW, Anderson GD. Clin Pharmacokinet 2002; 41:559-79.
Nau H, Kuhn W, Egger HJ, et al. Clin Pharmacokinet 1982; 7:508-43.
Puhó EH, Szunyogh M, Métneki J, Czeizel AE. Cleft Palate Craniofac J 2007; 44:194-202.
Shimoyama R, Ohkubo T, Sugawara K, et al. J Pharm Biomed Anal 1998; 17:863-9.
Steen B, Rane A, Lonnerholm G, et al. Ther Drug Monit 1982; 4:331-4.
Wide K, Henning E, Tomson T, Winbladh B. Acta Paediatr 2002; 91:409-14.

Summary

Pregnancy Category: D
Lactation Category: S

- **Phenytoin** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.
- As with most psychotropic drugs, the risks may be minimized by monotherapy and the smallest effective quantity given in divided doses to minimize the serum peaks.

Physostigmine—(Antilirium; Eserine Salicylate; Isopto Eserine)

International Brand Name—None identified.

Drug Class ..... Antidotes; Cholinesterase inhibitors

Indications ..... Glaucoma, open-angle

Mechanism ..... Reversible cholinesterase inhibitor prolonging the effect of ACh

Dosage with Qualifiers

Glaucoma, open-angle—1-2gtt per eye tid or qid
Reversal of anticholinergic syndrome—2mg IM or slow IV
Postanesthesia care—0.5-1.0mg IM or slow IV; repeat at intervals of 10-30min as needed for response

NOTE: 0.25% and 0.5% ophthalmic solutions.

- **Contraindications**—hypersensitivity to drug or class, acute uveitis, corneal abrasion, closed-angle glaucoma, asthma, gangrene, diabetes mellitus, CV disease
- **Caution**—unknown

Maternal Considerations

There are no adequate reports or well-controlled studies of **physostigmine** in pregnant women. The published experience is confined to scattered case reports.
Side effects include irritation, blurred vision, ocular pain, tearing, redness, and headache.

Fetal Considerations

There are no adequate reports or well-controlled studies of **physostigmine** in human fetuses. Considering the indications, dose, and route, it is unlikely the maternal systemic concentration will reach a clinically relevant level unless the woman is being treated for anticholinergic syndrome.

Breastfeeding Safety

There is no published experience in nursing women. It is unknown whether **physostigmine** enters human breast milk. However, considering the indication and dosing, **physostigmine** use is unlikely to pose a clinically significant risk to the breastfeeding neonate.

Drug Interactions

No clinically relevant interactions identified.

References

There are no current relevant references.

Summary

Pregnancy Category: C
Lactation Category: S (likely)
- **Physostigmine** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Phytonadione—(Aqua-Mephyton; Konakion; Mephyton; Vitamin K_1)

International Brand Name—Haemokion (Israel); Kaywan (Indonesia, Korea); Kenadion (India); Konakion (10 mg) (Costa Rica, Dominican Republic, El Salvador, England, Germany, Ghana, Guatemala, Honduras, Ireland, Israel, Italy, Kenya, Mexico, Netherlands, Nicaragua, Panama, South Africa, Sweden, Switzerland, Tanzania, Uganda, Zambia); Konakion 10 mg (Austria, Finland, Hungary); Konakion MM Pediatric (Australia, Colombia, Mexico); Microka (Mexico); Vitak (Japan); Vitamin K (Hong Kong)

Drug Class

Bleeding disorders; Vitamins/minerals

Indications

Hypoprothrombinemia, vitamin K deficiency

Mechanism

Cofactor for hepatic synthesis of factors II, VII, IX, X

Dosage with Qualifiers

Hypoprothrombinemia—10mg SC/IM/IV ×1; may repeat in 6-8h based on INR; or 2.5-25mg PO qd-qw, max 25mg/dose

NOTE: severe reactions, including fatalities, are reported after IV use.

- **Contraindications**—hypersensitivity to drug or class, hereditary hypoprothrombinemia
- **Caution**—heparin anticoagulation

Maternal Considerations	Hypoprothrombinemia may result from anticoagulation, antibiotic therapy, or GI disease, or may be drug-induced. The drugs listed are each vitamin K products with some pharmacologic differences. There are no adequate reports or well-controlled studies of **phytonadione** in pregnant women. ***Side effects*** include anticoagulant resistance, hypotension, taste changes, flushing, diaphoresis, dyspnea, edema, and injection site hematoma or pain.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. While **phytonadione** crosses the human placenta, it varies with the compound and is limited, seeming to preclude a significant fetal effect. Placental transport is more efficient in the rat. Animal teratogenicity studies apparently have not been conducted. **Phytonadione** is often given to neonates in hopes of preventing IVH. The evidence for this practice is weak.
Breastfeeding Safety	**Phytonadione** is concentrated in human breast milk, and may be useful as a supplement for the preterm, breastfeeding neonate. It is generally considered compatible with breastfeeding.
Drug Interactions	No clinically relevant interactions identified.
References	Anai T, Hirota Y, Yoshimatsu J, et al. Obstet Gynecol 1993; 81:251-4. Gullaumont MJ, Durr FM, Combet JM, et al. Dev Pharmacol Ther 1988; 11:57-64. Kazzi NJ, Ilagan NB, Liang KC, et al. Obstet Gynecol 1990; 75:334-7. Saga K, Terao T. Nippon Sanka Fujinka Gakkai Zasshi 1989; 41:1713-9.
Summary	**Pregnancy Category: C** **Lactation Category: S** • **Phytonadione** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Pilocarpine—(Adsorbocarpine; Akarpine; I-Pilopine; Isopto Carpine; Ocu-Carpine; Pilokair; Pilopine HS; Pilosol; Pilostat; Salagen; Spectro-Pilo; Storzine)

International Brand Name—Asthenopin (Philippines); Cendo Carpine (Indonesia); Glaucocarpine (Israel); Isopto Carpina (Argentina, Ecuador, Peru); Isopto Pilocarpine (France); Liocarpina (Italy); Miocarpine (Canada); Ocucarpine (Korea); Ocusert P-20 (Japan); Ocusert P-40 (Japan); Ocusert Pilo-20 (Australia, England); Ocusert Pilo-40 (Australia, England); Ocusert Pilocarpine (England); Oftan-Pilocarpin (Finland); O.P.D. (Taiwan); Pilocarpin (Korea); Pilocarpol (Germany); Pil Ofteno (Mexico); Pilogel (Germany, Italy, South Africa, Taiwan); Pilogel HS (Hong Kong, Philippines); Pilo Grin (Mexico); Pilokarpin Isopto (Denmark); Pilomann (Philippines); Pilomin (India); Pilotonina (Italy); Sanpilo (Taiwan); Sno Pilo (England); Spersacarpine (Hong Kong, Malaysia, Philippines, Sweden, Switzerland, Taiwan); Vistacarpin (Germany); Ximex Opticar (Indonesia)

Drug Class	Cholinergics; Miotics; Ophthalmics
Indications	Xerostomia secondary to Sjögren's syndrome or head/neck cancer
Mechanism	Cholinergic agonist
Dosage with Qualifiers	Xerostomia secondary to Sjögren's syndrome—5mg PO qid; response may take 6w

Xerostomia secondary to head/neck cancer—begin 5mg PO tid; max 30mg/d

NOTE: hepatic dosing.

- **Contraindications**—hypersensitivity to drug or class, acute asthma, narrow-angle glaucoma, acute iritis, severe hepatic dysfunction
- **Caution**—moderate hepatic dysfunction, asthma, COPD, chronic bronchitis, biliary disease, nephrolithiasis, psychiatric illness

Maternal Considerations

There is no published experience with **pilocarpine** in pregnancy. ***Side effects*** include pulmonary edema, visual impairment, impaired fertility, bradycardia, tachycardia, hypotension, hypertension, cholecystitis, biliary spasm, shock, sweating, chills, N/V, flushing, rhinitis, dizziness, weakness, diarrhea, headache, dyspepsia, edema, tremor, dysphagia, and voice changes.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **pilocarpine** crosses the human placenta. Only scant amounts cross the rat placenta (<.05%). In rabbits, pilocarpine accelerates fetal lung maturation.

Breastfeeding Safety

There is no published experience during lactation. It is unknown whether **pilocarpine** enters human breast milk.

Drug Interactions

Use cautously in patients taking β-adrenergic antagonists because of the possibility of conduction disturbances.
Drugs with parasympathomimetic effects administered concurrently would be expected to result in additive effects.
May antagonize the anticholinergic effects of co-administered drugs. These effects should be considered when anticholinergic properties contribute to the therapeutic effect of concomitant medication (e.g., **atropine,** inhaled **ipratropium**).

References

Omori Y, Endo T, Hara Y, et al. Arzneimittelforschung 2004; 54:171-8.
Smith DM, Shelley SA, Balis JU. Anat Rec 1982; 202:23-31.

Summary

Pregnancy Category: C
Lactation Category: S

- **Pilocarpine** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Pimecrolimus, topical—(Elidel)

International Brand Name—Elidel (Argentina, Brazil, Canada, Colombia, Ecuador, England, Germany, Hong Kong, Indonesia, Ireland, Israel, Korea, Malaysia, Mexico, New Zealand, Singapore, Taiwan, Thailand)

Drug Class

Dermatologics; Immunosuppressants

Indications

Atopic dermatitis

Mechanism

Inhibits T-lymphocyte activation

Dosage with Qualifiers

Atopic dermatitis (mild-moderate)—for resistant cases, apply topically bid for up to 6w

- **Contraindications**—hypersensitivity to drug or class, local infection, Netherton's syndrome
- **Caution**—HIV, VZV, or HSV infections; sun exposure

Maternal Considerations	There is no published experience with **pimecrolimus** in pregnancy. ***Side effects*** include viral reactivation, lymphadenopathy, skin burning, headache, cough, pharyngitis, skin papilloma, erythema, and pruritus.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **pimecrolimus** crosses the human placenta. Considering the dose and route, it is unlikely the maternal systemic concentration will reach a clinically relevant level. Rodent studies utilizing a topical application are reassuring, revealing no evidence of toxicity, teratogenicity, or IUGR despite the use of doses higher than those used clinically. **Pimecrolimus** does cross the rodent placenta after oral administration.
Breastfeeding Safety	There are no published reports of **pimecrolimus** use during breastfeeding. It is unknown whether it enters human breast milk.
Drug Interactions	Systemic drug interactions are not expected due to very low blood levels after topical application. Apply caution when using with CYP3A inhibitors (e.g., calcium channel blockers, **cimetidine, erythromycin, fluconazole, itraconazole, ketoconazole**).
References	There is no published experience in pregnancy or during lactation.
Summary	**Pregnancy Category: C** **Lactation Category: U** • **Pimecrolimus** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk. • There are alternative agents for which there is more experience regarding use during pregnancy and lactation.

Pimozide—(Orap; Pimodac)

International Brand Name—Orap (1 mg) (Hong Kong, Indonesia, Israel, Thailand); Orap Forte (4 mg) (Hong Kong, Indonesia, Israel, Peru, South Africa, Thailand); Pizide (Thailand)

Drug Class	Antipsychotics
Indications	Tourette's syndrome
Mechanism	Dopamine D_2 antagonist plus multiple other actions
Dosage with Qualifiers	Tourette's syndrome—begin 1-2mg PO qd; max 10mg/dl; alternatively 0.2mg/kg/d; max 10mg/d *NOTE: may cause sedation.* • **Contraindications**—hypersensitivity to drug or class, CNS depression, arrhythmia, prolonged QT interval syndrome, coma • **Caution**—unknown
Maternal Considerations	There are no adequate reports or well-controlled studies of **pimozide** in pregnant women. The published literature is limited to a single case report where the outcome was normal. **Pimozide** produces a dose-dependent increase in pituitary tumors in rats. ***Side effects*** include amenorrhea, neuroleptic malignant syndrome, seizure, arrhythmia, tachycardia, palpitations, hypotension, tremor, rigidity, akinesia, N/V, dyspepsia, rash, urticaria,

	increased salivation, diarrhea, constipation, sedation, lethargy, and dystonic reactions.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **pimozide** crosses the human placenta. Rodent studies are reassuring, revealing no evidence of teratogenicity, though IUGR and increased embryo resorption were noted at doses 8× the MRHD.
Breastfeeding Safety	There are no published reports of **pimozide** use in nursing women. It is unknown whether **pimozide** enters human breast milk. **Pimozide** stimulates prolactin secretion.
Drug Interactions	Prolongs the QT interval; thus, an additive effect on QT interval is possible if given with other drugs such as phenothiazines, TCAs, or antiarrhythmic agents, which prolong the QT interval. This combination is contraindicated. May potentiate CNS depressants, including analgesics, sedatives, anxiolytics, and ethanol.
References	Bjarnason NH, Rode L, Dalhoff K. J Reprod Med 2006; 51:443-4.
Summary	**Pregnancy Category: C** **Lactation Category: U** • **Pimozide** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Pindolol—(Bedrrenal; Betadren; Visken)

International Brand Name—Apo-Pindol (Malaysia); Apo-Pindolol (New Zealand); Barbloc (Australia, Taiwan); Betapindol (Switzerland); Blocklin (Taiwan); Carvisken (Japan); Decreten (Denmark, Norway); Dranolis (Greece); Durapindol (Germany); Hexapindol (Denmark, Norway, Sweden); Nonspi (Germany); Novo-Pindol (Canada); Pidol (Taiwan); Pinbetol (Germany); Pinden (Israel); Pindol (New Zealand); Pindomex (Finland); Pindoreal (Germany); Pinloc (Finland); Pinsken (Thailand); Pyndale (Philippines); Treparasen (Greece); Viskeen (Netherlands); Viskeen Retard (Netherlands); Viskene (Portugal); Vypen (New Zealand)

Drug Class	Adrenergic antagonists; β-Blockers
Indications	Hypertension, chronic stable angina
Mechanism	Nonselective β-blocker with intrinsic sympathomimetic activity
Dosage with Qualifiers	Hypertension—begin 5mg PO bid, increase by 10mg/d q3-4w; max 60mg/d Chronic stable angina—15-40mg PO qd *NOTE: hepatic dosing.* • **Contraindications**—hypersensitivity to drug or class, asthma, severe bradycardia, 2nd or 3rd degree AV block, CHF, severe COPD, cardiogenic shock • **Caution**—past history of CHF, abrupt withdrawal, major surgery, diabetes mellitus, thyrotoxicosis, hepatic dysfunction
Maternal Considerations	There are no adequate reports or well-controlled studies in pregnant women. **Pindolol** is considered a second-line drug (**methyldopa, labetolol,** or calcium channel blockers are first-line) for the treatment of nonsevere, chronic hypertension during pregnancy. It does not increase uterine contractility. **Pindolol** is superior to **propranolol** for the control of

preeclamptic hypertension when **hydralazine** alone is inadequate. Women with preeclampsia treated with **pindolol** reportedly have a greater decline in Doppler-determined uterine artery flow resistance compared to women treated with **propranolol.**
Side effects include CHF, severe bradycardia, bronchospasm, peripheral vascular disease, insomnia, dizziness, fatigue, muscle aches, joint pain, peripheral edema, nervousness, dyspnea, and elevated LFTs.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. **Pindolol** crosses the human placenta, achieving variable F:M ratios ranging from 0.4 to 4.5 measured at 6h. Doppler flow studies are reassuring with no detectable impact on fetal hemodynamics when given to women with mild preeclampsia. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically.

Breastfeeding Safety

There are no adequate reports or well-controlled studies in nursing women. **Pindolol** enters human breast milk, achieving variable M:P ratios ranging from 0.5 to 3.5.

Drug Interactions

May have an additive effect when given with β-blocking agents. Patients should be closely observed for hypotension and/or marked bradycardia, which may produce vertigo, syncope, or postural hypotension.
Increases the serum **thioridazine** levels. **Pindolol** levels may also be increased with this combination.
Patients with a history of severe anaphylactic reaction to a variety of allergens may be more reactive to repeated challenge while taking β-blockers and may be unresponsive to the usual doses of **epinephrine** used to treat allergic reactions.

References

Gonçalves PV, Cavalli RC, da Cunha SP, Lanchote VL. J Chromatogr B Analyt Technol Biomed Life Sci 2007; 852:640-5.
Goncalves PV, Matthes AC, Da Cunha SP, Lanchote VL. Chirality 2002; 14:683-7.
Krause W, Stoppelli I, Milia S, Rainer E. Eur J Pharmacol 1982; 22:53-5.
Meizner I, Paran E, Katz M, et al. J Clin Ultrasound 1992; 20:115-9.
Montan S, Ingemarsson I, Marsal K, Sjoberg NO. BMJ 1992; 304:946-9.
Paran E, Holzberg G, Mazor M, et al. Int J Pharmacol Ther 1995; 33:119-23.
Rasanen J, Jouppila P. Eur J Obstet Reprod Biol 1995; 62:195-201.
Rey E, LeLorier J, Burgess E, et al. CMAJ 1997; 157:1245-54.

Summary

Pregnancy Category: B
Lactation Category: U

- **Pindolol** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.
- It is a reasonable choice for treatment of women with chronic hypertension, and may be of use in some preeclamptic women.

Pioglitazone—(Actos)

International Brand Name—Actos (Argentina, Brazil, Canada, Chile, Colombia, Hong Kong, Indonesia, Korea, Peru, Philippines, South Africa, Thailand); Cereluc (Argentina); Glita (India); Glitase (India); Pioglit (India, Paraguay); Piomed (Uruguay); Zactos (Mexico)

Drug Class	Antidiabetic agents; Thiazolidinediones
Indications	Diabetes mellitus type 2
Mechanism	Increases insulin sensitivity and inhibits hepatic gluconeogenesis by activating PPAR-γ
Dosage with Qualifiers	Diabetes mellitus type 2—15-30mg PO qd, increase dose after 12w if no response; max 45mg/d *NOTE: check ALT periodically; may be combined with other oral agents; caution with insulin.* • **Contraindications**—hypersensitivity to drug or class, diabetes mellitus type 1, ketoacidosis, CHF of NYHA class III or IV • **Caution**—CHF of NYHA class I or II, hepatic dysfunction, hypertension, edema
Maternal Considerations	**Pioglitazone** improves glycemic control while decreasing circulating insulin and free fatty acid levels and increasing HDL and LDL. When used alone, it is slightly less potent than the sulfonylureas and **metformin.** Clearance is increased by 20-60% in nonpregnant women compared to men. There is no published experience in pregnancy. It may be useful in the treatment of infertility associated with PCOS. ***Side effects*** include hepatotoxicity, CHF, anemia, fluid retention, edema, weight gain, URI, headache, sinusitis, myalgia, pharyngitis, dyspepsia, and hypoglycemia.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **pioglitazone** crosses the human placenta. Rodent studies are for the most part reassuring, revealing no evidence of teratogenicity or functional or behavioral abnormalities despite the use of doses higher than those used clinically. There is evidence of embryotoxicity.
Breastfeeding Safety	There is no published experience with **pioglitazone** during lactation. It is unknown whether it enters human breast milk. **Pioglitazone** is excreted into rat breast milk.
Drug Interactions	*In vivo* drug-drug interaction studies suggest it may be a weak inducer of CYP3A4.
References	Ota H, Goto T, Yoshioka T, Ohyama N. Fertil Steril 2008; 90:709-31.
Summary	**Pregnancy Category: C** **Lactation Category: U** • There are alternative agents for which there is more experience regarding use during pregnancy and lactation.

Piperacillin—(Pipracil)

International Brand Name—Acopex (Korea); Avocin (Italy); Cypercil (Philippines); Ivacin (Denmark, Sweden); Pentcillin (Japan); Picillin (Israel, Italy); Picillina (Taiwan); Pipcil (Belgium, Netherlands); Piperacin (Korea); Piperilline (France); Pipracin (Israel); Pipraks (Israel); Pipril (Austria, Finland, Greece, Hungary, South Africa, Spain, Switzerland, Taiwan); Piprilin (Portugal); Pitamycin (Taiwan)

Drug Class

Antibiotics; Penicillins

Indications

Susceptible bacterial infections, including intra-abdominal, gonococcus, lower respiratory and urinary tracts, skin, and bone

Mechanism

Bactericidal—inhibits cell wall and septum mucopeptide synthesis

Dosage with Qualifiers

Bacterial infections (*Pseudomonas*, intra-abdominal, or sepsis)—3-4g IV/IM q4-6h ×3-10d
Post-gynecologic or post-cesarean prophylaxis—2g IV 30min preoperatively or at umbilical cord clamping, then q4-6h ×2
Gonorrhea, uncomplicated—1g **probenecid** PO 30min before 2g IM ×1

NOTE: renal dosing; may be combined with the β-lactamase inhibitor ***tazobactam*** *(Tazosyn; Zosyn).*

- **Contraindications**—hypersensitivity to drug or class
- **Caution**—cephalosporin allergy, uremia, hypokalemia, seizure disorder, nephrotoxic agents, renal dysfunction, sodium restriction

Maternal Considerations

Piperacillin is widely distributed, including therapeutic levels in bone, heart, bile, and CSF during inflammation. It is best studied during pregnancy for the treatment of gonorrhea, PPROM, and cesarean section prophylaxis. **Piperacillin** pharmacokinetics reveal a larger volume of distribution and higher clearance rate during pregnancy. This suggests higher doses are necessary for effective treatment of serious infections in pregnant women near term and in the puerperium. In reference to prophylaxis, no single antibiotic proved effective for prophylaxis (**ampicillin, cefazolin, cefotetan, piperacillin** [± **tazobactam**]) is superior to the other; cost and convenience are the deciding variables. **Piperacillin** may be given as a single 4g dose at cord clamping with little loss of efficacy. Several reports support the use of **piperacillin** (3-4g IV q6h ×72h) to prolong the latency interval between PPROM and the onset of labor.
Side effects include thrombocytopenia, seizures, fever, pseudomembranous enterocolitis, interstitial nephritis, neutropenia, hemolytic anemia, prolonged bleeding time, rash, bleeding, hypokalemia, headache, dizziness, fatigue, phlebitis, hyperbilirubinemia, and elevated LFTs.

Fetal Considerations

There are no adequate reports or well-controlled studies of **piperacillin** in human fetuses. Placental transfer is rapid, achieving an F:M ratio between 0.25 and 0.3. The concentration in AF is similar to fetal serum. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically.

Breastfeeding Safety

There are no adequate reports or well-controlled studies in nursing women. Only small amounts of **piperacillin** enter human breast milk, and poor oral absorption should limit availability. It is usually considered compatible with breastfeeding.

Drug Interactions

Mixing with an aminoglycoside *in vitro* produces substantial inactivation of the aminoglycoside.
May prolong the neuromuscular blockade of **vecuronium;** caution is indicated. Due to their similar mechanism of action, it is possible the neuromuscular blockade produced by any of the nondepolarizing muscle relaxants could be prolonged by **piperacillin.**
Probenecid before IM **piperacillin** produces about a 30% increase in the **piperacillin** peak serum levels.
Coagulation parameters should be tested more frequently during use with high doses of **heparin,** oral anticoagulants, or other drugs that may affect the blood coagulation system or thrombocyte function.
May reduce the excretion of **methotrexate.** Thus, serum levels of **methotrexate** should be monitored closely to avoid drug toxicity.

References

Brown CE, Christmas JT, Bawdon RE. Am J Obstet Gynecol 1990; 163:938-43.
Charles D, Larsen B. Gynecol Obstet Invest 1985; 20:194-8.
Ford LC, Hammil HA, Lebherz TB. Am J Obstet Gynecol 1987; 157:506-10.
Gall SA, Hill GB. Am J Obstet Gynecol 1987; 157:502-6.
Heikkila A, Erkkola R. J Antimicrob Chemother 1991; 28:419-23.
Lockwood CJ, Costigan K, Ghidini A, et al. Am J Obstet Gynecol 1993; 169:970-6.
Shah S, Mazher Y, John IS. Int J Gynaecol Obstet 1998; 62:23-9.
Wagner KJ, Bier U, Callies R, et al. Zentralbl Gynakol 2006; 128:149-52.

Summary

Pregnancy Category: B
Lactation Category: S

- **Piperacillin** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.
- It is an excellent agent for cesarean section prophylaxis and for the treatment of gonorrhea.
- Routine administration of **piperacillin** to women with PPROM may prolong latency, though erythromycin is better studied and preferred.

Piperacillin-tazobactam—(Tazosyn; Zosyn)

International Brand Name—Tazobac (Germany, Switzerland); Tazocel (Spain); Tazocilline (France); Tazocin (Belgium, Brazil, Canada, China, Colombia, Costa Rica, Czech Republic, Dominican Republic, Ecuador, El Salvador, England, Guatemala, Honduras, Hong Kong, Hungary, Indonesia, Ireland, Italy, Korea, Malaysia, Mexico, Netherlands, Nicaragua, Panama, Peru, Poland, Singapore, South Africa, Taiwan, Thailand); Tazomax (Uruguay); Tazonam (Argentina, Austria, Chile, Paraguay); Tazopril (Ecuador, Venezuela); Zosyn (India)

Drug Class

Antibiotics; Penicillins

Indications

Susceptible bacterial infections, including intra-abdominal, gonococcus, lower respiratory and urinary tracts, skin, and bone

Mechanism

Bactericidal—inhibits cell wall and septum mucopeptide synthesis

Dosage with Qualifiers

Bacterial infections (*Pseudomonas*, intra-abdominal, or sepsis)—3.375g IV q6h ×3-10d
Postpartum endomyometritis or PID—3.375g IV q6h ×3-10d

Community-acquired pneumonia—3.375g IV q6h ×3-10d

NOTE: renal dosing.

- **Contraindications**—hypersensitivity to drug or class
- **Caution**—cephalosporin allergy, uremia, hypokalemia, seizure disorder, nephrotoxic agents, renal dysfunction, sodium restriction

■ Maternal Considerations

Tazobactam is a β-lactamase inhibitor with no significant antibacterial activity; its addition expands the antibacterial spectrum of **piperacillin. Piperacillin-tazobactam** is active against most strains of the following **piperacillin**-resistant β-lactamase–producing microorganisms: MSSA, *E. coli*, *H. influenzae* (not ampicillin-resistant), and the *B. fragilis* group (*B. fragilis, B. ovatus, B. thetaiotaomicron,* or *B. vulgatus*).
The addition of **tazobactam** does not improve efficacy as a post–cesarean section prophylaxis agent over **piperacillin** alone.
Clearance of the combination appears enhanced during pregnancy. It is similar to **ampicillin-gentamicin** in efficacy for the treatment of postpartum endometritis.
Side effects include thrombocytopenia, seizures, fever, cholestatic jaundice, erythema multiforme, pseudomembranous enterocolitis, interstitial nephritis, neutropenia, hemolytic anemia, prolonged bleeding time, prolonged INR, rash, bleeding, hypokalemia, headache, dizziness, fatigue, phlebitis, hyperbilirubinemia, and elevated LFTs.

■ Fetal Considerations

There are no adequate reports or well-controlled studies of **piperacillin-tazobactam** in human fetuses. Placental transfer of **tazobactam** is rapid, reaching an F:M ratio between 0.25 and 0.3. The concentration in AF is similar to fetal serum. Rodent studies at doses up to 4× the MRHD are reassuring, showing no evidence of impaired fertility or teratogenicity. See **Piperacillin.**

■ Breastfeeding Safety

There are no adequate reports or well-controlled studies in nursing women. Only small amounts of **piperacillin** enter human breast milk, and poor oral absorption would limit availability. It is not known whether **tazobactam** enters human breast milk. It is usually considered compatible with breastfeeding.

■ Drug Interactions

Use with aminoglycosides may be associated inactivation of the aminoglycoside. However, **amikacin** and **gentamicin** are compatible at least *in vitro* with **piperacillin-tazobactam** containing EDTA and supplied in vials or bulk pharmacy containers in certain diluents at specific concentrations for a simultaneous Y-site. **Piperacillin-tazobactam** containing EDTA is not compatible with **tobramycin** for simultaneous administration via Y-site.
When used with aminoglycosides in end-stage renal disease patients requiring hemodialysis, the concentrations of the aminoglycosides (especially **tobramycin**) may be significantly altered and should be monitored.
Use with **probenecid** prolongs the half-life of **piperacillin** by 21% and that of **tazobactam** by 71%.
Coagulation parameters should be tested more frequently if used with high doses of **heparin,** oral anticoagulants, or other drugs that affect coagulation.
May prolong the neuromuscular blockade of **vecuronium.** The neuromuscular blockade produced by any of the nondepolarizing muscle relaxants could be prolonged by **piperacillin** due to their similar mechanism of action.
May reduce the clearance of **methotrexate** due to competition for renal secretion. The impact of **tazobactam** on the elimination of

methotrexate has not been evaluated. Serum concentrations of **methotrexate** should be monitored and symptoms of toxicity sought.

References

Bourget P, Sertin A, Lesne-Hulin A, et al. Eur J Obstet Gynecol Reprod Biol 1998; 76:21-7.
Figueroa-Damian R, Villagrana-Zesati R, San Martin Herrasti JM, Arredondo-Garcia JL. Ginecol Obstet Mex 1996; 64:214-8.
Wagner KJ, Bier U, Callies R, et al. Zentralbl Gynakol 2006; 128:149-52.

Summary

Pregnancy Category: B
Lactation Category: S (likely)
- **Piperacillin-tazobactam** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Piperazine—(Aloxin; Antcucs; Antepar; Ascalix; Expellin; Multifuge; Rotape; Vermidol; Vermizine; Worm)

International Brand Name—Piperazil (Ecuador); Vermex (Thailand); Vermichem (Dominican Republic)

Drug Class

Adrenergic agonists; Anthelmintics

Indications

Treatment of intestinal ascariasis (secondary to *Ascaris lumbricoides* [roundworms]); enterobiasis due to *Enterobius vermicularis* (pinworms)

Mechanism

Produces worm paralysis, allowing expulsion

Dosage with Qualifiers

Ascariasis—3.5g PO before breakfast qd ×2
Enterobiasis—65mg/kg before breakfast qd ×7d; max 2.5g/d

- **Contraindications**—hypersensitivity to drug or class, renal dysfunction, convulsive disorders
- **Caution**—hepatic dysfunction, malnutrition, anemia

Maternal Considerations

There are no adequate reports or well-controlled studies of **piperazine** in pregnant women. The long clinical experience is reassuring. Paralysis of the parasite is mediated by its agonist effects upon the inhibitory GABA receptor. Its selectivity for helminths is derived from the fact that vertebrates use GABA only in the CNS and the helminths' GABA receptor is a different isoform.
Side effects include N/V, abdominal cramps, diarrhea, urticaria, erythema multiforme, purpura, fever, arthralgia, headache, vertigo, ataxia, tremors, choreiform movement, muscular weakness, hyporeflexia, paresthesia, blurred vision, convulsions, EEG abnormalities, and memory deficit.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **piperazine** crosses the human placenta.

Breastfeeding Safety

There is no published experience in nursing women. It is unknown whether **piperazine** enters human breast milk.

Drug Interactions

No clinically relevant interactions identified.

References	Villar MA, Sibai BM. Am J Obstet Gynecol 1992; 166:549-50.
Summary	**Pregnancy Category: B** **Lactation Category: U** • **Piperazine** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Pirbuterol—(Maxair)

International Brand Name—Exirel (Austria, Zimbabwe); Spirolair (Belgium)

Drug Class	Bronchodilators; Sympathomimetics
Indications	Bronchospasm
Mechanism	β_2-Adrenergic agonist
Dosage with Qualifiers	Bronchospasm—1-2puffs (200mcg/puff) INH q4-6h; max 12puffs/d *NOTE: currently unavailable in the US.* • **Contraindications**—hypersensitivity to drug or class • **Caution**—diabetes mellitus, hyperthyroidism, seizures, CV disease, hypokalemia
Maternal Considerations	There is no published experience with **pirbuterol** in pregnancy. ***Side effects*** include arrhythmia, angina, anorexia, severe hypertension, tremor, nervousness, N/V, diarrhea, headache, vertigo, and taste changes.
Fetal Considerations	There are no adequate reports or well-controlled studies of **pirbuterol** in human fetuses. Rodent studies, both inhalational and oral, are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically. Fetal toxicity was noted at the higher doses tested.
Breastfeeding Safety	There is no published experience during lactation. It is unknown whether **pirbuterol** enters human breast milk.
Drug Interactions	May be additive with other β-adrenergic aerosol bronchodilators. β-Adrenergic agonists should be used cautiously in patients being treated with MAOIs or TCAs as the action of β-adrenergic agonists on the vascular system may be potentiated.
References	There are no current relevant references.
Summary	**Pregnancy Category: C** **Lactation Category: U** • **Pirbuterol** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk. • There are alternative agents for which there is more experience regarding use during pregnancy and lactation.

Piroxicam—(Brexicam; Feldene; Feline)

International Brand Name—Antiflog (Italy); Apo-Piroxicam (Canada, New Zealand); Arpyrox (Indonesia); Artrilase (Dominican Republic); Atidem (Peru); Baxo (Japan); Benoxicam (Indonesia); Brexic (India); Brexicam (Costa Rica, Dominican Republic, El Salvador, Guatemala, Honduras, Nicaragua, Panama); Brexin (Israel, Taiwan); Brexodin (Mexico); Camrox (Korea); Candyl-D (New Zealand); Capxidin (Singapore); Citoken T (Mexico); Dacam (Finland); Desinflam (Peru); Dixonal (Mexico); Doblexan (Spain); Dolonex (India); Exipan (Israel); Facicam (Mexico); Felcicam (Korea); Felden (Austria, Denmark, Finland, Germany, Norway, Sweden, Switzerland); Feldene Gel (South Africa, Thailand); Felrox (Thailand); Felxicam (Hong Kong, Malaysia); Flamic Gel (Thailand); Flaxine (Philippines); Flexirox (France); Floglugen (Taiwan); Flogosan (Mexico); Focus (Taiwan); Fulden (Korea); Hotemin (Hong Kong, Malaysia); Indene (Indonesia); Infeld (Indonesia); Inflamene (Brazil, Indonesia); Konshien (Taiwan); Kydoflam (Colombia); Larapam (England); Macroxam (Philippines); Mobilis (Australia); Movon-20 (India); Movon Gel (India); Moxicam (Thailand); Novopirocam (Canada); Nu-Pirox (Canada); Osteral (Mexico); Parixam (Philippines); Piraldene (Peru); Piram (Thailand); Piram-D (New Zealand); Pirax (Thailand); Pirkam (Denmark); Pirocutan (Germany); Pirocutan Gel (Germany); Pirohexal-D (Australia); Pirom (Denmark); Pirox (India); Piroxan (Mexico); Piroxedol (Colombia); Piroxim (Colombia, Israel, South Africa); Piroxton (Korea); Pixicam (South Africa); Posidene (Thailand); Priorheum (Germany); Proxalyoc (France); Pyrocaps (South Africa); Pyroxy (Thailand); Raxicam (Philippines); Rexicam (Indonesia); Rheugesic (South Africa); Rosic (Indonesia); Rosiden (Korea); Rosiden Gel (Korea); Rosig (Australia); Rosig-D (Australia); Roxicam (Israel, South Africa); Roxium (Thailand); Ruvamed (Greece); Scandene (Indonesia); Sefdene (Hong Kong); Sinalgico (Argentina); Sofden (Indonesia); Sotilen (Hong Kong, Israel, South Africa, Taiwan, Thailand); Stopen (Colombia); Tropidene (Indonesia); Unicam (Israel); Vidapirocam (Hong Kong); Xicalom (Indonesia); Xicam (Thailand); Xycam (South Africa); Zitumex (Greece); Zunden (Italy)

Drug Class	Analgesics, non-narcotic; NSAIDs; Oxicams
Indications	Osteoarthritis and rheumatoid arthritis, mild to moderate pain, dysmenorrhea
Mechanism	Inhibits prostaglandin biosynthesis
Dosage with Qualifiers	Osteoarthritis and rheumatoid arthritis—20-40mg PO qd with food Mild to moderate pain—20mg PO qd Dysmenorrhea—begin 40mg qd ×2d, then 20mg PO qd ×3d • **Contraindications**—hypersensitivity to drug or class, aspirin- or NSAID-induced asthma • **Caution**—GI bleeding, nasal polyps, hypertension, CHF
Maternal Considerations	**Piroxicam** is an orally absorbed oxicam with anti-inflammatory, analgesic, and antipyretic properties. There are no adequate reports or well-controlled studies in pregnant women. In a rodent model, **piroxicam** decreased the efficacy of IUD-mediated contraception. In one RCT, **piroxicam** was noted to increase implantation and pregnancy rates after embryo transfer in both fresh and frozen-thawed cycles during IVF. The beneficial effect seemed more pronounced in patients <40y with tubal, or male factor infertility, or endometriosis. ***Side effects*** include GI bleeding, acute renal failure, bronchospasm, thrombocytopenia, Stevens-Johnson syndrome, interstitial nephritis, hepatotoxicity, agranulocytosis, dyspepsia, nausea, abdominal pain, constipation, headache, dizziness, rash, drowsiness, tinnitus, fluid retention, and elevated LFTs.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. **Piroxicam** presumably crosses the human placenta as do other NSAIDs, and is associated with severe fetal oligohydramnios in case reports. **Piroxicam** increases the incidence of dystocia and delayed parturition in animals if administered continuously late into pregnancy. Toxic maternal doses are associated with fetal bone demineralization.

Breastfeeding Safety

There are no adequate reports or well-controlled studies in nursing women. Only trace quantities of **piroxicam** are excreted into human breast milk, and do not pose a threat to the breastfeeding neonate.

Drug Interactions

May displace other protein-bound drugs. Patients should be monitored closely for a change in dose requirements.
Plasma levels are depressed some 80% when used with **aspirin** (3900mg/d). As with other NSAIDs, use with **aspirin** is not recommended because of the potential for increased adverse effects.
NSAIDs may enhance **methotrexate** toxicity. Caution is recommended.
NSAIDs may diminish the antihypertensive effect of ACEIs.
May reduce the natriuretic effect of **furosemide** and thiazides due to a decrease in renal prostaglandin synthesis.
NSAIDs can increase **lithium** levels some 15% and decrease renal **lithium** clearance about 20%, presumably due to the inhibition of renal prostaglandin synthesis. Patients should be watched closely for signs of **lithium** toxicity.
Warfarin and NSAIDs synergistically increase the risk of serious GI bleeding.

References

Burdin F, Rozylo-Kalinowska I, Szumio J, et al. Cells Tissues Organs 2008; 187:221-32.
Moon HS, Park SH, Lee JO, et al. Fertil Steril 2004; 82:816-20.
Ostensen M, Matheson I, Laufen H. Eur J Clin Pharmacol 1988; 35:567-9.
Ozalp S, Tanir HM, Cakmak B, Hassa H. Eur J Contracept Reprod Health Care 2007; 12:107-10.
Powell JG Jr, Cochrane RL. Prostaglandins 1982; 23:469-88.
Voyer LE, Drut R, Mendez JH. Pediatr Nephrol 1994; 8:592-4.

Summary

Pregnancy Category: B (first 20w), **D** (thereafter)
Lactation Category: S

- **Piroxicam** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.
- NSAIDs should probably be avoided in the 1st trimester in light of the epidemiologic association with gastroschisis.
- There are alternative agents for which there is more experience regarding use during pregnancy and lactation.

Plicamycin—(Mithracin; Mithramycin)

International Brand Name—None identified.

Drug Class

Antibiotics; Antineoplastics, antibiotic

Indications

Hypercalcemia

Mechanism

Unknown; complexes with DNA, inhibits cellular and enzymatic RNA synthesis

Dosage with Qualifiers

Hypercalcemia and hypercalciuria—25mcg/kg IV qd given over 4-6h for 3-4d

- **Contraindications**—hypersensitivity to drug or class, thrombocytopenia, bleeding disorder, herpes zoster, recent varicella, pregnancy
- **Caution**—unknown

Maternal Considerations	There is no published experience with **plicamycin** in pregnancy. It is most commonly used for the treatment of testicular cancer. ***Side effects*** include hypocalcemia, hypophosphatemia, leukopenia, thrombocytopenia, bleeding, renal or hepatic dysfunction, N/V, anorexia, diarrhea, stomatitis, somnolence, phlebitis, rash, and flushing.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **plicamycin** crosses the human placenta. Rodent teratogenicity studies apparently have not been performed.
Breastfeeding Safety	There is no published experience in nursing women. It is unknown whether **plicamycin** enters human breast milk. It is unknown whether it alters the constituents of the milk produced.
Drug Interactions	No clinically relevant interactions identified.
References	There are no current relevant references.
Summary	**Pregnancy Category: X** **Lactation Category: U** • **Plicamycin** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Pneumococcal vaccine—(Pneumovax 23; Pnu-Imune 23)

International Brand Name—Moniarix (South Africa); Pneumo 23 (Argentina, Brazil, Canada, Chile, Colombia, France, Hong Kong, India, Italy, Malaysia, New Zealand, Paraguay, Peru, Philippines, Taiwan, Thailand, Uruguay); Pneumo 23 Imovax (Israel); Pneumovax (Japan); Pneumovax II (England, Ireland); Pneumovax 23 (Belgium, Hong Kong, Israel, Netherlands, South Africa, Switzerland, Taiwan, Thailand); Pnu-Imune 23 (Mexico); Prevenar (Australia, Brazil, Chile, Mexico); Prevnar (Canada, Costa Rica, Dominican Republic, El Salvador, Guatemala, Honduras, Nicaragua, Panama)

Drug Class	Vaccines
Indications	Enhanced susceptibility to pneumococcus
Mechanism	Active immunization
Dosage with Qualifiers	Immunocompetent patients with increased pneumococcal susceptibility—0.5ml IM ×1 *NOTE: avoid IV or intradermal administration.* • **Contraindications**—hypersensitivity to any component of the vaccine, Hodgkin's disease treated with either immunosuppressive or radiotherapy • **Caution**—unknown
Maternal Considerations	Pneumococcal infection is a leading cause of death and a major cause of pneumonia, meningitis, and otitis media. **Pneumococcal vaccine** is a mixture of highly purified capsular polysaccharides from the 23 clinically relevant pneumococcal types accounting for at least 90% of pneumococcal blood isolates. The antibody induced by the vaccine may persist for as long as 5 years. Susceptible patients at increased risk include HIV-infected women. ***Side effects*** include local injection site soreness, erythema and swelling, rash, urticaria, arthritis, arthralgia, serum sickness, adenitis, and fever.

Fetal Considerations

There are no adequate reports or well-controlled studies of **pneumococcal vaccine** in human fetuses. Stimulated antibodies are transferred across the placenta. While gestational age affects the efficiency of antibody transfer, vaccination is efficient and newborns of treated women have higher titers during the first 6mo to 1y of life. That said, there is insufficient evidence to conclude maternal pneumococcal vaccination will indeed reduce infant infection. Maternal immunization does not alter the neonatal response to vaccination. Rodent teratogenicity studies have not been performed, though there is no reason to expect an adverse fetal effect. Vaccinated rodents transfer enough antibody to their offspring to protect against otitis media.

Breastfeeding Safety

There are no adequate reports or well-controlled studies in nursing women. It is unknown whether **pneumococcal vaccine** enters human breast milk. However, the IgA antibody levels for many of the serotypes included are enhanced and may provide enhanced neonatal protection.

Drug Interactions

Immunosuppressive agents (e.g., corticosteroids, antimetabolites, alkylating agents, cytotoxic agents) may undermine active immunization.

References

Chaithongwongwatthana S, Yamasmit W, Limpongsanurak S, et al. Cochrane Database Syst Rev 2006; (1):CD004903.
Hajek DM, Quartey M, Giebink GS. Acta Otolaryngol 2002; 122:262-9.
Lehmann D, Pomat WS, Combs B, et al. Vaccine 2002; 20:1837-45.
Munoz FM, Englund JA, Cheesman CC, et al. Vaccine 2001; 20:826-37.
Obaro SK, Deubzer HE, Newman VO, et al. Pediatr Infect Dis J 2004; 23:1023-9.
Okoko BJ, Wesumperuma LH, Hart AC. Vaccine 2001; 20:647-50.
Quiambao BP, Nohynek HM, Käyhty H, et al. Vaccine 2007; 25:4470-7.
Shahid NS, Steinhoff MC, Hoque SS, et al. Lancet 1995; 346:1252-7.
Yoon JK, Lee HH, Choi BM, et al. J Korean Med Sci 2001; 16:9-14.

Summary

Pregnancy Category: C
Lactation Category: S

- **Pneumococcal vaccine** may be beneficial for mother and newborn in some patient populations.

Podofilox—(Condylox)

International Brand Name—Condyline (Belgium, Canada, Denmark, England, Finland, France, Italy, Netherlands, Norway, Portugal, Sweden, Switzerland); Condyline Liquid (New Zealand); Condyline Paint (Australia); Podofilox (Greece); Warix (Switzerland); Wartec (Denmark, Finland, Germany, Greece, Hong Kong, Norway, South Africa, Spain, Sweden); Warticon (England)

Drug Class

Antivirals; Dermatologics

Indications

Genital or perianal warts

Mechanism

Unknown; antimitotic

Dosage with Qualifiers

Genital or perianal warts—apply topically bid ×3d; repeat weekly for up to 4w

- **Contraindications**—hypersensitivity to drug or class
- **Caution**—unknown

Maternal Considerations

Podofilox is related to **podophyllum resin.** There are no adequate reports or well-controlled studies in pregnant women. Toxicity with overuse is reported, but systemic absorption of doses up to 1.5ml is low. **Podofilox** should not be used to treat large lesions during pregnancy. Though an effective agent, there are other therapies, such as laser and cryotherapy, that pose fewer risks. ***Side effects*** include burning and inflammation.

Fetal Considerations

There are no adequate reports or well-controlled studies of **podofilox** in human fetuses. While many antimitotic drugs are embryotoxic, topical applications of 0.1-1.5ml produce peak serum levels <17ng/ml 1-2h after the application. The elimination t/2 is <4.5h and it does not accumulate after multiple treatments. Considering the dose and route, it is unlikely the maternal systemic concentration will reach a clinically relevant level after the treatment of small warts. Limited rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically.

Breastfeeding Safety

There are no adequate reports or well-controlled studies in nursing women. It is unknown whether **podofilox** enters human breast milk. However, considering the indication and dosing, **podofilox** use is unlikely to pose a clinically significant risk to the breastfeeding neonate.

Drug Interactions

No clinically relevant interactions identified.

References

There are no current relevant references.

Summary

Pregnancy Category: C
Lactation Category: S (likely)

- **Podofilox** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.
- The risk when used during pregnancy for small lesions is low.
- There are other therapies, such as laser and cryotherapy, that pose even fewer risks.

Podophyllum resin—(Podoben; Podocon-25; Pododerm; Podofin)

International Brand Name—Condil (Mexico); Condiver (Colombia); Podoben (Venezuela); Podofilia No. 2 (Mexico); Podofilm (Canada, China, Hong Kong); Podowart Paint (India)

Drug Class

Antivirals; Dermatologics

Indications

Genital or perianal warts

Mechanism

Unknown; antimitotic

Dosage with Qualifiers

Condylomata acuminata—apply qw for up to 3w

- **Contraindications**—hypersensitivity to drug or class, diabetes mellitus, patients chronically receiving corticosteroids
- **Caution**—unknown

Maternal Considerations	**Podophyllum resin** is a mixture of resins from the mandrake *(Podophyllum peltatum Linné)*, a perennial plant of the northern and middle US. It is made exclusively from American podophyllin, which has a lower level of podophyllotoxin than the Indian resin. There are no adequate reports or well-controlled studies in pregnant women. Though systemic absorption of doses up to 1.5ml is low, toxicity is reported with overuse. Thus, **podophyllum resin** should not be used during pregnancy for large lesions. Though an effective agent, there are other therapies, such as laser and cryotherapy, that pose fewer risks. ***Side effects*** include paresthesia, polyneuritis, paralytic ileus, pyrexia, leukopenia, thrombocytopenia, coma, and death.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **podophyllum resin** crosses the human placenta. Considering the dose and route, it is unlikely the maternal systemic concentration will reach a clinically relevant level after the treatment of small warts. There are reports of complications associated with the topical use of podophyllin on condylomata of pregnant patients, including birth defects, fetal death, and stillbirth. The relationship of outcome to the use of **podophyllum resin** is unclear.
Breastfeeding Safety	There are no adequate reports or well-controlled studies in nursing women. It is unknown whether **podophyllum resin** enters human breast milk. However, considering the indications and dosing, **podophyllum resin** use is unlikely to pose a clinically significant risk to the breastfeeding neonate.
Drug Interactions	No clinically relevant interactions identified.
References	Karol MD, Conner CS, Watanabe AS, Murphrey KJ. Clin Toxicol 1980; 16:283-6. Moher LM, Maurer SA. J Fam Pract 1979; 9:237-40.
Summary	**Pregnancy Category: X** **Lactation Category: S** (likely) • **Podophyllum resin** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk. • The risk when used during pregnancy for small lesions is low. • There are other therapies, such as laser and cryotherapy, that pose even fewer risks.

Poliovirus vaccine, inactivated—(Ipol; Poliovax)

International Brand Name—Imovax Polio (Belgium, Bulgaria, Czech Republic, Finland, Hong Kong, Hungary, Israel, Italy, Poland); Ipol (New Zealand); Polio Salk ''Sero'' (Austria)

Drug Class	Vaccines
Indications	Poliovirus susceptibility
Mechanism	Active immunization
Dosage with Qualifiers	Poliovirus susceptibility, adult—1 vial IM in the deltoid; repeat 1-2mo later and again in 6-12mo

- **Contraindications**—hypersensitivity to drug or class; hypersensitivity to **neomycin, streptomycin,** and polymyxin B; acute febrile illness
- **Caution**—unknown

Maternal Considerations

Inactivated poliovirus vaccine is a sterile suspension of three types [type 1 (Mahoney), type 2 (MEF-1), and type 3 (Saukett)] grown in culture and inactivated with formaldehyde. **Neomycin, streptomycin,** and **polymyxin B** are each used in vaccine production. Paralytic poliomyelitis has not been reported after vaccination. Routine primary poliovirus vaccination of adults (>18y) living in the US is not recommended. Adults at increased risk of exposure but not previously immunized should be vaccinated. This group includes travelers to regions where poliomyelitis is endemic or epidemic, health care workers in close contact with patients who may be excreting polioviruses, laboratory workers handling specimens that may contain polioviruses, members of groups with disease caused by wild polioviruses, and incompletely vaccinated or unvaccinated adults in contact with children given **live oral poliovirus vaccine.** Vaccination during pregnancy is effective, and the antibodies are detectable in the fetus. ***Side effects*** include erythema at the injection site, fever, and decreased appetite.

Fetal Considerations

There are no adequate reports or well-controlled studies of **inactivated poliovirus vaccine** in human fetuses. Poliovirus antibodies cross the human placenta and may offer some perinatal protection. Rodent teratogenicity studies have not been conducted, though an inactivated virus should not pose a significant fetal risk.

Breastfeeding Safety

There are no adequate reports or well-controlled studies in nursing women. While it is unknown whether **inactivated poliovirus vaccine** enters human breast milk, the resulting antibodies might. However, it appears the oral vaccine is superior for the stimulation of IgA.

Drug Interactions

No clinically relevant interactions identified.

References

Hanson LA, Carlsson B, Jalil F, et al. Rev Infect Dis 1984; 6(Suppl 2):S356-60.
Munoz FM, Englund JA. Pediatr Clin North Am 2000; 47:449-63.

Summary

Pregnancy Category: C
Lactation Category: S

- **Inactivated poliovirus vaccine** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.
- It is preferred over the live vaccine in adults.

Poliovirus vaccine, oral live—(Orimune)

International Brand Name—Buccapol Berna (Hong Kong, Malaysia, Peru); Imovax Polio (Korea); Imovax Polio Sabin (Taiwan); OPV-Merieux (South Africa); Oral Poliomyelitis Vaccine-Sabine (Australia); Oral Polio Vaccine (Israel, South Africa); Oral Virelon (Germany, New Zealand); Orimune (Ecuador); Polio-Kovax (Korea); Polioral (Israel, Korea, Malaysia, Mexico, Philippines, South Africa, Taiwan, Thailand); Polioral Trivalent (Israel); Polio Sabin (Ecuador, Israel, Mexico, Philippines, Taiwan, Thailand); Polio Sabin Oral (Austria); Polio ''Sabin'' Oral Vaccine (Austria, Czech Republic, Ecuador); Polio Sabin OS (Italy); Polio Sabin-S (Germany); Tri-Polio (Korea)

Drug Class

Vaccines

Indications

Poliovirus susceptibility

Mechanism

Active immunization

Dosage with Qualifiers

Poliovirus 1-3 susceptibility in adults—0.5ml PO repeated 8w later, with a 3rd dose 6-12mo after the 2nd

- **Contraindications**—hypersensitivity to drug or class; hypersensitivity to **neomycin, streptomycin,** and polymyxin B; immune deficiency states or altered immunity due to disease or therapy; acute febrile illness
- **Caution**—unknown

Maternal Considerations

Oral poliovirus vaccine is a live, trivalent mixture of three types of attenuated polioviruses grown in monkey kidney cell culture. **Oral poliovirus vaccine** simulates natural infection, inducing active mucosal and systemic immunity without producing symptoms of disease. Routine primary poliovirus vaccination of adults (>18y) living in the US is not recommended. Adults who are at increased risk of exposure and who have not been adequately immunized should receive poliovirus vaccination. This group includes travelers to regions where poliomyelitis is endemic or epidemic, health care workers in close contact with patients who may be excreting polioviruses, laboratory workers handling specimens that may contain polioviruses, and members of groups with disease caused by wild polioviruses. **Oral poliovirus vaccine** is used for epidemic control. Vaccination during pregnancy is effective and does not increase the risk of a pregnancy complication.

Side effects include paralytic disease (1/1.2 million 1st doses, 1/25 million 2nd or 3rd doses), and Guillain-Barré syndrome.

Fetal Considerations

There are no adequate reports or well-controlled studies of **oral poliovirus vaccine** in human fetuses. Maternal vaccination results in a level of passive immunity for the newborn. There is no evidence of teratogenicity or fetal toxicity. Rodent teratogenicity studies have not been performed.

Breastfeeding Safety

There are no adequate reports or well-controlled studies in nursing women. Antibodies are found in breast milk. While it is unknown whether **oral poliovirus vaccine** enters human breast milk, the resulting IgA antibodies do and may offer a level of neonatal protection. It is generally considered compatible with breastfeeding.

Drug Interactions

No clinically relevant interactions identified.

References

Bavdekar SB, Naik S, Nadkarni SS, et al. Indian J Pediatr 1999; 66:45-8.
Hanson LA, Carlsson B, Jalil F, et al. Rev Infect Dis 1984; 6(Suppl 2):S356-60.
Harjulehto-Mervaala T, Aro T, Hiilesmaa VK, et al. Clin Infect Dis 1994; 18:414-20.
Harjulehto-Mervaala T, Hovi T, Aro T, et al. Acta Obstet Gynecol Scand 1995; 74:262-5.

Summary

Pregnancy Category: C
Lactation Category: S

- Although one might intuit that a live vaccine should be avoided during pregnancy in favor of an inactivated preparation, the largest studies are reassuring.
- The inactivated preparation is preferred for the immunization of adults.

Polyethylene glycol—(MiraLax)

International Brand Name—None identified.

Drug Class	Laxatives
Indications	Constipation
Mechanism	Unknown; osmotic agent that causes water retention in stool
Dosage with Qualifiers	Constipation—17g PO qd for up to 2w • **Contraindications**—hypersensitivity to drug or class, bowel obstruction • **Caution**—elderly
Maternal Considerations	There is little if any systemic absorption of **polyethylene glycol.** There are no adequate reports or well-controlled studies in pregnant women. It is used successfully for the treatment of puerperal constipation. ***Side effects*** include nausea, abdominal bloating, cramping, flatulence, diarrhea, urticaria, and electrolyte disorders.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **polyethylene glycol** crosses the human placenta. However, it is unlikely a clinically significant quantity is absorbed systemically. Rodent teratogenicity studies have not been performed.
Breastfeeding Safety	There are no adequate reports or well-controlled studies in nursing women. It is unknown whether **polyethylene glycol** enters human breast milk. Considering the lack of systemic absorption, **polyethylene glycol** is unlikely to achieve clinically relevant levels in breast milk.
Drug Interactions	No clinically relevant interactions identified.
References	Nardulli G, Limongi F, Sue G, et al. GEN 1995; 49:224-6.
Summary	**Pregnancy Category: C** **Lactation Category: S** • **Polyethylene glycol** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk. • There are alternative agents for which there is more experience regarding use during pregnancy and lactation.

Polymyxin B–trimethoprim—(Polytrim)

International Brand Name—Destrim (Colombia); Neoftalm (Argentina); Oftlamotrim (Malaysia); Polytrim (Austria, Belgium, Canada, Netherlands, Portugal, Spain); Primoptic (Thailand)

Drug Class	Antibacterials; Antibiotics; Ophthalmics
Indications	Ophthalmic infection
Mechanism	Bacteriostatic, bactericidal (see **Trimethoprim**)

Dosage with Qualifiers	Ophthalmic infection—1gt each eye q3h ×7d; max 6 doses/d • **Contraindications**—hypersensitivity to drug or class • **Caution**—unknown
Maternal Considerations	There are no adequate reports or well-controlled studies of **polymyxin B–trimethoprim** in pregnant women. (See **Trimethoprim.**) ***Side effects*** include superinfection, increased perspiration, burning, stinging, itching, circumocular rash, and eyelid edema.
Fetal Considerations	There are no adequate reports or well-controlled studies of **polymyxin B–trimethoprim** in human fetuses. Considering the dose and route, it is unlikely the maternal systemic concentrations will reach clinically relevant levels. (See **Trimethoprim.**)
Breastfeeding Safety	There are no adequate reports or well-controlled studies in nursing women. It is unknown whether **polymyxin B–trimethoprim** enters human breast milk. However, considering the indication, route, and dosing, **polymyxin B–trimethoprim** use is unlikely to pose a clinically significant risk to the breastfeeding neonate. (See **Trimethoprim.**)
Drug Interactions	See **Trimethoprim.**
References	There are no current relevant references.
Summary	**Pregnancy Category: C** **Lactation Category: S** • **Polymyxin B–trimethoprim** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Polythiazide-prazosin—(Minizide)

International Brand Name—None identified.

Drug Class	Adrenergic antagonists; Antihypertensives; Diuretics
Indications	Hypertension
Mechanism	See **individual drugs**
Dosage with Qualifiers	Hypertension—1 tab PO bid or tid, beginning in the evening • **Contraindications**—hypersensitivity to drug or class, anuria, hypersensitivity to sulfonamides • **Caution**—unknown
Maternal Considerations	There are no adequate reports or well-controlled studies of **polythiazide-prazosin** in pregnant women. (See **Prazosin.**) ***Side effects*** include 1st-dose hypotension and/or syncope, orthostatic hypotension, dizziness, headache, somnolence, weakness, palpitations, nausea, paresthesias, tinnitus, abdominal pain, arthralgia, myalgia, and pruritus.
Fetal Considerations	There are no adequate reports or well-controlled studies of **polythiazide-prazosin** in human fetuses. (See **Prazosin.**)

Breastfeeding Safety	There are no adequate reports or well-controlled studies in nursing women. It is unknown whether **polythiazide-prazosin** enters human breast milk. (See **Prazosin.**)
Drug Interactions	See **Prazosin.**
References	There is no published experience in pregnancy or during lactation.
Summary	**Pregnancy Category: C** **Lactation Category: S** • **Polythiazide-prazosin** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk. • There are alternative agents for which there is more experience regarding use during pregnancy and lactation.

Potassium chloride—(Cena-K; Chloropotassuril; Durules; K-10; Kadalex; Kaochlor; Kaon Cl; Kay Ciel; K-Care; K-Dur; K-Lease; K-Lor; Klor-Con; Klorvess; Klotrix; K-Lyte Cl; K-Norm; Kolyum; K-Sol; K Tab; Micro-K; Rum-K; Slow-K; Ten-K; Ultra-K-Chlor)

International Brand Name—Acronitol (Greece); Addi-K (Malaysia, South Africa, Taiwan); Apo-K (Canada, Malaysia); Beacon K SR (Malaysia); Celeka (Argentina); Chlorvescent (New Zealand); Clor-K-Zaf (Mexico); Diffu-K (France); Durekal (Finland); Durules-K (Argentina); Kaleorid (Denmark, France, Norway, Sweden); Kaliduron (Finland); Kaliglutol (Switzerland); Kalilente (Norway); Kalinorm (Denmark, Finland); Kalinorm Depottab (Norway); Kalinor-Retard P (Germany); Kaliolite (Mexico); Kalipor (Finland, Sweden); Kalipoz (Poland); Kalitabs (Sweden); Kalitrans Retard (Germany); Kalium (Netherlands, Philippines, South Africa); Kalium-Durettes (Belgium, Netherlands); Kalium Duriles (Germany); Kalium-R (Hungary, Switzerland); Kalium Retard (Norway); Kay-Cee-L (England, Ireland); KCL Retard (Austria, Czech Republic, Greece, Hungary, Israel, Italy, Spain); K-Contin (South Africa); K-Contin Continus (Korea); Keylyte (India); K-SR (New Zealand); KSR (Australia, Indonesia); KSR 600 (Australia); K-Tab (Puerto Rico); Lento-Kalium (Italy); Leo-K (England, Ireland); Micro-K (Canada); Micro-Kalium Retard (Austria); Micro-K Extentcaps (Puerto Rico); Miopotasio (Spain); Nu-K (England, Ireland); Perennum (Paraguay); Plus Kalium Retard (Switzerland); Potasion (Spain); Rekawan (Germany); Rekawan Retard (Austria); Slow-K (Argentina, Canada, Chile, China, Japan, Malaysia, Netherlands, Taiwan, Uruguay); Span-K (Australia, Malaysia, New Zealand)

Drug Class	Electrolyte replacements
Indications	Hypokalemia, treatment and prophylaxis
Mechanism	Electrolyte replacement
Dosage with Qualifiers	Hypokalemia treatment—400mEq PO qd if K^+ <2mEq/L; 10-20mEq/h PO if ECG changes Hypokalemia prophylaxis—begin 20mEq PO qd, adjust as needed • **Contraindications**—hypersensitivity to drug or class, untreated Addison's disease, hyperkalemia, renal failure • **Caution**—renal dysfunction, CV disease
Maternal Considerations	There are no adequate reports or well-controlled studies of **potassium chloride** in pregnant women. The most common cause of hypokalemia during pregnancy is the administration of β-mimetic agents for the treatment of preterm labor (see **Ritodrine, Terbutaline**). However, the decreased serum potassium does not reflect total body depletion, but rather increased intracellular potassium. Routine treatment is not necessary.

	Side effects include arrhythmia, dyspepsia, N/V, diarrhea, rash, and bleeding.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. **Potassium chloride** readily crosses the human placenta. It is unlikely that potassium supplementation would have an adverse effect on the fetus without maternal toxicity. Rodent reproduction studies have not been performed.
Breastfeeding Safety	There are no adequate reports or well-controlled studies in nursing women. **Potassium chloride** enters human breast milk; supplementation is generally considered compatible with breastfeeding.
Drug Interactions	Potassium-sparing diuretics and ACEIs may lead to hyperkalemia.
References	There are no current relevant references.
Summary	**Pregnancy Category: C** **Lactation Category: S** • **Potassium chloride** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Potassium iodide—(SSKI)

International Brand Name—None identified.

Drug Class	Electrolytes; Thyroid agents; Vitamins/minerals
Indications	Thyrotoxicosis, preoperative thyroidectomy, expectorant; radiation exposure
Mechanism	Inhibits thyroid hormone synthesis
Dosage with Qualifiers	Thyrotoxicosis—50-250mg PO tid Preoperative thyroidectomy—50-250mg PO tid beginning 10-14d before surgery Expectorant—50-250mg PO tid; max 500mg/dose Radiation exposure—130mg/d if expected exposure >5cGy; continue until risk of exposure has passed • **Contraindications**—hypersensitivity to drug or class, hyperkalemia, severe volume depletion, Addison's disease, hypothyroidism, acute bronchitis, TB • **Caution**—renal dysfunction, CV disease, cystic fibrosis
Maternal Considerations	**Potassium iodide** effectively reduces thyroid uptake of radioactive iodide and is an adjunct for women with hyperthyroidism associated with Graves' disease. There are no adequate reports or well-controlled studies in pregnant women. **Potassium iodide** replacement is effective during pregnancy for the treatment of mild to moderate iodine deficiency. ***Side effects*** include arrhythmia, GI bleeding, angioedema, parotitis, goiter, thyroid adenoma, metallic taste, dyspepsia, urticaria, headache, acne, fever, rhinitis, lymphadenopathy, arthralgia, eosinophilia, confusion, numbness, and paresthesia.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. **Potassium iodide** crosses the human placenta,

and an excess can cause fetal goiter and hypothyroidism. The limited rodent studies are reassuring.

Breastfeeding Safety — There are no adequate reports or well-controlled studies in nursing women. Supplementation with **potassium iodide** has little effect on the iodine concentration of human breast milk. It is probably compatible with breastfeeding.

Drug Interactions — Potassium-sparing diuretics and ACEIs may lead to hyperkalemia.

References

Chierici R, Saccomandi D, Vigi V. Acta Paediatr Suppl 1999; 88:7-13.
Glinoer D, De Nayer P, Delange F, et al. J Clin Endocrinol Metab 1995; 80:258-69.
Morales de Villalobos LM, Campos G, Ryder E. Enzyme 1986; 35:96-101.
Reinhardt W, Kohl S, Hollmann D, et al. Eur J Med Res 1998; 3:203-10.
Vicens-Calvet E, Potau N, Carreras E, et al. J Pediatr 1998; 133:147-8.

Summary

Pregnancy Category: D
Lactation Category: S

- **Potassium iodide** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Pralidoxime—(Protopam)

International Brand Name—Aldopam (India); Contrathion (Argentina, Brazil, France, Italy); PAM (Korea, New Zealand); PAM-A (Korea); Pamcl (Taiwan); Pampara (Taiwan); Pralidoxime Iodide (Australia); Protopam Chloride (Canada)

Drug Class — Antidotes; Toxicology

Indications — Organophosphate poisoning, anticholinesterase overdose

Mechanism — Reactivates cholinesterase

Dosage with Qualifiers

Organophosphate poisoning—1-2g IV over 15-30min; may repeat in 1h if clinically indicated
Anticholinesterase overdose—1-2g IV over 15-30min

- **Contraindications**—hypersensitivity to drug or class
- **Caution**—myasthenia gravis, renal dysfunction

Maternal Considerations — There are no adequate reports or well-controlled studies of **pralidoxime** in pregnant women. The published experience is limited to case reports.
Side effects include transient neuromuscular blockade, laryngospasm, muscle rigidity, blurred vision, diplopia, dizziness, headache, N/V, hypertension, tachycardia, maculopapular rash, and elevated LFTs.

Fetal Considerations — There are no adequate reports or well-controlled studies in human fetuses. It is not known whether **pralidoxime** crosses the human placenta. Rodent teratogenicity studies have not been conducted.

Breastfeeding Safety — There is no published experience in nursing women. It is unknown whether **pralidoxime** enters human breast milk.

	However, considering the indication and dosing, one-time **pralidoxime** use is unlikely to pose a clinically significant risk to the breastfeeding neonate.
Drug Interactions	Signs of atropinization (flushing, mydriasis, tachycardia, dryness of the mouth and nose) may occur earlier than might be expected when used with **atropine.** This is especially true if the total dose of **atropine** is large and the administration of **pralidoxime** was delayed.
References	Bailey B. Ann Emerg Med 1997; 29:299.
Summary	**Pregnancy Category: C** **Lactation Category: U** • **Pralidoxime** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Pramipexole—(Mirapex; Sifrol)

International Brand Name—Pexola (Colombia); Sifrol (Israel)

Drug Class	Antiparkinson agents; Dopaminergics
Indications	Parkinsonism
Mechanism	Nonergot dopamine receptor agonist
Dosage with Qualifiers	Restless Leg Syndrome—begin 0.125mg q hs PO; increase q4-7d with a max dose of 0.75mg Parkinsonism—begin 0.125mg PO tid; increase by 0.25mg/d q7d ×7w *NOTE: renal dosing.* • **Contraindications**—hypersensitivity to drug or class • **Caution**—renal dysfunction
Maternal Considerations	**Pramipexole** clearance is 30% lower in women than men; most of this difference reflects body weight. The published experience during pregnancy is limited to two case reports. ***Side effects*** include hallucinations, orthostatic hypotension, dyskinesia, asthenia, dizziness, insomnia, somnolence, peripheral edema, dry mouth, headache, anorexia, and visual abnormalities.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **pramipexole** crosses the human placenta. **Pramipexole** in rodents reduces implantation and is embryotoxic. Teratogenicity studies have not been performed.
Breastfeeding Safety	There is no published experience in nursing women. It is unknown whether **pramipexole** enters human breast milk. **Pramipexole** is concentrated in rodent milk.
Drug Interactions	Increases the **levodopa** C_{max} by about 40% and decreases the T_{max} from 2.5 to 0.5h. Population pharmacokinetics study suggests that the use of drugs that are secreted by the cationic transport system (e.g., **cimetidine, diltiazem, quinidine, quinine, ranitidine, triamterene, verapamil**) decreases the oral clearance of

pramipexole by about 20%. In one study, **cimetidine** caused a 50% increase in **pramipexole** AUC and a 40% increase in t/2. Dopamine antagonists, such as the neuroleptics (phenothiazines, butyrophenones, thioxanthenes) or **metoclopramide,** may diminish the effectiveness of **pramipexole.**

References

Kanzato N, Nishihira T, Murao H, Takara H. Rinsho Shinkeigaku 2006; 46:400-3.
Mucchiut M, Belgrado E, Cutuli D, et al. Mov Disord 2004; 19:1114-5.

Summary

Pregnancy Category: C
Lactation Category: U

- **Pramipexole** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Pravastatin—(Pravachol)

International Brand Name—Astin (Mexico); Bristacol (Spain); Cholespar (Indonesia); Elisor (France); Kenstatin (Mexico); Lipemol (Spain); Lipidal (Israel); Liplat (Spain); Lipostat (Bulgaria, Czech Republic, England, Hungary, Ireland, Israel, New Zealand, Philippines, Poland); Liprevil (Germany); Mevalotin (China, Germany, Indonesia, Japan, Korea, Taiwan, Thailand); Novales (Indonesia); Prascolend (Mexico); Prastan (Korea); Prava (Slovenia, South Africa); Pravachol (Australia, Canada, Colombia, Costa Rica, Denmark, El Salvador, Finland, Greece, Guatemala, Honduras, Hong Kong, Indonesia, Malaysia, Nicaragua, Norway, Panama, Peru, Sweden, Venezuela); Pravacol (Argentina, Brazil, Chile, Ecuador, Peru, Portugal); Pravaselect (Italy); Pravasin (Germany); Pravasine (Belgium); Pravastatin Natrium ''Mayrho Fer'' (Austria); Pravator (India); Pravyl (Colombia); Sanaprav (Italy); Selectin (Italy); Selektine (Netherlands); Selipran (Switzerland); Stanidine (Philippines); Vasopran (Korea); Vasten (France); Xipral (Mexico)

Drug Class

Antihyperlipidemics; HMG-CoA reductase inhibitors

Indications

Hypercholesterolemia

Mechanism

Inhibits HMG-CoA reductase

Dosage with Qualifiers

Hypercholesterolemia—begin 40mg/d; max 80mg/d

NOTE: renal and hepatic dosing; monitor hepatic transaminases at baseline and either q3mo or prior to increasing dose.

- **Contraindications**—hypersensitivity to drug or class, active liver disease
- **Caution**—alcohol abuse, hepatic or renal dysfunction

Maternal Considerations

Pravastatin lowers lipids in two ways. First, it modestly reduces the intracellular pool of cholesterol by the reversible inhibition of HMG-CoA reductase, increasing the number of LDL receptors on cell surfaces and enhancing receptor-mediated catabolism and clearance of circulating LDL. Second, **pravastatin** inhibits LDL production by inhibiting hepatic synthesis of VLDL, the LDL precursor. There are no adequate reports or well-controlled studies in pregnant women. Atherosclerosis is a chronic process; discontinuation of **pravastatin** during pregnancy should have little impact on long-term maternal outcome.
Side effects include rhabdomyolysis, hepatotoxicity, cholelithiasis, dyspepsia, abdominal pain, flatulence, constipation, rash, myalgia, asthenia, and elevated CPK or LFTs.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **pravastatin** crosses the

human placenta. It is lipophilic and should equilibrate between maternal and fetal compartments. **Pravastatin** inhibits P-glycoprotein and therefore may increase the placental transfer of other compounds to the fetus. One recent review of 214 pregnancy exposures to statins noted 31 adverse outcomes, including 22 cases with structural defects and 5 fetal deaths. There were two principal categories of recurrent structural defects: **cerivastatin** and **lovastatin** were associated with 4 reports of severe midline CNS defects; **simvastatin, lovastatin,** and **atorvastatin** were associated with reports of limb deficiencies, including 2 similar complex lower limb defects after **simvastatin** exposure. There were 2 cases of VACTERL among the limb deficiency cases. No adverse outcomes were reported after exposure to **pravastatin,** which is poorly transported across the rodent placenta. These authors concluded that statins may have secondary effects on sterol-dependent morphogens such as Sonic Hedgehog.

Breastfeeding Safety

There are no adequate reports or well-controlled studies in nursing women. It is unknown whether **pravastatin** enters human breast milk. Certainly cholesterol and its by-products are important components of breast milk. In the absence of further study, **pravastatin** should be considered incompatible with breastfeeding.

Drug Interactions

Itraconazole (a potent CYP3A4 inhibitor that also inhibits P-glycoprotein transport) increased the mean AUC and C_{max} for **pravastatin** by factors of 1.7 and 2.5, respectively. The mean t/2 was not affected, suggesting the relatively small increases in C_{max} and AUC were due solely to increased bioavailability rather than a decrease in clearance, consistent with inhibition of P-glycoprotein transport by **itraconazole.**

Cholestyramine and **colestipol** use resulted in a 40-50% decrease in the mean AUC of **pravastatin.** However, when **pravastatin** was administered 1h before or 4h after **cholestyramine** or 1h before **colestipol** and a standard meal, there was no clinically significant decrease in bioavailability or therapeutic effect.

A significant difference was observed between the AUCs for **pravastatin** when given with **cimetidine** compared to that when administered with antacid.

In a crossover study of 20 healthy males given single doses of **pravastatin** and **gemfibrozil,** there was a significant decrease in urinary excretion and protein binding of **pravastatin.** In addition, there was a significant increase in AUC, C_{max}, and T_{max} for the **pravastatin** metabolite SQ 31,906. Combination therapy with **pravastatin** and **gemfibrozil** is not recommended.

References

Edison RJ, Muenke M. Am J Med Genet A 2004; 131:287-98.
Teelucksingh S, El-Youssef J, Sohan K, Ramsewak S. Reprod Toxicol 2004; 18:299-300.

Summary

Pregnancy Category: X
Lactation Category: NS (possibly)

- **Pravastatin** decreases cholesterol synthesis and potentially other biologically active substances derived from cholesterol.
- It should be considered contraindicated during pregnancy and lactation until additional study has been completed.
- Atherosclerosis is a chronic process; discontinuation of **pravastatin** during pregnancy should have little impact on long-term outcome for most patients.

Praziquantel—(Biltricide)

International Brand Name—Biltricide (Australia, Canada, France, Germany, Hong Kong, Japan, Netherlands, Taiwan); Cesol (Mexico); Cisticid (Ecuador, Mexico, Peru, Venezuela); Distocide (Israel, Korea); Ehliten (Mexico); Helmiben (Peru); Kalcide (Taiwan); Mycotricide (Thailand); Opticide (Thailand); Prazite (Thailand); Prazitral (Argentina); Teniken (Mexico); Wormicide (Thailand); Z-Queen (Thailand)

Drug Class	Anthelmintics; Antiparasitics
Indications	Schistosomiasis, tapeworms, liver flukes
Mechanism	Enhances cell membrane permeability
Dosage with Qualifiers	Schistosomiasis—20mg/kg PO q4-6h ×1d Tapeworms—5-25mg/kg PO ×1 Liver flukes—25mg/kg PO q4-6h ×1d • **Contraindications**—hypersensitivity to drug or class, ocular schistosomiasis or cysticercosis • **Caution**—hepatic dysfunction
Maternal Considerations	Schistosomiasis affects approximately 40 million women of childbearing age, yet little is known about schistosome-associated morbidity in pregnant women and their offspring. The WHO has recommended treatment of infected pregnant and lactating women. The main complication of helminth infection during pregnancy is anemia. Neurocysticercosis is a cause of first-time convulsions in pregnant patients, and there are several case reports of its successful treatment with **praziquantel** during pregnancy. **Praziquantel** has also been used during the puerperium to successfully treat hypersplenism secondary to chronic hepatosplenic schistosomiasis. Recent study documents that pregnancy suppresses a potentially beneficial boost in cytokine responses associated with **praziquantel**. ***Side effects*** include CSF reaction syndrome, malaise, headache, dizziness, abdominal pain, nausea, fever, urticaria, bitter taste, drowsiness, anorexia, sweating, and fever.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. It is not known whether **praziquantel** crosses the human placenta. Congenital helminthic infection in humans is exceedingly rare. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically. However, some studies report **praziquantel** is embryotoxic and may be genotoxic.
Breastfeeding Safety	There are no adequate reports or well-controlled studies in nursing women. **Praziquantel** enters human breast milk with an M:P ratio approximating 0.25 or a peak milk concentration of 0.5mg/ml. However, the mean excretion with the milk in 24h approximates 0.0008% of the given dose. Thus, the unsupplemented neonate of a woman treated for tapeworm would ingest less than 1mg of drug given to its mother.
Drug Interactions	No clinically relevant interactions identified.
References	Friedman JF, Mital P, Kanzaria HK, et al. Trends Parasitol 2007; 23:159-64. Frohberg H. Arzneimittelforschung 1984; 34:1137-44. Kopelman JN, Miyazawa K. Am J Perinatol 1990; 7:380-3. Kurl R, Montella KR. Am J Perinatol 1994; 11:409-11.

Montero R, Ostrosky P. Mutat Res 1997; 387:123-39.
Putter J, Held F. Eur J Drug Metab Pharmacokinet 1979; 4:193-8.
Tweyongyene R, Mawa PA, Ngom-Wegi S, et al. J Infect Dis 2008; 198:1870-9.

Summary

Pregnancy Category: B
Lactation Category: S (likely)

- **Praziquantel** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.
- The WHO recommends treatment of schistosome-infected pregnant and lactating women.

Prazosin—(Hypovase; Lopres; Minipress)

International Brand Name—Alti-Prazosi (Canada); Apo-Prazo (Canada); Novo-Prazin (Canada); Pratisol (Finland)

Drug Class

Adrenergic antagonists; α-Blockers; Antihypertensives

Indications

Hypertension

Mechanism

Unknown; peripheral α_1-adrenergic antagonist

Dosage with Qualifiers

Hypertension—begin 1mg PO bid; usual dose 3-20mg/d

- **Contraindications**—hypersensitivity to drug or class
- **Caution**—hepatic or renal dysfunction

Maternal Considerations

Unlike many other antihypertensive drugs, the effect of **prazosin** is closely related to its plasma concentration. The T_{max} is increased and its elimination t/2 prolonged during pregnancy. **Prazosin** is a secondary agent for the treatment of preeclamptic hypertension. While as effective as **nifedipine,** the associated fetal death rate is higher. **Prazosin** has revolutionized the treatment of severe scorpion stings.
Side effects include syncope after the 1st dose, postural hypotension, dizziness, palpitations, edema, N/V, diarrhea, headache, paresthesias, blurred vision, drowsiness, malaise, dry mouth, arthralgia, fever, and pruritus.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. **Prazosin** crosses the human placenta, achieving an F:M ratio of 0.20. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically. Some decrease in litter size occurs at doses >200× the MRHD. There is no apparent explanation for the increased perinatal mortality rate when used to treat preeclamptic hypertension.

Breastfeeding Safety

There are no adequate reports or well-controlled studies in nursing women. Small quantities of **prazosin** enter human breast milk; however, it is generally considered compatible with breastfeeding.

Drug Interactions

The addition of a diuretic or another antihypertensive agent may cause an additive hypotensive effect that can be minimized by decreasing the **prazosin** to 1-2mg tid, introducing additional antihypertensive drugs cautiously, and then re-titrating **prazosin** based on clinical response.

References

Bourget P, Fernandez H, Edouard D, et al. Eur J Drug Metab Pharmacokinet 1995; 20:233-41.
Hall DR, Odendaal HJ, Steyn DW, Smith M. BJOG 2000; 107:759-65.
Lowe SA, Rubin PC. J Hypertens 1992; 10:201-7.
Rubin PC, Butters L, Low RA, Reid JL. Br J Clin Pharmacol 1983; 16:543-7.

Summary

Pregnancy Category: C
Lactation Category: S

- **Prazosin** is one of many second-line alternatives for the treatment of preeclamptic and chronic hypertension during pregnancy.
- **Prazosin** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Prednicarbate topical—(Dermatop)

International Brand Name—Pretop (Korea); Titibe (Korea)

Drug Class

Corticosteroids; Dermatologics

Indications

Steroid-responsive dermatitis

Mechanism

Unknown

Dosage with Qualifiers

Steroid-responsive dermatitis—apply bid

- **Contraindications**—hypersensitivity to drug or class
- **Caution**—avoid prolonged use on face, groin, axilla, or skin creases

Maternal Considerations

Prednicarbate (0.1%) does not suppress the HPA-axis if used at 30g/d for 1w. There are no published studies in pregnant women. ***Side effects*** include pruritus, skin atrophy, and acne.

Fetal Considerations

There are no published studies in human fetuses. It is unknown whether **prednicarbate** crosses the human placenta. Considering the dose and route, it is unlikely the maternal systemic concentration will reach a clinically relevant level. In some rodent studies, **prednicarbate** is teratogenic and embryotoxic if given SC at doses 45× the recommended topical human dose, assuming a percutaneous absorption of approximately 3%.

Breastfeeding Safety

There is no published experience in nursing women. It is unknown whether **prednicarbate** enters human breast milk. Some systemically administered corticosteroids are excreted in breast milk. However, considering the route and concentration, limited **prednicarbate** use is unlikely to pose a clinically significant risk to the breastfeeding neonate.

Drug Interactions

No clinically relevant interactions identified.

References

There is no published experience in pregnancy or during lactation.

Summary

Pregnancy Category: C
Lactation Category: S (likely)

- **Prednicarbate** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Prednisolone—(Adnisolone; Cortalone; Delta-Cortef; Orapred; Prelone; Ultracortenol)

International Brand Name—Adelcort (Greece); Aprednislon (Austria); Capsoid (South Africa); Compresolon (Taiwan); Dacortin H (Spain); Decaprednil (Germany); Decortin H (Bulgaria); Deltacortril (Belgium, England, Germany, Ireland, Republic of Yemen, Syria, United Arab Emirates); Deltastab (England, Ireland); Dermosolon (Germany); Dhasolone (Malaysia); Di-Adreson-F (Hong Kong, Hungary, Thailand); Hefasolon (Germany); Hostacortin H (Korea); Hydrocortancyl (France); Lenisolone (South Africa); Liquipred (France); Lygal Kopftinktur N (Germany); Meticortelone (Italy, South Africa); Opredsone (Thailand); Panafcortelone (Australia, Hong Kong); Pelonine (Taiwan); Preconin (Taiwan); Precortisyl (England, Ireland); Predeltilone (South Africa); Predisole (Thailand); Predisyr (Philippines); Prednecort (Philippines); Prednicortelone (Belgium); Predni-Helvacort (Switzerland); Prednisil (Thailand); Prednisolona (Colombia); Predonine (Taiwan); Prelon (Taiwan); Prelone (Brazil, South Africa); Prenilone (Thailand); Prenin (Taiwan); Preventan (Chile); Prezolon (Greece); Rubycort (Korea); Scherisolona (Colombia, Uruguay); Solondo (Korea); Solone (Australia); Solupred (France); Ultracortenol (Colombia); Walesolone (Singapore); Wysolone (India)

Drug Class	Corticosteroids
Indications	Inflammatory disorders, MS, asthma (acute or persistent severe), adrenal insufficiency
Mechanism	Unknown
Dosage with Qualifiers	Inflammatory disorders—5-60mg/d PO/IV/IM, may give in divided doses Relapsing MS—begin 200mg PO qd ×1w, then 80mg PO qod ×1mo Asthma (acute)—begin 120-180mg/d PO/IV/IM in 3-4 divided doses, then 60-80mg/d PO/IV/IM for severe exacerbations Asthma (persistent severe)—7.5-80mg PO qd or qod, taper slowly Adrenal insufficiency—4-5mg/m^2 PO qd *NOTE: available in various tablet, syrup, parenteral, and ophthalmic preparations.* • **Contraindications**—hypersensitivity to drug or class, systemic fungal infection • **Caution**—seizure disorder, diabetes mellitus, hypertension, TB, osteoporosis, hepatic dysfunction
Maternal Considerations	**Prednisolone** is a metabolite of **prednisone.** It provides effective relief (10mg PO tid) of severe hyperemesis unresponsive to primary therapy and characterized by at least a 10% weight loss. Dermatologic and ophthalmic applications have been used for decades during pregnancy without apparent sequelae. **Prednisolone** is used widely for the treatment of inflammatory/autoimmune disorders that are common in reproductive-age women. Once used for the treatment antiphospholipid syndrome, several trials document a higher loss rate with **prednisolone** and **aspirin** than **heparin** and **aspirin.** Similarly, the combination of **prednisone, aspirin,** and **progesterone** is no better than **enoxaparin** alone for the treatment of idiopathic, recurrent miscarriage. ***Side effects*** include adrenal insufficiency, steroid psychosis, immunosuppression, peptic ulcer, CHF, osteoporosis, pseudotumor cerebri, N/V, dyspepsia, edema, headache, dizziness, mood swings, insomnia, anxiety, menstrual irregularities, ecchymosis, acne, skin atrophy, impaired wound healing, hypertension, hypokalemia, and hyperglycemia.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. The human placenta metabolizes **prednisone,** reducing fetal exposure to perhaps 10% of the maternal level.

One study of **prenisolone** placental transfer noted the same F:M of 0.10. **Prednisone** is often used as salvage therapy for the treatment of fetal alloimmune thrombocytopenia in fetuses unresponsive to immune globulin infusion. Some authors suggest emotional stress during organogenesis could cause congenital malformations by increasing the level of glucocorticoids. Older epidemiologic studies examined the association of oral clefting with corticosteroids exposure and concluded prenatal exposure carried 6-fold increase in risk for cleft lip with or without cleft palate. IUGR and shortening of the head and mandible were also suggested as sequelae. However, the Collaborative Perinatal Project followed women treated during the 1st trimester. While the number of exposures was limited, no increase in congenital malformations was detected. More recent studies also dismiss the risk of teratogenicity for all malformations except clefting. There is no increase in risk of anomalies when exposure occurs after organogenesis. Women exposed to topical **prednisone**-like compounds during pregnancy have no significantly increased risk of delivering a child with birth defects. In sum, the evidence that **corticosteroids** are human teratogens is weak, and confined only to cleft lip. Female rats exposed to **cortisone** *in utero* exhibit premature vaginal opening. **Cortisone** accelerates fetal rat intestinal maturation, perhaps explaining why corticosteroids decrease the incidence of NEC.

Breastfeeding Safety

There are no adequate reports or well-controlled studies in nursing women. It is unknown whether **prednisolone** enters human breast milk. However, long clinical experience suggests **prednisolone** therapy is compatible with breastfeeding.

Drug Interactions

Drugs such as barbiturates, **phenytoin, ephedrine,** and **rifampin,** which induce liver microsomal drug-metabolizing enzyme activity, may enhance metabolism and require the dose of **prednisolone** be increased.
Increases activity of both **cyclosporine** and corticosteroids with concurrent use.
Estrogens may decrease the liver metabolism of some corticosteroids, thus increasing their effect.
Ketoconazole decreases the metabolism of some corticosteroids by up to 60%, leading to an increased risk of corticosteroid side effects.
May decrease the response to **warfarin;** clotting indices should be monitored closely.
Use with **aspirin** (or other NSAIDs) increases the risk of GI side effects. **Aspirin** should be used cautiously with corticosteroids in hypoprothrombinemia. Salicylate clearance may be increased by corticosteroids.
Observe patients closely for hypokalemia if used with potassium-depleting agents (i.e., diuretics, **amphotericin B**). Hypokalemia increases the risk of arrhythmia in patients on digitalis glycosides.
Use with anticholinesterase agents may produce severe weakness in patients with myasthenia gravis. Anticholinesterase agents should be stopped at least 24h before initiating corticosteroid therapy if possible.
Patients on prolonged corticosteroid therapy may exhibit a diminished response to toxoids and live or inactivated vaccines. Corticosteroids may also potentiate the replication of some organisms contained in live, attenuated vaccines. The routine administration of vaccines or toxoids should be deferred until corticosteroid therapy is discontinued if possible. Corticosteroids may suppress skin test reactions.

May increase blood glucose concentration, necessitating a dose adjustment of hypoglycemic agents.

References

Berkowitz RL, Bussel JB, McFarland JG. Am J Obstet Gynecol 2006; 195:907-13.
Berkowitz RL, Lesser ML, McFarland JG, et al. Obstet Gynecol 2007; 110:249-55.
Fawzy M, Shokeir T, El-Tatongy M, et al. Arch Gynecol Obstet 2008; 278:33-8.
Guillonneau M, Jacqz-Aigrain E. J Gynecol Obstet Biol Reprod (Paris) 1996; 25:160-7.
Moran P, Taylor R. QJM 2002; 95:153-8.
Park-Wyllie L, Mazzotta P, Pastuszak A, et al. Teratology 2000; 62:385-92.
Rodriguez-Pinnilla E, Martinez-Frias ML. Teratology 1998; 58:2-5.
van Runnard Heimel PJ, Schobben AF, Huisjes AJ, et al. Placenta 2005; 26:842-5.

Summary

Pregnancy Category: B
Lactation Category: S (likely)

- **Prednisolone** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Prednisone—(Adasone; Cartancyl; Colisone; Cordrol; Cortan; Dacortin; Deltasone; Orasone; Paracort; Prednicot; Sterapred; Sterapred DS)

International Brand Name—Alfacort (Uruguay); Apo-Prednisone (Canada, New Zealand); Cortancyl (France); Cortiprex (Chile, Peru); Cutason (Germany); Dacorten (Spain); Dacortin (Spain); Decortin (Bulgaria, Germany, Poland); Decortisyl (England, Ireland, Philippines); Delcortin (Denmark); Dellacort A (Indonesia); Deltacortene (Italy); Deltacortone (Japan); Deltasone (Hong Kong, New Zealand); Deltison (Sweden); Deltisona (Argentina); Di-Adreson (Japan); Drazone (Philippines); Encorton (Poland); Hostacortin (Indonesia); Me-Korti (Finland); Meticorten (Argentina, Brazil, Chile, Costa Rica, Dominican Republic, Ecuador, El Salvador, Guatemala, Honduras, Japan, Mexico, Nicaragua, Panama, Peru, South Africa, Venezuela); Nisona (Peru); Oracort (Philippines); Panafcort (Australia, South Africa); Pehacort (Indonesia); Prednicorm (Germany); Prednicort (Belgium); Prednidib (Mexico); Prednitone (Israel); Pulmison (South Africa); Sone (Australia); Steerometz (Philippines); Ultracorten (Germany); Winpred (Canada)

Drug Class

Corticosteroids

Indications

Inflammatory disorders, MS, *Pneumocystis* pneumonia, adrenal insufficiency

Mechanism

Unknown

Dosage with Qualifiers

Inflammatory disorders (e.g., Crohn's disease)—5-60mg PO qd
Relapsing MS—begin 200mg PO qd ×1w, then 80mg PO qod ×1mo
Pneumocystis pneumonia—begin 40mg PO bid ×5d, then 40mg qd ×5d, then 20mg qd
Adrenal insufficiency—4-5mg/m^2 PO qd

- **Contraindications**—hypersensitivity to drug or class, systemic fungal infection
- **Caution**—seizure disorder, diabetes mellitus, hypertension, TB, osteoporosis, hepatic dysfunction

Maternal Considerations

There are no adequate reports or well-controlled studies of **prednisone** in pregnant women. Crohn's disease and other chronic inflammatory diseases often affect reproductive-age women. The available data show that women with Crohn's disease can expect to conceive successfully, carry to term, and deliver a healthy baby. Control of disease activity before conception and during pregnancy is critical to optimize both maternal and fetal health. The pharmacologic therapy during pregnancy is similar to that for nonpregnant patients. Patients maintained in remission by way of pharmacologic therapy should continue it throughout their pregnancy. Although **prednisolone** was previously used for the treatment antiphospholipid syndrome, several trials report the loss rate is higher with **prednisolone** and **aspirin** versus **heparin** and **aspirin.** Though there are several case series suggesting **prednisone** is of benefit, there is insufficient evidence to determine whether adjunctive steroid use in HELLP syndrome decreases maternal and perinatal mortality or major maternal and perinatal morbidity.
Side effects include adrenal insufficiency, steroid psychosis, immunosuppression, peptic ulcer, CHF, osteoporosis, pseudotumor cerebri, N/V, dyspepsia, edema, headache, dizziness, mood swings, insomnia, anxiety, menstrual irregularities, ecchymosis, acne, skin atrophy, impaired wound healing, hypertension, hypokalemia, and hyperglycemia.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. The human placenta metabolizes **prednisone,** reducing fetal exposure to perhaps 10% of the maternal level. Some authors suggest emotional stress during organogenesis could cause congenital malformations by increasing the level of glucocorticoids. **Prednisone** is used as a rescue therapy for the treatment of fetal alloimmune thrombocytopenia when IVIG has failed. Older epidemiologic studies examined the association of oral clefting with corticosteroids exposure and concluded prenatal exposure carry a 6-fold increase in risk for cleft lip with or without cleft palate. IUGR and shortening of the head and mandible were also suggested as sequelae. However, the Collaborative Perinatal Project followed women treated during the 1st trimester. While the number of exposures was limited, no increase in congenital malformations was detected. More recent studies also dismiss the risk of teratogenicity for all malformations except clefting. There is no increase in risk of anomalies when exposure occurs after organogenesis. Women exposed to topical **prednisone**-like compounds during pregnancy have no significantly increased risk of delivering a child with birth defects. In sum, the evidence that **corticosteroids** are human teratogens is weak, and confined only to cleft lip. Female rats exposed to **cortisone** *in utero* exhibit premature vaginal opening. **Cortisone** accelerates fetal rat intestinal maturation, perhaps explaining why corticosteroids decrease the incidence of NEC.

Breastfeeding Safety

There are no adequate reports or well-controlled studies in nursing women. It is unknown whether **prednisone** enters human breast milk. However, most asthma medications, including oral **prednisone,** are considered compatible with breastfeeding.

Drug Interactions

Drugs that induce liver enzymes (e.g., **phenobarbital, phenytoin, rifampin**) may increase the clearance of corticosteroids and may require increases in corticosteroid dose to achieve the desired response. Drugs such as **troleandomycin** and **ketoconazole** may inhibit the metabolism of corticosteroids and thus decrease their clearance. The dose of corticosteroid should be titrated to avoid steroid toxicity.

May increase the clearance of chronic high-dose **aspirin,** leading to decreased serum salicylate levels or an increased risk of salicylate toxicity when the corticosteroid is withdrawn. **Aspirin** should be used cautiously in conjunction with corticosteroids in patients suffering from hypoprothrombinemia.
The effect on oral anticoagulants is variable. There are reports of enhanced as well as diminished effects of anticoagulants when given concurrently with corticosteroids. Thus, coagulation indices should be monitored closely.

References

Berkowitz RL, Lesser ML, McFarland JG, et al. Obstet Gynecol 2007; 110:249-55.
Empson M, Lassere M, Craig JC, Scott JR. Obstet Gynecol 2002; 99:135-44.
Fawzy M, Shokeir T, El-Tatongy M, et al. Arch Gynecol Obstet 2008; 278:33-8.
Matchaba P, Moodley J. Cochrane Database Syst Rev 2004; (1):CD002076.
Park-Wyllie L, Mazzotta P, Pastuszak A, et al. Teratology 2000; 62:385-92.
Rodriguez-Pinnilla E, Martinez-Frias ML. Teratology 1998; 58:2-5.
Rotmensch S, Liberati M, Celentano C, et al. Acta Obstet Gynecol Scand 1999; 78:768-73.

Summary

Pregnancy Category: B
Lactation Category: S

- **Prednisone** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Prilocaine—(Citanest)

International Brand Name—Citanest (Canada, England, Ireland, New Zealand, Spain); Xylonest (Germany)

Drug Class

Anesthetics, local

Indications

Dental nerve block

Mechanism

Inhibits propagation of nerve impulse by inhibiting transneuronal membrane ionic flux

Dosage with Qualifiers

Dental nerve block—1-2ml infiltrated in the anatomically correct zone; max 600mg/24h

NOTE: 1% and 4% solution; avoid IV administration; onset 2-3min, duration 2-3h.

- **Contraindications**—hypersensitivity to drug or class, congenital or idiopathic methemoglobinemia
- **Caution**—severe hepatic dysfunction

Maternal Considerations

There are no adequate reports or well-controlled studies in pregnant women. **Prilocaine** is used in some locales for pudendal nerve block at delivery. **Prilocaine** causes vascular smooth muscle contraction in *in vitro* studies, suggesting injection in the region of the uterine artery for a paracervical block may be a risk.
Prilocaine is also available solid as a cream with **lidocaine.**
In one RCT, **lidocaine-prilocaine** cream did not decrease the discomfort associated with amniocentesis.
Side effects include light-headedness, nervousness, apprehension, euphoria, confusion, dizziness, drowsiness, tinnitus, blurred or

	double vision, vomiting, twitching, tremors, convulsions, unconsciousness, respiratory depression or arrest, vasovagal reaction, and sensations of heat, cold, or numbness.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. **Prilocaine** crosses the human placenta, and after pudendal nerve block achieves an F:M ratio near unity. There are several reports of neonatal methemoglobinemia after **prilocaine.** Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically.
Breastfeeding Safety	There are no adequate reports or well-controlled studies in nursing women. It is unknown whether **prilocaine** enters human breast milk. However, considering the indication and dosing, one-time **prilocaine** use is unlikely to pose a clinically significant risk to the breastfeeding neonate.
Drug Interactions	Use of local anesthetic solutions containing **epinephrine** or NE to patients on an MAOI, TCA, or phenothiazine may produce severe, prolonged hypotension or hypertension. Concurrent use should generally be avoided. In situations when concurrent therapy is necessary, careful patient monitoring is essential. Use with vasopressor or ergot-type oxytocic drugs may cause severe, persistent hypertension or CVA.
References	Nau H. Dev Pharmacol Ther 1985; 8:149-81. Pongrojpaw D, Somprasit C, Chanthasenanont A. J Med Assoc Thai 2007; 90:1992-6. Tuvemo T, Willdeck-Lund G. Acta Anaesthesiol Scand 1982; 26:104-7. Shnider SM, Gildea J. Am J Obstet Gynecol 1973; 116:320-5.
Summary	**Pregnancy Category: B** **Lactation Category: S** • **Prilocaine** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk. • There are superior alternatives for labor analgesia.

Primaquine—(Primaquine)

International Brand Name—Malaquin (Korea); Malirid (India); Palum (Mexico); PMQ-INGA (India); Primacin (Australia); Primaquine Phosphate (Germany); Vivaquine (Korea)

Drug Class	Antimalarials; Antiprotozoals
Indications	Malaria, PCP
Mechanism	Unknown
Dosage with Qualifiers	Malaria—1tab (15mg) PO qd ×14d PCP—1-2tabs (15-30mg) PO qd in combination with **clindamycin** • **Contraindications**—hypersensitivity to drug or class, bone marrow suppression, rheumatoid arthritis, SLE, recent quinacrine use • **Caution**—G6PD deficiency, favism

Maternal Considerations	There are no adequate reports or well-controlled studies in pregnant women. **Primaquine** is mainly used to treat the *P. vivax* or *P. ovale* malaria. Once the parasite has been eliminated from the bloodstream, the remaining hypnozoites must be removed from the liver by administering a 14d course of **primaquine** (the so-called radical cure). **Primaquine** is considered by some to be contraindicated in pregnancy since the G6PD status of the fetus will be unknown. A pregnant woman should take weekly **chloroquine** prophylaxis until after delivery when hypnozoite eradication can be initiated. **Primaquine** is not routinely used to prevent malaria in travelers, and as such is only used when no other alternatives exist. It is not licensed for this use in the US or UK. **Primaquine** causes methemoglobinemia in all patients (levels of up to 18% are reported, normal level <1%), but this seldom causes symptoms and is always self-limiting. Dangerous levels of methemoglobinemia only occur in patients with G6PD deficiency. ***Side effects*** include hemolytic anemia, methemoglobinemia, leukopenia, retinopathy, N/V, abdominal pain, headache, pruritus, and vision disturbances.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. **Primaquine** likely crosses the human placenta, as it may be associated with a hemolytic crisis in a G6PD-deficient fetus. Except for the tetracyclines, there is no evidence that at recommended doses any of the antimalarial drugs are teratogenic. **Primaquine** is generally *not* recommended because of its theoretic potential to cause fetal hemolytic anemia. Rodent teratogenicity studies apparently have not been performed.
Breastfeeding Safety	There are no adequate reports or well-controlled studies in nursing women. It is unknown whether **primaquine** enters human breast milk.
Drug Interactions	No clinically relevant interactions identified.
References	Lalloo DG, Shingadia D, Pasvol G, et al; HPA Advisory Committee on Malaria Prevention in UK Travellers. J Infect 2007; 54:111-21. Phillips-Howard PA, Wood D. Drug Saf 1996; 14:131-45.
Summary	**Pregnancy Category: C** **Lactation Category: U** • **Primaquine** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Primidone—(Midone; Mylepsin; Mysoline; PMS Primidone; Prysoline)

International Brand Name—Apo-Primidone (Canada, New Zealand); Cyral (Austria); Liskantin (Bulgaria, Germany); Mizodin (Poland); Mutigan (Venezuela); Mylepsin (Sweden); Mylepsinum (Germany); Mysolin (Bulgaria); Mysoline (Argentina, Australia, Brazil, Canada, Chile, Ecuador, Hong Kong, India, Indonesia, Malaysia, Paraguay, Taiwan, Uruguay); Prysoline (Israel); Resimatil (Germany); Sertan (Hungary)

Drug Class	Anticonvulsants
Indications	Seizure disorder, essential tremor

Mechanism

Unknown

Dosage with Qualifiers

Seizure disorder—begin 100-125mg PO qhs ×3d, then 100-125mg PO bid ×3d, then 250mg PO tid or qid; max 2g/d
Essential tremor—begin 12.5-25mg PO qhs, increase 12.5-25mg/d qw; max 750mg/d

NOTE: renal dosing.

- **Contraindications**—hypersensitivity to drug or class, porphyria
- **Caution**—unknown

Maternal Considerations

Primidone is metabolized to **phenobarbital** and PEMA. PEMA potentiates the effect of **phenobarbital.** There are no adequate reports or well-controlled studies in pregnant women, though levels reportedly decline with advancing gestation. **Primidone** is used mainly to treat complex partial, simple partial, generalized tonic-clonic, myoclonic, and akinetic seizures. It has been a valuable alternative to **propranolol** for the treatment of essential tremor. Unlike other AEDs such as **carbamazepine** and **valproic acid**, **primidone** is rarely used in the treatment of bipolar disorder or any other psychiatric problem. It has occasionally been used to treat long QT syndrome, cerebral palsy, and athetosis. AEDs should not be discontinued in patients to whom they are given to prevent major seizures because of the strong possibility of precipitating status epilepticus with attendant hypoxia and threat to life. In individual cases where the severity and frequency of the seizure disorder are such that the removal of medication does not pose a serious threat to the patient, discontinuation of the drug may be considered prior to and during pregnancy, although it cannot be said with any confidence that even minor seizures do not pose some hazard to the developing embryo or fetus.
Side effects include dyspnea, megaloblastic anemia, thrombocytopenia, ataxia, vertigo, N/V, anorexia, fatigue, irritability, diplopia, nystagmus, drowsiness, rash, and osteopenia.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. **Phenobarbital** and PEMA readily crosses the human placenta, and are distributed throughout fetus. The highest concentrations are found in the placenta and fetal liver and brain. Withdrawal symptoms may occur in infants exposed to barbiturates throughout the 3rd trimester. Reports suggesting an increased rate of birth defects (oral clefting and cardiac malformations) in children of drug-treated epileptic women are not adequate to prove a cause-and-effect relationship, but there does appear to be a clear increased risk of neurologic dysfunction. The likelihood of congenital abnormalities in children exposed *in utero* to **carbamazepine, phenobarbital, phenytoin,** and **primidone** is reduced but not eliminated by folic acid supplementation 5-12w from LMP. The majority of mothers on anticonvulsant medication deliver normal infants. Anticonvulsant drugs should *not* be discontinued in patients in whom the drug is administered to prevent major seizures because of the strong possibility of precipitating status epilepticus with attendant hypoxia and threat to life. As for most psychotropic drugs, monotherapy and the lowest effective quantity given in divided doses to minimize the peaks can minimize the fetal risks. It is controversial whether enzyme-inducing drugs such as **primidone** increase the risk of neonatal bleeding. Though the most recent studies indicate not, the administration of 1mg vitamin K IM at birth is common.

Breastfeeding Safety

There is no published experience in nursing women. **Primidone** and its metabolites are excreted into human breast milk and have been associated with neonatal sedation. If breastfeeding continues, the infant should be monitored for possible adverse effects, the drug given at the lowest effective dose, and breastfeeding avoided at times of peak drug levels.

Drug Interactions

Drug interactions between enzyme-inducing AEDs and contraceptives are well documented. Higher dosages of oral contraceptives or a second contraceptive method are recommended for women using an enzyme-inducing AED.

References

Arpino C, Brescianini S, Robert E, et al. Epilepsia 2000; 41:1436-43.
Bruno MK, Harden CL. Curr Treat Options Neurol 2002; 4:31-40.
Crowther CA, Henderson-Smart DJ. Cochrane Database Syst Rev 2001; (2):CD000164.
Dessens AB, Cohen-Kettenis PT, Mellenbergh GJ, et al. Teratology 2001; 64:181-8.
Hagg S, Spigset O. Drug Saf 2000; 22:425-40.
Kaaja E, Kaaja R, Matila R, Hiilesmaa V. Neurology 2002; 58:549-53.
Kjaer D, Horvath-Puhó E, Christensen J, et al. BJOG 2008; 115:98-103.
Kuhnz W, Koch S, Helge H, Nau H. Dev Pharmacol Ther 1988; 11:147-54.
Shankaran S, Papile LA, Wright LL, et al. Am J Obstet Gynecol 2002; 187:171-7.

Summary

Pregnancy Category: B
Lactation Category: NS (possibly)

- **Primidone** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.
- There are alternative agents for which there is more experience regarding use during pregnancy and lactation.

Probenecid—(Benemid; Panuric; Probalan; Solpurin; Urocid)

International Brand Name—Benacid (Thailand); Bencid (India, Thailand); Benecid (Japan, Mexico); Benemide (Finland); Benuryl (Canada); Probecid (Finland, Norway, Sweden); Probenemid (Japan); Probenid (Indonesia); Pro-Cid (Australia); Procid (Taiwan)

Drug Class

Antigouts; Uricosurics

Indications

Adjunct to penicillin, gout

Mechanism

Inhibits penicillin secretion and urate resorption by the renal tubules

Dosage with Qualifiers

Adjunct to penicillin therapy—500mg PO qid
Gout—begin 250mg PO bid ×7d; max 2-3g/d

- **Contraindications**—hypersensitivity to drug or class, CrCl <50ml/h, urate stones, acute gout
- **Caution**—hypersensitivity to sulfa drugs, peptic ulcer disease, renal dysfunction

Maternal Considerations

Probenecid is used during pregnancy with a penicillin almost exclusively for the treatment of STDs.

Side effects include hemolytic anemia, aplastic anemia, hepatic necrosis, headache, dizziness, anorexia, N/V, sore gums, nephrotic syndrome, renal colic, dermatitis, pruritus, flushing, fever, and exacerbation of gout.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. **Probenecid** crosses the human placenta, but is not associated with adverse fetal effects. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically.

Breastfeeding Safety

Experience is limited to a single informative case report. A breastfed infant of a 30y-old woman being treated with **probenecid** and **cephalexin** for a breast infection developed severe diarrhea and associated symptoms. Milk was collected over a dose interval at steady-state, and concentrations of **probenecid** and **cephalexin** measured by HPLC. The average concentrations of **probenecid** and **cephalexin** in the milk were 964 and 745mcg/L, respectively, corresponding to absolute and relative infant doses of 145mcg/kg/d and 0.7% for **probenecid** and 112mcg/kg/d and 0.5% for **cephalexin.** Neither drug level is such that an effect would be expected. Considering the indication and dosing, the typically one-time use of **probenecid** is unlikely to pose a clinically significant risk to the breastfeeding neonate.

Drug Interactions

Decreases the renal clearance of many drugs, and as such is used to elevate plasma concentrations of penicillin or other β-lactams.
High plasma concentrations of the other drug may increase the incidence of adverse reactions associated with that drug.
Psychiatric disturbances have been reported when combined with penicillin or other β-lactams.
Salicylates and **pyrazinamide** antagonize the uricosuric action of **probenecid.**
May prolong or enhance the action of oral sulfonylureas and thereby increase the risk of hypoglycemia.
Patients receiving **probenecid** require less **thiopental** for induction of anesthesia. In addition, **ketamine** and **thiopental** anesthesia are significantly prolonged in rats receiving **probenecid.**
May increase the mean plasma elimination t/2 of a number of drugs, including **acetaminophen, indomethacin, ketoprofen, lorazepam, meclofenamate, naproxen,** and **rifampin.** Although the clinical significance of this observation has not been established, a lower dosage of the drug in question may be required to produce a therapeutic effect, and increases in dosage of the drug should be made cautiously and in small increments when **probenecid** is being co-administrated.
In animals and in humans, **probenecid** has been reported to increase plasma concentrations of **methotrexate.**
Falsely high readings for **theophylline** have been reported *in vitro* when measured using the Schack and Waxler technique.

References

Ilett KF, Hackett LP, Ingle B, Bretz PJ. Ann Pharmacother 2006; 40:986-9.

Summary

Pregnancy Category: B
Lactation Category: S

- **Probenecid** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Probucol—(Not marketed in the US.)

International Brand Name—(Bifenabid; Lesterol; Lorelco; Lurselle; Panesclerina; Sinlestal; Superlipid)

Drug Class	Antihyperlipidemics
Indications	Hyperlipidemia
Mechanism	Increases the fractional rate of LDL catabolism; inhibits early stages of cholesterol biosynthesis
Dosage with Qualifiers	Hyperlipidemia—500mg PO bid *NOTE: do not begin if QT interval exceeds rate-dependent guideline; any hypomagnesemia, hypokalemia, or severe bradycardia should be resolved before initiating.* • **Contraindications**—hypersensitivity to drug or class, recent or progressive myocardial damage, prolonged QT interval syndrome, ventricular arrhythmia • **Caution**—unknown
Maternal Considerations	**Probucol** is not marketed in the US. There is no published experience with **probucol** during pregnancy. Atherosclerosis is a chronic process; discontinuation of **probucol** during pregnancy should have little impact on the long-term outcome of the disease process. ***Side effects*** include prolongation of the QT interval, syncope, ventricular arrhythmia, sudden death, diarrhea, abdominal pain, N/V, dyspepsia, GI bleeding, headache, dizziness, paresthesia, insomnia, tinnitus, peripheral neuritis, rash, pruritus, ecchymosis, petechiae, eosinophilia, anemia, and thrombocytopenia.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **probucol** crosses the human placenta. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically.
Breastfeeding Safety	There is no published experience in nursing women. It is unknown whether **probucol** enters human breast milk. Certainly cholesterol and its by-products are important components of breast milk. In the absence of further study, **probucol** should be considered incompatible with breastfeeding.
Drug Interactions	No clinically relevant interactions identified.
References	There is no published experience in pregnancy or during lactation.
Summary	**Pregnancy Category: B** **Lactation Category: NS** (possibly) • **Probucol** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk. • Cholesterol and other products of cholesterol biosynthesis are essential components for fetal development. • Atherosclerosis is a chronic process; discontinuation of **probucol** during pregnancy should have little impact on long-term outcome.

Procainamide—(Biocoryl; Procanbid; Procan SR; Promine; Pronestyl; Ritmocam)

International Brand Name—Amisalin (Taiwan); Biocoryl (Spain); Cardiorytmin (Finland); Gima (Indonesia); Procan-SR (Canada); Pronestyl (Australia, Belgium, England, Ethiopia, India, Ireland, Japan, Kenya, Malaysia, Netherlands, South Africa, Switzerland, Taiwan, Tanzania, Uganda, Uruguay); Pronestyl-SR (Canada)

Drug Class	Antiarrhythmics, class IA
Indications	Atrial or ventricular arrhythmia
Mechanism	Stabilizes membrane potential, depressing the phase 0 action potential
Dosage with Qualifiers	Atrial or ventricular arrhythmia—100mg IV over 5min, repeat up to 500mg then wait ≥10min before restarting infusion; alternatively, 15-17mg/kg IV over 30-60min until either QRS widens 50% or abnormality resolves, then 1-6mg/min IV; max 1.5g load, 9g/d maintenance *NOTE: renal dosing; therapeutic levels = 4-10mcg/ml, or 10-30mcg/ml* ***procainamide*** *+ NAPA.* • **Contraindications**—hypersensitivity to drug or class, 2nd or 3rd degree AV block, myasthenia gravis, SLE, torsades de pointes • **Caution**—bone marrow depression, CHF, renal dysfunction
Maternal Considerations	There are no adequate reports or well-controlled studies in pregnant women. **Procainamide** is well tolerated, and is a first-line agent for the treatment of acute, undiagnosed, wide-complex tachycardia. It may be used alone or in combination with **digoxin.** All class IA agents should be administered in the hospital under continuous cardiac monitoring due to the potential risk of ventricular arrhythmia. Electrical cardioversion is necessary in all patients who are hemodynamically unstable with life-threatening ventricular tachyarrhythmias. In hemodynamically stable patients, initial therapy with ajmaline, **procainamide,** or **lidocaine** is indicated. ***Side effects*** include asystole, VF, seizures, lupus-like syndrome, hemolytic anemia, neutropenia, thrombocytopenia, agranulocytosis, hypotension, bradycardia, flushing, urticaria, pruritus, angioedema, rash, fever, N/V, bitter taste, hallucinations, confusion, depression, diarrhea, dizziness, and elevated LFTs.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. **Procainamide** crosses the human placenta and is not bound by the placenta. There are numerous case reports of its use as a transplacental agent to treat fetal arrhythmia. *In vitro,* it produces dose-dependent relaxation of the placental vasculature. Rodent teratogenicity studies have not been performed.
Breastfeeding Safety	There are no adequate reports or well-controlled studies in nursing women. Both **procainamide** and its main metabolite, NAPA, are excreted into human breast milk and absorbed by the nursing neonate. Yet, the circulating level achieved is low and **procainamide** is considered compatible with breastfeeding.
Drug Interactions	Additive effects on the heart may occur if other antiarrhythmic drugs are used, and dosage reduction may be necessary.

Anticholinergic drugs may produce additive antivagal effects on AV nodal conduction, although this is not as well-documented for **procainamide** as it is for quinidine.
May require less neuromuscular blocking agents such as **succinylcholine,** due to **procainamide** effects on reducing ACh release.

References

Bailey DN. Ann Clin Lab Sci 1999; 29:209-12.
Dumesic DA, Silverman NH, Tobias S, Golbus MS. N Engl J Med 1982; 307:1128-31.
Ito S, Magee L, Smallhorn J. Clin Perinatol 1994; 21:543-72.
Joglar JA, Page RL. Drug Saf 1999; 20:85-94.
Omar HA, Rhodes LA, Ramirez R, et al. J Cardiovasc Electrophysiol 1996; 7:1197-203.
Pittard WB 3rd, Glazier H. J Pediatr 1983; 102:631-3.
Trappe HJ. J Intensive Care Med 2006; 21:305-15.
Weiner CP, Thompson MI. Am J Obstet Gynecol 1988; 158:570-3.

Summary

Pregnancy Category: C
Lactation Category: S

- **Procainamide** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Procaine—(Novocain)

International Brand Name—Novanaest purum 1% (Austria); Novanaest purum 2% (Austria); Novocain (Germany); Pasconeural-Injektopas 1% (Germany); Polocainum (Poland); Procadolor N (Germany)

Drug Class

Anesthetics, local

Indications

Local and regional anesthesia

Mechanism

Inhibits propagation of nerve impulse by inhibition of transneuronal membrane ion flux

Dosage with Qualifiers

Local and regional anesthesia—dose varies; max 10mg/kg

NOTE: typical onset 2-5min, duration 30-90min.

- **Contraindications**—hypersensitivity to drug or class, infection at site
- **Caution**—heart block, hypotension, cholinesterase deficiency, sulfite allergy, renal disease, impaired CV function

Maternal Considerations

There are no adequate reports or well-controlled studies in pregnant women. **Procaine** has been used for decades during labor to create spinal, nerve block, or infiltration anesthesia. ***Side effects*** include CNS toxicity, myocardial depression, cardiac arrest, convulsions, RDS, unconsciousness, heart block, hypotension, arrhythmia, drowsiness, nervousness, blurred vision, tremors, N/V, pupil constriction, tinnitus, chills, and pruritus.

Fetal Considerations

There are no adequate reports or well-controlled studies of **procaine** in human fetuses. Local anesthetics rapidly cross the placenta. The long clinical experience is reassuring. Rodent teratogenicity studies have not been performed.

Breastfeeding Safety

There is no published experience in nursing women. It is unknown whether **procaine** enters human breast milk. However, considering

	the indication and dosing, one-time **procaine** use is unlikely to pose a clinically significant risk to the breastfeeding neonate.
Drug Interactions	The administration of local anesthetic solutions containing **epinephrine** or NE to patients receiving MAOIs or TCAs may produce severe, prolonged hypertension. Use of these agents should generally be avoided. Phenothiazines and butyrophenones may reduce or reverse the pressor effect of **epinephrine.** Use of vasopressor or ergot-type oxytocic drugs may cause severe, persistent hypertension or CVAs. **Procaine** should not be used with a sulfonamide drug since *para*-aminobenzoic acid inhibits the action of sulfonamide.
References	There are no current relevant references.
Summary	**Pregnancy Category: C** **Lactation Category: S** (likely) • **Procaine** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Procarbazine—(Matulane)

International Brand Name—Matulane (Philippines); Natulan (Austria, Czech Republic, Denmark, Finland, France, Australia, Japan, Malaysia, Peru, South Africa)

Drug Class	Antineoplastics, miscellaneous
Indications	Lymphomas, brain and lung cancers
Mechanism	Unknown
Dosage with Qualifiers	Lymphomas, brain and lung cancers—dosing protocols vary • **Contraindications**—hypersensitivity to drug or class, bone marrow depression • **Caution**—hepatic or renal dysfunction
Maternal Considerations	There are no adequate reports or well-controlled studies in pregnant women. **Procarbazine** is usually combined with other potent antineoplastic agents. Yet the outcomes for most treated pregnancies and the 2nd-generation children are normal. ***Side effects*** include seizures, coma, thrombocytopenia, bleeding, leukopenia, anemia, hemolytic anemia, pleural effusion, N/V, hallucinations, nervousness, dermatitis, anorexia, dry mouth, tachycardia, and neuropathy.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. While it is unknown whether **procarbazine** crosses the human placenta, there are case reports of malformations in the offspring of women exposed to **procarbazine** in combination with other antineoplastic agents. Rodent studies performed at multiples of the MRHD reveal a spectrum of malformations, including a dose-dependent increase in microcephaly and cleft lip/palate. Supplementation with folate reduces the prevalence with a gender-specific effect (M>F).
Breastfeeding Safety	There is no published experience in nursing women. It is unknown whether **procarbazine** enters human breast milk.

Drug Interactions ..... No clinically relevant interactions identified.

References .....

Aviles A, Neri N. Clin Lymphoma 2001; 2:173-7.
Johnson JM, Thompson DJ, Haggerty GC, et al. Teratology 1985; 32:203-12.
Lishner M, Zemlickis D, Degendorfer P, et al. Br J Cancer 1992; 65:114-7.
Malek FA, Möritz KU, Fanghänel J, Bienengräber V. Pathol Res Pract 2004; 200:33-40.

Summary .....

Pregnancy Category: D
Lactation Category: U

- **Procarbazine** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.
- Though the risks of chemotherapy to the fetus are real, most pregnancies end without complication.

Prochlorperazine—(Buccastem; Compa-Z; Compazine; Cotranzine; Nautisol; Novomit; Prochlorperazine Edisylate; Prochlorperazine Maleate; Steremal; Tementil; Ultrazine-10; Vertigon)

International Brand Name—Antinaus (New Zealand); Dhaperazine (Hong Kong, Malaysia); Klometil (Finland); Nautisol (Malaysia, South Africa); Nibromin (Japan); Normalmin (Japan); Novamin (Japan, Taiwan); Pasotomin (Japan); Prochlor (Malaysia, Singapore); Proclozine (Thailand); Stemetil (Bulgaria, Canada, Denmark, England, Finland, India, Indonesia, Iran, Ireland, Italy, Jordan, Malaysia, Netherlands, Norway, Peru, Sweden, Thailand); Stemzine (Australia)

Drug Class ..... Antiemetics; Antipsychotics; Antivertigo; Phenothiazines

Indications ..... N/V, anxiety, psychosis

Mechanism ..... Unknown

Dosage with Qualifiers .....

N/V—5-10mg PO/IM tid or qid, or 25mg PR bid, or 5-10mg IV over 2min; max 40mg/d
Psychosis—5-10mg PO tid or qid; max 150mg/d

- **Contraindications**—hypersensitivity to drug or class, CNS depression, adrenergic blockade, phenothiazine blood dyscrasia
- **Caution**—glaucoma, epilepsy, CV disease, bone marrow depression

Maternal Considerations .....

Prochlorperazine is most often used for the short-time treatment of N/V and vertigo. There are no adequate reports or well-controlled studies in pregnant women. In the UK, **prochlorperazine** is available OTC as Buccastem M in buccal form for the treatment of migraine. In this indication it blocks the chemoreceptor trigger zone in the brain that is responsible for causing severe N/V. Its OTC use is restricted to a maximum of 2d because of the potentially severe side effects of **prochlorperazine.** Long clinical experience indicates efficacy for the treatment of hyperemesis when combined with hydration and rest. **Prochlorperazine** (10mg IV) is superior to **meclopramide** (10mg IV) for the relief of acute migraine headache. However, the oral combination of **pyridoxine** and **metoclopramide** is superior to **prochlorperazine** alone.
Side effects include agranulocytosis, thrombocytopenia, hemolytic anemia, ECG abnormalities, exfoliative dermatitis, tardive

	dyskinesia, neuroleptic malignant syndrome, hepatotoxicity, leukopenia, drowsiness, amenorrhea, blurred vision, rash, orthostatic hypotension, jaundice, dry mouth, constipation, photosensitivity, anxiety, oculogyric crisis, and extrapyramidal effects.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **prochlorperazine** crosses the human placenta. The extensive clinical experience during pregnancy is reassuring, without any substantial evidence of teratogenicity. Rodent teratogenicity studies have not been performed.
Breastfeeding Safety	There are no adequate reports or well-controlled studies in nursing women. **Prochlorperazine** enters human breast milk, but the kinetics remain to be elucidated.
Drug Interactions	No clinically relevant interactions identified.
References	Bsat FA, Hoffman DE, Seubert DE. J Perinatol 2003; 23:531-5. Coppola M, Yealy DM, Leibold RA. Ann Emerg Med 1995; 26:541-6. Mazotta P, Magee LA. Drugs 2000; 59:781-800.
Summary	**Pregnancy Category: C** **Lactation Category: U** • **Prochlorperazine** is a commonly used agent for the treatment of nausea during pregnancy. • It should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Procyclidine—(Apricolin; Kemadren; Kemadrin; Osnervan)

International Brand Name—Kemadrin (India, Japan, New Zealand, Uruguay)

Drug Class	Anticholinergics; Antiparkinson agents
Indications	Parkinson's disease
Mechanism	Anticholinergic
Dosage with Qualifiers	Parkinson's disease—2.5mg PO tid; increase slowly to 5mg PO tid • **Contraindications**—hypersensitivity to drug or class, angle-closure glaucoma • **Caution**—unknown
Maternal Considerations	There is no published experience with **procyclidine** in pregnancy. ***Side effects*** include dryness of the mouth, mydriasis, blurring of vision, giddiness, light-headedness, and GI disturbances such as N/V, epigastric distress, and constipation.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **procyclidine** crosses the human placenta. Rodent teratogenicity studies have not been performed.
Breastfeeding Safety	There is no published experience in nursing women. It is unknown whether **procyclidine** enters human breast milk.
Drug Interactions	No clinically relevant interactions identified.
References	There is no published experience in pregnancy or during lactation.

Summary

Pregnancy Category: C
Lactation Category: U

- **Procyclidine** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Progesterone—(Crinone; Gesterol 50; Lutolin-S; Progestaject-50; Prometrium)

International Brand Name—Crinone (Canada, Hong Kong, Korea, Thailand); Cyclogest (Singapore); Endometrin (Hong Kong, Israel); Estima Ge (France); Evapause (France); Gepromi (Mexico); Geslutin (Colombia, Mexico); Geslutin PNM (Peru); Lutogynestryl Fuerte (Peru); Mafel (Argentina); Naturogest (India); Progering (Peru); Progest (India); Progestogel (Hong Kong); Prometrium (Canada); Utrogestan (Austria, Belgium, Brazil, China, Czech Republic, Ecuador, France, Hungary, Ireland, Mexico, South Africa, Spain, Switzerland, Uruguay)

Drug Class

Contraceptives; Hormones; Progestins

Indications

Amenorrhea, secondary amenorrhea, hormone replacement, infertility, prevention of idiopathic preterm birth

Mechanism

Inhibits GnRH, transforms proliferative into secretory endometrium

Dosage with Qualifiers

Amenorrhea—400mg PO qd ×10d
Secondary amenorrhea—1 applicator 4% PV qod
Hormone replacement—200mg PO given each day with estrogen
Infertility, progesterone deficiency—1 applicator 8% PV qd; continue through 10-12w of pregnancy
Infertility, ovarian failure—1 applicator 8% PV bid
Prevention of idiopathic preterm birth—1 applicator 8% PV qod or bid

NOTE: available in tablet, parenteral, or vaginal cream (Crinone, 4% = 45mg/applicator) forms.

- **Contraindications**—hypersensitivity to drug or class, peanut allergy, pregnancy, thromboembolism, breast cancer, undiagnosed vaginal bleeding, missed abortion
- **Caution**—CHF, hepatic dysfunction, lactation

Maternal Considerations

Progesterone is central for reproduction. This section applies only to native hormone and not synthetic compounds, which may differ significantly depending upon their receptor profile (see individual progestogens). **Progesterone** is used throughout the 1st trimester to provide luteal-phase support for women undergoing ovulation induction and IVF. Other than those, there are no proved indications for its use during pregnancy.
Progesterone administration does not prevent pregnancy loss in women with spontaneous, clinically recognized conceptions greater than 7w when the placenta is hormonally functional and the pregnancy no longer corpus luteum dependent. The evidence that **progesterone** is an effective treatment for supposed luteal-phase defects is weak.
Recent study suggests the administration of micronized **progesterone** vaginal gel or cream to women with a sonographically short cervix (10-15mm) between 22 and 24w gestation is associated with a 40% reduction in the incidence of idiopathic preterm birth. While the MFMU Network trial also concluded 17-hydroxy progesterone caproate administered weekly IM had a similar efficacy in women with at least one prior

idiopathic preterm birth, a more recent investigation mounted to obtain FDA approval for the vaginal gel failed to reproduce this conclusion. However, in a secondary analysis, these investigators did find a significant reduction in the incidence of idiopathic preterm birth when treated subjects had a sonographic cervical length at randomization <28mm. This finding is consistent with the finding that pregnant women with a prior idiopathic preterm birth but a normal sonographic cervical length in the current gestation are *not* at increased risk for recurrent idiopathic preterm birth.

Side effects include menstrual irregularities, amenorrhea, breast tenderness, weight gain, stroke, thromboembolism, MI, breast cancer, gallbladder disease, cholestatic jaundice, hypertension, headache, fluid retention, depression, rash, pruritus, libido changes, acne, hirsutism, galactorrhea, and alopecia.

Fetal Considerations

There are no adequate reports or well-controlled studies of **progesterone** in human fetuses. Progestogens differ in their hormonal effects. Masculinization of the female fetus is attributed to some progestogens. The evidence that natural **progesterone** is a teratogen is weak.

Breastfeeding Safety

There are no adequate reports or well-controlled studies in nursing women. Exogenous **progesterone** enters human breast milk. The quantity of milk produced correlates with the antenatal **progesterone** level.

Drug Interactions

Metabolism is inhibited by **ketoconazole** (50% inhibitory concentration <0.1μM), a known inhibitor of CYP3A4. The clinical relevance of the *in vitro* findings is unknown.

References

Carp H, Torchinsky A, Fein A, Toder V. Gynecol Endocrinol 2001; 15:472-83.

da Fonseca EB, Bittar RE, Carvalho MH, Zugaib M. Am J Obstet Gynecol 2003; 188:419-24.

Dawood MY. Curr Opin Obstet Gynecol 1994; 6:121-7.

DeFranco EA, O'Brien JM, Adair CD, et al. Ultrasound Obstet Gynecol 2007; 30:697-705.

Fonseca EB, Celik E, Parra M, et al; Fetal Medicine Foundation Second Trimester Screening Group. N Engl J Med 2007; 357:462-9.

Ingram JC, Woolridge MW, Greenwood RJ, McGrath L. Acta Paediatr 1999; 88:493-9.

Meis PJ, Klebanoff M, Thom E, et al; National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network. N Engl J Med 2003; 348:2379-85.

Norwitz ER, Schust DJ, Fisher SJ. N Engl J Med 2001; 345:1400-8.

O'Brien JM, Adair CD, Lewis DF, et al. Ultrasound Obstet Gynecol 2007; 30:687-96.

Yost NP, Owen J, Berghella V, et al; National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network. Am J Obstet Gynecol 2004; 191:241-6.

Summary

Pregnancy Category: D
Lactation Category: S

- **Progesterone** may be used during pregnancy only for luteal-phase support after ovulation induction.
- The administration of micronized **progesterone** vaginal gel/cream to women with a sonographically short cervix is associated with a 40% reduction in the incidence of idiopathic preterm birth regardless of their past obstetric history. There appears to be no benefit selecting patients based on history alone.

Promazine—(Liranol; Prazine; Primazine; Protactyl; Prozine-50; Savamine; Sparine; Talofen)

International Brand Name—None identified.

Drug Class	Antipsychotics; Phenothiazines
Indications	Psychotic disorders
Mechanism	Unknown
Dosage with Qualifiers	Psychotic disorders—begin 50-150mg IM; up to 300mg additional may be given after 30min to achieve desired effect; thereafter, 10-200mg PO q4-6h *NOTE: dose and route dictated by severity of the condition; IM preferred.* • **Contraindications**—hypersensitivity to drug or class, drug-induced CNS depression, intra-arterial injection, bone marrow suppression • **Caution**—atherosclerosis, severe hypotension, abrupt cessation
Maternal Considerations	**Promazine** is a prototype phenothiazine used with variable success for the treatment of depressive neurosis, alcohol withdrawal, N/V, symptoms of dementia, Tourette's syndrome, Huntington's chorea, and Reye's syndrome. An older medication used to treat schizophrenia, its use has largely been replaced by newer agents such as **olanzapine** and **quetiapine.** Though **promazine** has been used in obstetrics for almost 3 decades, there are no adequate reports or well-controlled studies in pregnant women. ***Side effects*** include tardive dyskinesia, drowsiness, jaundice, agranulocytosis, eosinophilia, leukopenia, hemolytic anemia, thrombocytopenic purpura, fever, decreased appetite, paradoxical exacerbation of psychotic symptoms, seizures, cerebral edema, amenorrhea, galactorrhea, and dry mouth.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **promazine** crosses the human placenta. However, it undergoes placental peroxidation, and the free radicals produced may be one source of fetal toxicity. Older reports suggest a relationship between antenatal **promazine** and neonatal hyperbilirubinemia. In one study, **promazine** had no effect on fetal CV function of sheep. In a second study performed using a higher dose, **promazine** caused fetal hypotension and tachycardia, and exacerbated the effect of umbilical cord compression. Rodent teratogenicity studies have not been performed.
Breastfeeding Safety	There are no adequate reports or well-controlled studies in nursing women. It is unknown whether **promazine** enters human breast milk.
Drug Interactions	No clinically relevant interactions identified.
References	Ayromlooi J. Dev Pharmacol Ther 1985; 8:302-10. Cottle MK, Van Patten GR, van Muyden P. Am J Obstet Gynecol 1983; 146:686-92. Yang X, Kulkkarni AP. Terat Carcinog Mutagen 1997; 17:139-51.

Summary

Pregnancy Category: C
Lactation Category: U

- **Promazine** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Promethazine—(Anergan; Antiallersin; Camergan; Fargan; Metaryl; Pentazine; Phenergan; Phenerzine; Promethacon; Prozine; Sayomol; Xepagan)

International Brand Name—Allerfen (Italy); Atosil (Germany); Bonnox (Germany); Farganesse (Italy); Fenazine (Israel); Fenergan (Argentina, Peru); Goodnight (New Zealand); Hibechin (Japan); Hiberna (Japan); Insomn-Eze (Australia); Lergigan (Sweden); Prome (Indonesia); Proneurin (Germany); Prothiazine (Israel); Pyrethia (Japan)

Drug Class

Antiemetics; Antihistamines; Phenothiazines

Indications

N/V, motion sickness, sedation, allergic rhinitis

Mechanism

Antagonizes central and peripheral H_1 receptors

Dosage with Qualifiers

N/V—12.5-25mg PO/PR/IM q4-6h prn
Motion sickness—25mg PO bid
Sedation—25-50mg PO/PR/IM q4-6h prn
Allergic rhinitis—12.5-25mg PO q6h, or 25mg PO qhs

NOTE: may be combined with ***codeine.***

- **Contraindications**—hypersensitivity to drug or class, narrow-angle glaucoma
- **Caution**—seizure disorder, asthma, hepatic dysfunction, bone marrow suppression

Maternal Considerations

Promethazine has been used for decades in obstetrics to treat N/V, as a sedative, and to relieve apprehension during the latent phase of labor. It is often combined with a narcotic such as **meperidine. Promethazine** (25mg tid ×3w) is similar to **ondansetron** but inferior to a short course (3d) of **methylprednisolone** for the relief of N/V of pregnancy. **Promethazine** was a frequent component of lytic cocktails used in preeclamptic women to prevent seizures. These cocktails have been abandoned in favor of **magnesium sulfate.** Initial hopes that **promethazine** would ameliorate severe Rh alloimmunization have not been substantiated but remain poorly studied. It is not effective for the relief of nausea following **thiopentone** anesthesia for abortion. Controlled trials do not support the use of **promethazine** as an adjuvant to reduce postoperative adhesions. It has been used unsuccessfully for the relief of postepidural pruritus associated with **morphine** injection.
Side effects include tardive dyskinesia, extrapyramidal effects, respiratory depression, hypotension, bradycardia, tachycardia, agranulocytosis, thrombocytopenia, dry mouth, sedation, drowsiness, N/V, rash, and thickened bronchial secretions.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **promethazine** crosses the human placenta. Human epidemiologic studies are reassuring. The combination of **promethazine** and **meperidine** during labor reduces FHR reactivity. There was no effect on somatic

development in one study. Transport across the mouse placenta is limited. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically. A recent epidemiological study found no adverse outcomes after an attempted suicide with **promethazine.**

Breastfeeding Safety

There is no published experience in nursing women. It is unknown whether **promethazine** enters human breast milk.

Drug Interactions

May increase, prolong, or intensify the sedative action of CNS depressants, such as ethanol, sedative-hypnotics (including barbiturates), general anesthetics, narcotics, narcotic analgesics, and tranquilizers. The dose of barbiturates should be reduced by at least ½, and the dose of narcotics should be reduced by ¼ to ½.

Excessive amounts of **promethazine** injection relative to a narcotic may lead to restlessness and motor hyperactivity in the patient with pain; these symptoms usually disappear with adequate control of the pain.

Although reversal of the vasopressor effect of **epinephrine** has not been reported with **promethazine** injection, it is recommended that **epinephrine** *not* be used in case of **promethazine** injection overdose.

Concomitant use with other agents with anticholinergic properties should be undertaken cautiously.

Drug interactions, including an increased incidence of extrapyramidal effects, have been reported between some MAOIs and phenothiazines. Although such a reaction has not been reported with **promethazine,** the possibility should be considered.

References

Bártfai Z, Kocsis J, Puhó EH, Czeizel AE. Reprod Toxicol 2008; 25:276-85.

Czeizel AE, Szegal BA, Joffe JM, Racz J. Neurotoxicol 1999; 21:157-67.

Duley L, Gulmezoglu AM. Cochrane Database Syst Rev 2001; (1):CD002960.

Gibble JW, Ness PM. Clin Lab Med 1992; 12:553-76.

Horta ML, Morejon LC, da Cruz AW, et al. Br J Anaesth 2006; 96:796-800.

Jonkman JH, Westenberg HG, Rijntjes NV, et al. Arzneimittelforschung 1983; 33:223-8.

Petik D, Acs N, Banhidy F, Czeizel AE. Toxicol Ind Health 2008; 24:87-96.

Safari HR, Fassett MJ, Souter IC, et al. Am J Obstet Gynecol 1998; 179:921-4.

Sandhya Yaddanapudi LN. Singapore Med J 1994; 35:271-3.

Solt I, Ganadry S, Weiner Z. Isr Med Assoc J 2002; 4:178-80.

Sullivan CA, Johnson CA, Roach H, et al. Am J Obstet Gynecol 1996; 174:1565-8.

Watson A, Vanderkerckhove P, Lilford R. Hum Fertil 1999; 2:149-57.

Summary

Pregnancy Category: C
Lactation Category: U

- **Promethazine** is effective as an antiemetic under certain circumstances.

Propafenone—(Arythmol; Norfenon; Normorytmin; Rythmol; Rytmonorm)

International Brand Name—Arythmol (England, Ireland); Jutanorm (Germany); Nistaken (Mexico); Norfenon (Mexico); Normorytmin (Argentina); Profex (Israel); Pronon (Japan); Ritmocor (Chile); Ritmonorm (Brazil, Paraguay); Rythmex (Israel); Rythmol (Canada, France, South Africa); Rytmocard (Philippines); Rytmogenat (Germany); Rytmonorm (Belgium, Bulgaria, China, Colombia, Costa Rica, Czech Republic, Denmark, Dominican Republic, El Salvador, Finland, Germany, Greece, Guatemala, Honduras, Hong Kong, Hungary, Indonesia, Italy, Jordan, Korea, Netherlands, New Zealand, Nicaragua, Panama, Peru, Poland, Portugal, Spain, Sweden, Switzerland, Taiwan, Thailand, Uruguay, Venezuela); Rytmonorma (Austria)

Drug Class	Antiarrhythmics, class IC
Indications	Ventricular arrhythmia
Mechanism	Stabilizes membrane potential; depresses the phase 0 action potential
Dosage with Qualifiers	Ventricular arrhythmia—150mg PO q8h; may increase over 3-4d to a max of 900mg/d • **Contraindications**—hypersensitivity to drug or class, CHF, bradycardia, SA or AV conduction defects, severe hypotension, bronchospasm, electrolyte imbalances • **Caution**—unknown
Maternal Considerations	There are no adequate reports or well-controlled studies of **propafenone** in pregnant women. The published experience is confined to case reports. ***Side effects*** include CHF, ventricular arrhythmia, N/V, dizziness, constipation, taste change, dyspnea, fatigue, headache, blurred vision, palpitations, rash, angina, dry mouth, and syncope.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. **Propafenone** crosses the human placenta, though the kinetics remain to be elucidated. Rodent studies reveal embryotoxicity but no evidence of teratogenicity. Embryotoxicity occurs increasingly with escalating doses.
Breastfeeding Safety	There are no adequate reports or well-controlled studies in nursing women. Limited study suggests low quantities of **propafenone** enter human breast milk, with an M:P ratio of 0.25 and a theoretic infant dose of 0.1% of the daily maternal dose.
Drug Interactions	Drugs that inhibit CYP2D6, CYP1A2, and CYP3A4 might increase plasma levels of **propafenone.** Patients should be closely monitored and the dose adjusted as needed. Small doses of **quinidine** completely inhibit the hydroxylation pathway, making all patients slow metabolizers. There is, as yet, too little information to recommend concomitant use of **propafenone** and **quinidine.** Use with local anesthetics (i.e., during pacemaker implantations, surgery, or dental use) may increase the risks of CNS side effects. Produces dose-related increases in serum **digoxin** levels ranging from about 35% at 450mg/d to 85% at 900mg/d of **propafenone** without affecting **digoxin** renal clearance. **Digoxin** levels should be measured, and the **digoxin** dosage either reduced or aggressively adjusted when **propafenone** is started. Increases the **propranolol** plasma concentration and elimination t/2 with no change in **propafenone** plasma levels from control.

Similar observations have been reported with **metoprolol.**
Propafenone appears to inhibit the hydroxylation pathway for the two β-antagonists (just as **quinidine** inhibits **propafenone** metabolism). While the therapeutic range for β-blockers is wide, a reduction in dosage may be necessary.
Increases the mean steady-state **warfarin** plasma concentration 39% with a corresponding increase in the PT of some 25%. It is recommended that PT be monitored and the dose of **warfarin** be adjusted.
Cimetidine resultes in a 20% increase in steady-state **propafenone** plasma concentrations.
May elevate **desipramine** serum levels. Both **desipramine**, a TCA, and **propafenone** are cleared by oxidative pathways of demethylation and hydroxylation carried out by the hepatic CYPs.
May increase the level of **cyclosporine.**
May increase **theophylline,** with the development of **theophylline** toxicity.
Rifampin may accelerate the metabolism and decrease the plasma levels and antiarrhythmic efficacy of **propafenone.**

References

Braverman AC, Bromley BS, Rutherford JD. Int J Cardiol 1991; 33:409-12.
Grand A. Rev Fr Gynecol Obstet 1993; 88:297-312.
Libardoni M, Piovan D, Busato E, Padrini R. Br J Clin Pharmacol 1991; 32:527-81.
Wakaumi M, Tsuruoka S, Sakamoto K, et al. Br J Clin Pharmacol 2005; 59:120-2.

Summary

Pregnancy Category: C
Lactation Category: S (probably)

- **Propafenone** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.
- There are alternative agents for which there is more experience regarding use during pregnancy and lactation.

Propantheline—(Bropantil; Corrigast; Ercoril; Norproban; Pantheline; Pro-Banthine)

International Brand Name—Bropantil (Mexico); Corrigast (Germany); Ercoril (Denmark); Ercotina (Sweden); Pro Banthin (Switzerland); Pro-Banthine (Hong Kong, India, Indonesia, Japan, Netherlands, Sweden, Taiwan); Propantel (Mexico); Propanthel (Canada)

Drug Class

Antispasmodics; Antiulcer agents; Gastrointestinals

Indications

Peptic ulcer

Mechanism

Cholinergic antagonist

Dosage with Qualifiers

Peptic ulcer—begin 15mg PO qac, 30mg qhs; max 60mg PO qid

- **Contraindications**—hypersensitivity to drug or class, bowel obstruction, myasthenia gravis, angle-closure glaucoma, bleeding, reflux esophagitis
- **Caution**—CAD, ulcerative colitis

Maternal Considerations

There is no published experience with **propantheline** in pregnancy.

	Side effects include dry mouth, blurred vision, confusion, palpitations, headache, orthostatic hypotension, insomnia, somnolence, tachycardia, mydriasis, cycloplegia, constipation, nausea, bloating, urticaria, anhidrosis, and respiratory distress.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **propantheline** crosses the human placenta. Rodent teratogenicity studies apparently have not been performed.
Breastfeeding Safety	There is no published experience during lactation. It is unknown whether **propantheline** enters human breast milk.
Drug Interactions	Anticholinergics may delay absorption of other medication given concomitantly. Excessive cholinergic blockade may occur if given concomitantly with **belladonna** alkaloids, synthetic or semisynthetic anticholinergic agents, narcotic analgesics such as **meperidine,** class I antiarrhythmic drugs (e.g., **disopyramide**, **procainamide, quinidine**), antihistamines, phenothiazines, TCAs, or other psychoactive drugs. May potentiate the sedative effect of phenothiazines. Increased intraocular pressure may result from concurrent use with anticholinergics and corticosteroids. Use with slow-dissolving tablets of **digoxin** may cause increased serum **digoxin** levels. This interaction can be avoided by using only those **digoxin** tablets that rapidly dissolve by USP standards.
References	There are no current relevant references.
Summary	**Pregnancy Category: C** **Lactation Category: U** • **Propantheline** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk. • There are alternative agents for which there is more experience regarding use during pregnancy and lactation.

Propofol—(Diprivan)

International Brand Name—Anepol (Korea); Cryotol (Mexico); Diprivan (Argentina, Brazil, Canada, Chile, Ecuador, Hong Kong, India, Indonesia, Japan, Korea, Malaysia, Mexico, Peru, Philippines, Taiwan, Uruguay, Venezuela); Diprofol (Israel); Disoprivan (Germany); Fresofol (China, Korea, Philippines, Taiwan, Thailand); Gobbifol (Argentina); Pofol (Singapore, Thailand); Propocam (Mexico); Propofol-Lipuro (Colombia); Recofol (Australia, Indonesia, Israel, Mexico, Singapore, Thailand); Safol (Indonesia)

Drug Class	Anesthesia, induction/maintenance
Indications	Anesthesia induction and maintenance, sedation for ventilated patients
Mechanism	Unknown; positively modulates inhibitory function of GABA
Dosage with Qualifiers	Anesthesia induction—dose varies widely depending on patient health; typically 2-2.5mg/kg IV administered as 40mg q10sec until desired effect Anesthesia maintenance—dose varies widely depending on patient health; typically 0.1-0.4mg/kg/min IV depending on use of INH or other IV anesthetics

Sedation for ventilated patients—begin 5mcg/kg/min IV, then increase by 5-10mcg/kg/min q5-10min until desired effect

- **Contraindications**—hypersensitivity to drug or class, allergy to either soybean, egg lecithin, or glycerol
- **Caution**—lipid metabolism disorder, increased ICP

Maternal Considerations

Propofol is popular for a variety of procedures including oocyte retrieval and suction curettage. Its administration (1.0mg/kg/h) after cord clamping at cesarean delivery performed under general anesthesia reduces postoperative N/V. In addition, an IV bolus (20mg) decreases pruritus associated with intrathecal **morphine.** Its clearance, as reflected in the dose required to produce unconsciousness, is unaltered during early pregnancy. It has a direct inhibitory effect on uterine contractions, caused at least in part by interfering with calcium transport. In small series of patients whose anesthesia for cesarean delivery was induced and maintained with **propofol,** there were no differences in neonatal outcome as compared to more commonly administered anesthetic agents.
Side effects include pulmonary edema, pancreatitis, opisthotonus, apnea, bradycardia, hypotension, involuntary movement, N/V, and injection site reactions.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. **Propofol** crosses the human placenta in a time-dependent manner, at a rate dependent on uterine and umbilical blood flows. The maternal albumin level also impacts on the extent of transfer. Reports of F:M ratio range widely from 0.35 to 1.0. **Propofol** infusions adequate for conscious sedation during cesarean section seem to have no adverse neonatal effects. In the ewe, a 6mg/kg IV bolus followed by a continuous infusion of 0.4mg/kg/min produced an AUC and C_{max} of 8.6 mg/h/ml and 9.5mg/ml, respectively, higher than those of the fetus (1.6mg/h/ml and 1.19 mg/ml, respectively). The mean t/2 was 0.5h in the ewe and 1.1h in the fetus, suggesting accumulation may occur. While rodent studies are reassuring, revealing no evidence of teratogenicity, breastfed pups of treated mothers have a higher mortality rate. **Propofol** transiently blocks NMDA receptors that lead to an increase in neuronal apoptosis in rodents.

Breastfeeding Safety

A small amount of **propofol** is excreted in human breast milk. However, considering the indications, prior exposure to **propofol** is not likely to pose a significant risk to the breastfeeding neonate.

Drug Interactions

The CNS-depressant effect is additive with that of other CNS depressants, including ethanol.

References

Andaluz A, Tusell J, Trasserres O, et al. Vet J 2003; 166:198-204.
Gaynot JS, Wertz EM, Alvis M, Turner AS. J Vet Pharmacol Ther 1998; 21:69-73.
He YL, Seno H, Sasaki K, Tashiro C. Anesth Analg 2002; 94:1312-4.
He YL, Seno H, Tsujimoto S, Tashiro C. Anesth Analg 2001; 93:151-6.
Higuchi H, Adachi Y, Arimura S, et al. Anesth Analg 2001; 93:1565-9.
Horta ML, Morejon LC, da Cruz AW, et al. Br J Anaesth 2006; 96:796-800.
Ikonomidou C, Bittigau P, Koch C, et al. Biochem Pharmacol 2001; 62:401-5.

Nitsun M, Szokol JW, Saleh HJ, et al. Clin Pharmacol Ther 2006; 79:549-57.
Tsujiguchi N, Yamakage M, Namika A. Anesthesiology 2001; 95:1245-55.
Sanchez-Alcaraz A, Quintana MB, Laguarda M. J Clin Pharm Ther 1998; 23:19-23.

Summary

Pregnancy Category: B
Lactation Category: S (likely)
- **Propofol** is an excellent anesthetic agent during pregnancy and lactation for a variety of indications.

Propoxyphene—(Abalgin; Darvon; Deprancol; Develin; Dolotard; Dolpoxene; Margesic; Parvon)

International Brand Name—Adalgin (Denmark)

Drug Class

Analgesics, narcotic

Indications

Mild to moderate pain

Mechanism

Binds to opioid receptors

Dosage with Qualifiers

Mild to moderate pain—65mg PO q4h prn; max 390mg/d

NOTE: often combined with one of several analgesic and antihistaminic compounds.

- **Contraindications**—hypersensitivity to drug or class
- **Caution**—history of substance abuse, depression, suicidal ideation, hepatic or renal dysfunction

Maternal Considerations

Propoxyphene is a narcotic, and its combination with other CNS depressants such as alcohol has an additive effect. There are no adequate reports or well-controlled studies in pregnant women. **Propoxyphene** combinations offer no clinical advantage over NSAIDs for the treatment of episiotomy pain.
Side effects include respiratory depression, dependency, somnolence, dizziness, hallucinations, dysphoria, constipation, hepatic dysfunction, and painful myopathy.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. Both **propoxyphene** and its principal active metabolite, norporpoxyphene, cross the human placenta, and and achieve an M:F ratio of unity within 1h. Neonatal addiction/withdrawal occur. Though there are scattered case reports of miscellaneous birth defects, no pattern has emerged.

Breastfeeding Safety

There are no adequate reports or well-controlled studies in nursing women. While low levels of **propoxyphene** are excreted into human breast milk, its use as directed is generally considered compatible with breastfeeding.

Drug Interactions

The CNS-depressant effect is additive with that of other CNS depressants, including ethanol.
May slow the metabolism of a concomitantly administered drug. Should this occur, the higher serum concentrations of that drug may result in increased pharmacologic or adverse effects of

that drug. Such occurrences have been reported with antidepressants, anticonvulsants, and **warfarin**-like drugs. Several neurologic signs, including coma, have occurred with concurrent use of **carbamazepine.**

References

Bloomfield SS, Barden TP, Mitchell J. Clin Pharmacol Ther 1980; 27:502-7.
Golden NL, King KC, Sokol RJ. Clin Pediatr 1982; 21:752-4.
Gruber CM Jr, Bauer RO, Bettigole JB, et al. J Med 1979; 10:65-98.
Kunka RL, Venkataramanan R, Stern RM, Ladik CF. Clin Pharmacol Ther 1984; 35:675-80.
Weigand UW, Chou RC, Maulik D, Levy G. Pediatr Pharmacol 1984; 4:145-53.

Summary

Pregnancy Category: C
Lactation Category: S

- **Propoxyphene** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.
- There are non-narcotic alternatives that provide similar or superior analgesia for most indications.

Propranolol—(Inderal)

International Brand Name—Acifol (Mexico); Adrexan (France); Alperol (Thailand); Angilol (England, Ireland, New Zealand); Angilol LA (New Zealand); Apo-Propranolol (Canada, New Zealand); Apsolol (England); Artensol (Colombia); Atensin (Thailand); Avlocardyl (France); Becardin (Hong Kong); Berkolol (England, Hong Kong, Ireland); Betabloc (India); Beta-Timelets (Germany); Blocard (Indonesia); Blocaryl (Argentina); Cardinol (New Zealand); Cardinol LA (New Zealand); Ciplar (India); Corbeta (India); Deralin (Australia, Israel); Dibudinate (Argentina); Dociton (Germany); Duranol (Philippines); Elbrol (Germany); Emforal (Thailand); Farmadral (Indonesia); Farprolol (Mexico); Frekven (Denmark); Frina (Hungary); Hopranolol (Hong Kong); Impral (Mexico); Indicardin (South Africa); Inpanol (Hong Kong); Noloten (Argentina); Oposim (Argentina); Phanerol (Philippines); Prestoral (Indonesia); Prolol (Hong Kong, Israel, Thailand); Prolol Plus (Hong Kong); Propalong (Argentina); Propayerst (Argentina); Propral (Finland); Reducor (Finland); Rexigen (South Africa); Slow Deralin (Israel); Sumial (Spain); Tenomal (Greece); Tensiflex (Argentina); Waucoton (Greece)

Drug Class

Adrenergic antagonists; Antiarrhythmics, class II; β-Blockers

Indications

Hypertension, migraine headache prophylaxis, SVT, angina

Mechanism

Nonselective β-antagonist

Dosage with Qualifiers

Hypertension—begin 40mg PO bid, increasing q3-7d; max 640mg/d
Migraine headache prophylaxis—begin 20mg PO qd; increase gradually to 40-60mg PO qid
SVT—begin 1-3mg IV at 1mg/min; may repeat 2min later; if control, then 10-30mg PO tid or qid beginning 4h later
Angina—80-120mg PO bid; may increase q7-10d

- **Contraindications**—hypersensitivity to drug or class, asthma, CHF, cardiogenic shock, 2nd or 3rd degree heart block, severe sinus bradycardia
- **Caution**—diabetes mellitus, hepatic or renal dysfunction

Maternal Considerations

Propranolol is used extensively during pregnancy for the treatment of maternal hypertension, arrhythmia, and migraine headache, and is generally considered safe. It is also used acutely to provide relief of symptoms from thyrotoxicosis and pheochromocytoma. Several studies suggest the administration of

propranolol (2mg IV) to nulliparas who require **oxytocin** augmentation for dysfunctional labor reduces the likelihood of a cesarean delivery by almost ½. The studies of **propranolol** as an oral hypotensive are small. It appears as effective as α-**methyldopa,** and is often coupled with other hypotensive agents such as **hydralazine.**
Side effects include CHF, arrhythmia, bronchospasm, bradycardia, dizziness, insomnia, weakness, fatigue, hallucinations, N/V, abdominal pain, diarrhea, constipation, pharyngitis, rash, alopecia, and agranulocytosis.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. **Propranolol** crosses the human placenta, but has no effect on either uterine or umbilical Doppler-determined resistances in chronically hypertensive women. There are case reports of its use, usually with **digoxin,** for the treatment of SVT, though there are superior agents. The impact of **propranolol** on the fetus of women with chronic hypertension is unclear. Frequently combined with another agent, the risk of IUGR is reportedly increased. However, IUGR is more common when the maternal pressure is suboptimally controlled and in need of higher doses. The most recent information suggests the increased risk of IUGR reflects excessive maternal β blockade adequate to decrease maternal cardiac output. Other neonatal sequelae reported include bradycardia and hypoglycemia.

Breastfeeding Safety

Less than 1% of the maternal dose of **propranolol** enters human breast milk; it should not pose a risk to the breastfed neonate.

Drug Interactions

Use with ACEIs can cause hypotension, particularly in the setting of acute MI. Use with some ACEIs increases bronchial hyperreactivity.
May antagonize the antihypertensive effects of **clonidine.**
Prazosin may prolong 1st-dose hypotension.
Propafenone has negative inotropic and β-blocking properties that can be additive to those of **propranolol.**
Quinidine increases the **propranolol** concentration and produces greater degrees of clinical β blockade and may cause postural hypotension.
Disopyramide has been associated with severe bradycardia, asystole, and heart failure when administered with **propranolol.**
The negative chronotropic properties of **amiodarone** may be additive to those seen with **propranolol.**
Reduces the clearance of **lidocaine.**
Caution should be exercised when patients receiving a β-blocker are administered a calcium channel–blocking drug with negative inotropic and/or chronotropic effects. Both agents may depress myocardial contractility or AV conduction.
Patients on long-term therapy may experience uncontrolled hypertension if given **epinephrine** as a consequence of unopposed α-receptor stimulation.
Patients receiving catecholamine-depleting drugs such as **reserpine** should be closely observed for hypotension, marked bradycardia, vertigo, syncopal attacks, or orthostatic hypotension.
Propranolol may also potentiate depression.
Methoxyflurane and **trichloroethylene** may depress myocardial contractility.
The hypotensive effects of MAOIs or TCAs may be exacerbated when administered with β-blockers.
Hypotension and cardiac arrest have been reported when used with **haloperidol.**

NSAIDs blunt the antihypertensive effect.
May increase the concentration of **warfarin.** Monitor the PT closely.
Aluminum hydroxide gel greatly reduces intestinal absorption.
Ethanol slows the rate of absorption.
Phenytoin, phenobarbitone, and **rifampin** accelerate **propranolol** clearance.
Chlorpromazine increases the plasma levels of both drugs.
Cimetidine decreases the hepatic metabolism of **propranolol,** delaying elimination and increasing blood levels.
Theophylline clearance is reduced.

References

Aube M. Neurology 1999; 53:S26-8.
Chow T, Galvin J, McGovern B. Am J Cardiol 1998; 82:58I-62I.
Easterling TR, Carr DB, Brateng D, et al. Obstet Gynecol 2001; 98:427-33.
Livingstone I, Craswell PW, Bevan EB, et al. Clin Exp Hypertens B 1983; 2:341-50.
Meizner I, Paran E, Katz M, et al. J Clin Ultrasound 1992; 20:115-9.
Oudijk MA, Ruskamp JM, Ambachtsheer BE, et al. Paediatr Drugs 2002; 4:49-63.
Sanchez-Ramos L, Quillen MJ, Kaunitz AM. Obstet Gynecol 1996; 88:517-20.
Smith MT, Livingstone I, Hooper WD, et al. Ther Drug Monit 1983; 5:87-93.

Summary

Pregnancy Category: C
Lactation Category: S
- **Propranolol** should be used during pregnancy only if the benefit justifies the potential perinatal risk.

Propylthiouracil—(PTU)

International Brand Name—Antiroid (Korea); Propacil (Japan); Propycil (Bulgaria, Czech Republic, Germany, Portugal); Thyreostat II (Germany); Tiotil (Sweden); Tirostat (Colombia); Uracil (Thailand)

Drug Class

Antithyroid agents; Hormone modifiers; Hormones

Indications

Hyperthyroidism

Mechanism

Inhibits thyroid synthesis

Dosage with Qualifiers

Hyperthyroidism (Graves' disease)—begin 100-125mg PO tid; 200-300mg PO qid if thyroid storm

NOTE: renal dosing.

- **Contraindications**—hypersensitivity to drug or class
- **Caution**—pregnancy, renal dysfunction, concurrent hepatotoxic or agranulocytosis agents, bone marrow suppression

Maternal Considerations

Hyperthyroidism occurs in approximately 1 in every 1000-2000 pregnancies. **Propylthiouracil** historically was the agent of choice for the treatment of Graves' disease during pregnancy because it was believed to have less potential for fetal/neonatal hypothyrodism, to cross the placenta, or to enter breast milk, and to be less teratogenic than **methimazole** or carbimazole. None of these reasons has been validated in recent studies. There are no

adequate reports or well-controlled studies in pregnant women. **Methimazole** is equally effective. It is generally recommended that the minimum dose of **propylthiouracil** necessary to control the maternal thyroid be used. However, this is a poor approach as the maternal dosage correlates poorly with the newborn TSH. Clearly, dosing must be individualized to achieve optimal maternal and fetal outcome. Women with a history of Graves' disease in the past should be screened for the continued presence of thyroid-stimulating immunoglobulin even if they previously received definitive treatment, since fetal hyperthyroidism is still likely when positive. Fetal treatment may be necessary, and the patient should be appropriately evaluated in a fetal care unit. ***Side effects*** include agranulocytosis, leukopenia, thrombocytopenia, aplastic anemia, hepatotoxicity, exfoliative dermatitis, urticaria, vasculitis, interstitial pneumonitis, N/V, rash, drowsiness, dizziness, headache, arthralgia, lymphadenopathy, paresthesias, hyperpigmentation, jaundice, alopecia, and neuritis.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. **Propylthiouracil** crosses the human placenta. The fetuses of mothers treated with **propylthiouracil** are rarely euthyroid, and a fetal evaluation is mandatory. Hydrops fetalis has been reported as a rare complication of fetal hypothyroidism. Aplasia cutis is a rare complication of maternal therapy. Compromised neurodevelopment in the rodent reflects decreased T4.

Breastfeeding Safety

There are no adequate reports or well-controlled studies in nursing women. Small quantities of **propylthiouracil** are excreted into human breast milk, but thyroid function of breastfed neonates is unaffected.

Drug Interactions

The activity of anticoagulants may be potentiated by anti–vitamin K activity attributed to **propylthiouracil.**

References

Axelstad M, Hansen PR, Bobeng J, et al. Toxicol Appl Pharmacol 2008; 232:1-13.
Brunner JP, Dellinger EH. Fetal Diagn Ther 1997; 12:200-4.
Chattaway JM, Klepser TB. Ann Pharmacother 2007; 41:1018-22.
Kampmann JP, Johansen K, Hansen JM, Helweg J. Lancet 1980; 1:736-7.
Lee A, Moretti ME, Collantes A, et al. Pediatrics 2000; 106:27-30.
Momotani N, Noh JY, Ishikawa N, Ito K. J Clin Endocrinol Metab 1997; 82:3633-6.
Momotani N, Yamashita R, Makino F, et al. Clin Endocrinol 2000; 53:177-81.
Mortimer RH, Cannell GR, Addison RS, et al. J Clin Endocrinol Metab 1997; 82:3099-102.
Nachum Z, Rakover Y, Weiner E, Shalev E. Am J Obstet Gynecol 2003; 189:159-65.
Polak M, Leger J, Luton D, et al. Ann Endocrinol 1997; 58:338-42.
Wenstrom KD, Weiner CP, Williamson RA, Grant SS. Obstet Gynecol 1990; 76:513-17.
Yanai N, Shveiky D. Ultrasound Obstet Gynecol 2004; 23:198-201.

Summary

Pregnancy Category: D
Lactation Category: S (likely)

- **Propylthiouracil** should be used during pregnancy only if the benefit justifies the potential perinatal risk.

Protamine

International Brand Name—None identified.

Drug Class	Antidotes, bleeding disorders
Indications	Heparin reversal
Mechanism	Binds heparin
Dosage with Qualifiers	Heparin reversal—1-1.5mg IV per 100U **heparin** estimated to remain in the body: if 0-30min from last dose, give 1-1.5mg/100U; if 30-60min, give 0.5-0.75mg/100U; if >2h, give 0.25-0.375mg/100U *NOTE: monitor BP, ECG, and aPTT during reversal.* • **Contraindications**—hypersensitivity to drug or class • **Caution**—fish allergy or prior exposure to various protamine insulins
Maternal Considerations	There are no adequate reports or well-controlled studies of **protamine** in pregnant women. Case reports note acute hypotension, bradycardia, and anaphylactic reactions. **Protamine** does not reverse anticoagulation secondary to the LMWHs. ***Side effects*** include anaphylaxis, bronchospasm, fatigue, angioedema, circulatory collapse (due to sudden pulmonary hypertension, right ventricular then biventricular failure followed by circulatory collapse), bradycardia, bleeding, paradoxical hemorrhage, leukopenia, thrombocytopenia, dyspnea, flushing, urticaria, and N/V.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **protamine** crosses the human placenta. Rodent teratogenicity studies have not been conducted. However, insulin coupled to **protamine** has a long safety record.
Breastfeeding Safety	There is no published experience in nursing women. It is unknown whether **protamine** enters human breast milk. However, insulin coupled to **protamine** has a long safety record.
Drug Interactions	**Protamine** is incompatible with certain antibiotics, including several of the cephalosporins and penicillins.
References	There are no current relevant references.
Summary	**Pregnancy Category: C** **Lactation Category: S** (likely) • **Protamine** sulfate should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Protriptyline—(Concordin; Triptil; Vivactil)

International Brand Name—None identified.

Drug Class	Antidepressants; Tricyclics
Indications	Depression
Mechanism	Unknown; inhibits NE and serotonin reuptake
Dosage with Qualifiers	Depression—5-10mg PO tid or qid; max 60mg/d • **Contraindications**—hypersensitivity to drug or class, SSRI use • **Caution**—hyperthyroidism, epilepsy, CAD
Maternal Considerations	There are no published reports of **protriptyline** use in pregnancy. ***Side effects*** include MI, AV block, arrhythmia, stroke, seizures, fever, agranulocytosis, leukopenia, jaundice, agitation, anxiety, tachycardia, palpitations, hypotension, N/V, blurred vision, dry mouth, mydriasis, photosensitivity, hallucinations, ataxia, peripheral neuropathy, SIADH, itching, rash, and black tongue.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **protriptyline** crosses the human placenta. There is no evidence after 5y that either TCAs or **fluoxetine** adversely affect cognition and language development. In contrast, maternal depression is associated with lower language and cognitive achievement. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically.
Breastfeeding Safety	There are no published reports in nursing women. It is unknown whether **protriptyline** enters human breast milk.
Drug Interactions	Close supervision and careful adjustment of dosages are required when given with anticholinergic agents or sympathomimetic drugs, including **epinephrine** combined with local anesthetics. Hyperpyrexia has been reported when TCAs are administered with anticholinergic agents or neuroleptic drugs, particularly during hot weather. "Poor metabolizers" of CYP2D6 (about 7-10% of Caucasians) have higher than expected plasma concentrations. Depending on the fraction of drug metabolized by CYP2D6, the increase in plasma concentration may be small or quite large (8-fold increase in plasma AUC of the TCA). Certain drugs inhibit CYP2D6 and make normal metabolizers resemble poor metabolizers. A patient who is stable on a given dose of TCA may become abruptly toxic when given one of these inhibiting drugs. CYP2D6 inhibitors include some that are not metabolized by the enzyme (e.g., **cimetidine, quinidine**) and many that are substrates for CYP2D6 (many other antidepressants, phenothiazines, and the class IC antiarrhythmics **propafenone** and **flecainide**). While all SSRIs (e.g., **fluoxetine, paroxetine, sertraline**) inhibit CYP2D6, they vary in the extent of inhibition. The extent to which SSRI-TCA interactions pose clinical problems depends on the degree of inhibition and the pharmacokinetics of the SSRI involved. Caution is indicated in using TCAs with any of the SSRIs, and also in switching from one class to the other. Sufficient time must elapse before initiating TCA treatment in patients being withdrawn from **fluoxetine,** given the long t/2 of the parent and active metabolite (at least 5w may be necessary).

■ **References** ..... Nulman I, Rovet J, Stewart DE, et al. Am J Psychiatry 2002; 159:1889-95.

■ **Summary** .....

Pregnancy Category: C
Lactation Category: S

- **Protriptyline** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.
- There are alternative agents for which there is more experience regarding use during pregnancy and lactation.

Pseudoephedrine—(Bronalin; Cenafed; Chlordrine; Novafed; Sufedrin)

International Brand Name—Acunaso (South Africa); Dimetapp Sinus Liquid caps (Australia); Drixora (South Africa); Logicin Plus (Hong Kong); Monofed (South Africa); NASA-12 (Belgium); Otrinol (Israel); Pseudono (Thailand); Sinumed (South Africa); Sinutab Decongestant (New Zealand); Subulin (Taiwan); Sudafed (Australia, Belgium, Canada, England, France, India, Indonesia, Ireland, Israel, Italy, Korea, Malaysia, Mexico, Peru, Portugal, South Africa, Spain); Sudafed 12h (Australia); Sudomyl (New Zealand); Sudosian (Thailand); Symptofed (South Africa); Tiptipot (Israel)

■ **Drug Class** ..... Decongestants; Sympathomimetics

■ **Indications** ..... Nasal decongestion

■ **Mechanism** ..... α-Agonist

■ **Dosage with Qualifiers** .....

Nasal decongestion—30-60mg PO q4-6h prn; max 240mg/d

NOTE: available in a sustained-release form, and in combination with either the antihistamine triprolidine (Actifed) or ***codeine.***

- **Contraindications**—hypersensitivity to drug or class, MAOI use <14d, narrow-angle glaucoma, severe hypertension, severe CAD
- **Caution**—hypertension, diabetes mellitus, mild/moderate CAD, hyperthyroidism, renal dysfunction, PKU

■ **Maternal Considerations** .....

Pseudoephedrine is second-line therapy behind 1st- and 2nd-generation antihistamines. There are no adequate reports or well-controlled studies in pregnant women.
Side effects include hypertension, arrhythmia, N/V, headache, dizziness, nervousness, excitability, agitation, anxiety, palpitations, weakness, and tremor.

■ **Fetal Considerations** .....

There are no adequate reports or well-controlled studies in human fetuses. The chemical structure of **pseudoephedrine** suggests it crosses the human placenta. Epidemiologic study suggests exposed fetuses are at increased risk of gastroschisis by as much as 4-fold and, to a lesser degree, small intestinal atresias. The risk may be enhanced by tobacco use. There is a single case report suggesting a relationship with fetal tachycardia.
Rodent teratogenicity studies have not been conducted.

■ **Breastfeeding Safety** .....

There are no adequate reports or well-controlled studies in nursing women. Less than 1% of the maternal dose of **pseudoephedrine** is excreted into human breast milk. Though generally considered compatible with breastfeeding, a recent study suggests a single 60mg dose of **pseudoephedrine** reduces milk volume by 25%. Thus, women with low milk production should

consider another decongestant. In this same study, neonatal ingestion was quantified as the product of average steady-state drug concentration in milk, with an estimated milk production rate of 0.15L/kg/d, and expressed relative to the maternal weight-adjusted dose. Assuming maternal dose of 60mg **pseudoephedrine** PO qid, the estimated infant dose was <5% of the weight-adjusted maternal dose.

Drug Interactions

Effects are increased by MAOIs and β-blockers.
May reduce the antihypertensive effects of **mecamylamine, methyldopa, reserpine,** and veratrum alkaloids.

References

Aljazaf K, Hale TW, Ilett KF, et al. Br J Clin Pharmacol 2003; 56:18-24.
Anastasio GD, Harston PR. J Am Board Fam Pract 1992; 5:527-8.
Findlay JW, Butz RF, Sailstad JM, et al. Br J Pharmacol 1984; 18:901-6.
Mitchell JL. J Hum Lact 1999; 15:347-9.
[No authors]. Prescirre Int 2004; 13:141-3.
Werler MM, Sheehan JE, Mitchell AA. Am J Epidemiol 2002; 155:26-31.
Werler MM, Sheehan JE, Mitchell AA. Epidemiology 2003; 14:349-54.

Summary

Pregnancy Category: C
Lactation Category: S

- **Pseudoephedrine** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.
- Avoid use in 1st and early 2nd trimester.
- Antihistamines are the drugs of choice for the treatment of nasal congestion during pregnancy.
- **Pseudoephedrine** may reduce milk volume and should perhaps be avoided during lactation in women with suboptimal production.

Psyllium—(Metamucil)

International Brand Name—None identified.

Drug Class — Laxatives

Indications — Constipation

Mechanism — Increases stool bulk

Dosage with Qualifiers

Constipation—1-2tsp PO dissolved in water or juice qd to tid

- **Contraindications**—hypersensitivity to drug or class, suspected appendicitis, intestinal obstruction
- **Caution**—unknown

Maternal Considerations

There are no adequate reports or well-controlled studies in pregnant women. **Psyllium** is not absorbed systemically.
Side effects include esophageal obstruction, bowel obstruction, constipation, diarrhea, abdominal cramps, bronchospasm, rhinitis, and conjunctivitis.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. **Psyllium** is not absorbed systemically and poses no direct threat to the fetus.

Breastfeeding Safety	There is no published experience in nursing women. As **psyllium** is not absorbed systemically, it is unlikely to be excreted into human breast milk.
Drug Interactions	No clinically relevant interactions identified.
References	There is no published experience in pregnancy or during lactation.
Summary	**Pregnancy Category: C** **Lactation Category: S** • **Psyllium** is not absorbed systemically. It should pose no additional risk during pregnancy and lactation.

Pyrantel pamoate—(Antiminth)

International Brand Name—None identified.

Drug Class	Antiparasitics
Indications	Pinworm, roundworm, hookworm, whipworm
Mechanism	Depolarizing agent causing worm paralysis
Dosage with Qualifiers	Pinworm—11mg/kg PO qd ×1d; may take with milk or juice, treat all family members Roundworm—11mg/kg PO qd ×1d; may take with milk or juice Hookworm—11mg/kg PO qd ×3d; may take with milk or juice Whipworm—11mg/kg PO qd ×1d; may take with milk or juice • **Contraindications**—hypersensitivity to drug or class • **Caution**—hepatic dysfunction, malnutrition
Maternal Considerations	There are no published reports of **pyrantel pamoate** use in pregnancy. ***Side effects*** include anorexia, N/V, abdominal cramps, diarrhea, dizziness, drowsiness, insomnia, tenesmus, rash, weakness, and elevated hepatic transaminases.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **pyrantel pamoate** crosses the human placenta. Rodent teratogenicity studies have not been conducted.
Breastfeeding Safety	There is no published experience in nursing women. It is unknown whether **pyrantel pamoate** enters human breast milk.
Drug Interactions	No clinically relevant interactions identified.
References	There is no published experience in pregnancy or during lactation.
Summary	**Pregnancy Category: C** **Lactation Category: S** • **Pyrantel pamoate** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Pyrazinamide

International Brand Name—Braccopiral (Mexico, Philippines); Corsazinmid (Indonesia); Pezetamid (Germany); Piraldina (India, Israel, Italy); Pirilene (France); Prazina (Indonesia); Pyrafat (Austria, Germany, Hong Kong); Pyramide (Japan); Pyzamed (Philippines); P-Zide (India); Rozide (South Africa); Tebrazid (Belgium, Canada, Switzerland); Tisamid (Finland); Zapedia (Philippines); Zinamide (England)

Drug Class	Antimycobacterials
Indications	TB, adjuvant
Mechanism	Unknown
Dosage with Qualifiers	TB, adjuvant—15-30mg/kg PO qd given as part of a multidrug regimen; max 3g/d • **Contraindications**—hypersensitivity to drug or class, severe hepatic dysfunction • **Caution**—renal dysfunction, diabetes mellitus, gout
Maternal Considerations	**Pyrazinamide** should only be given with other antituberculosis agents. It has an excellent safety record during pregnancy. However, there are no adequate reports or well-controlled studies in pregnant women. Most publications consist of case reports or limited series. ***Side effects*** include interstitial nephritis, hepatotoxicity, thrombocytopenia, elevated LFTs, hyperuricemia, anorexia, urticaria, rash, N/V, arthralgia, malaise, photosensitivity, and gout.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **pyrazinamide** crosses the human placenta. Rodent teratogenicity studies have not been conducted.
Breastfeeding Safety	There are no adequate reports or well-controlled studies in nursing women. In one woman taking 1g **pyrazinamide** PO, the maternal plasma level 3h later was 1.5mg/L with a theoretic infant daily dose of 0.2mg/kg/d.
Drug Interactions	No clinically relevant interactions identified.
References	Bothamley G. Drug Saf 2001; 24:553-65. Holdiness MR. Arch Intern Med 1984; 144:1888-9.
Summary	**Pregnancy Category: C** **Lactation Category: S** (possibly) • **Pyrazinamide** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Pyridostigmine—(Mestinon)

International Brand Name—Kalymin (Germany)

Drug Class	Cholinesterase inhibitors; Musculoskeletal agents
Indications	Myasthenia gravis
Mechanism	Cholinesterase inhibitor
Dosage with Qualifiers	Myasthenia gravis—begin 60mg PO q8h, individualizing to response and side effects; max 1500mg/d • **Contraindications**—hypersensitivity to drug or class, mechanical GI obstruction • **Caution**—asthma, peptic ulcer disease, arrhythmia, bradycardia, seizures, renal dysfunction
Maternal Considerations	There are no adequate reports or well-controlled studies of **pyridostigmine** in pregnant women. The published literature consists of small series and case reports. ***Side effects*** include bronchospasm, bradycardia, hypertension, cholinergic crisis, paralysis, AV block, arrhythmia, cardiac or respiratory arrest, N/V, diarrhea, dyspepsia, abdominal pain, weakness, rash, muscle cramps, increased bronchial secretions or salivation, miosis, and tearing.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **pyridostigmine** crosses the human placenta. Several case reports suggest a relationship between **pyridostigmine** and neurologic abnormalities, including arthrogryposis multiplex and microcephaly. Rodent teratogenicity studies have not been conducted.
Breastfeeding Safety	There are no adequate reports or well-controlled studies in nursing women. **Pyridostigmine** is excreted into human breast milk at low concentration (5-25mcg/L). In light of the poor oral absorption, the estimated daily intake would be <0.5% of the maternal dose.
Drug Interactions	No clinically relevant interactions identified.
References	Garcia SA, Ogata AJ, Patriota RG, et al. Rev Paul Med 1989; 107:144-8. Hardell LI, Lindstrom B, Lonnerholm G, Osterman PO. Br J Clin Pharmacol 1982; 14:565-7. Niesen CE, Shah NS. Neurology 2000; 54:1873-4. Pelufo-Pellicer A, Monte-Boquet E, Romá-Sánchez E, et al. Ann Pharmacother 2006; 40:762-6. Pijinenborg JM, Hansen EC, Brolmann HA, et al. Gynecol Obstet Invest 2000; 50:142-3.
Summary	**Pregnancy Category: C** **Lactation Category: S** (likely) • **Pyridostigmine** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Pyridoxine—(Beesix; Hexa-Betalin; Rodex; Vitamin B_6)

International Brand Name—B_6-Vicotrat (Germany); Benadon (Peru); Bexivit (Greece); Bonadon N (Germany); Hexobion 100 (Germany); Pyroxin (Australia)

Drug Class ..... Vitamins/minerals

Indications ..... Morning sickness; pyridoxine deficiency or supplementation, PMS, isoniazid adjunct

Mechanism ..... Replacement

Dosage with Qualifiers .....

Morning sickness—10mg PO bid or tid
Pyridoxine deficiency—10-20mg PO/IM/IV qd ×3w, then 2-5mg/d PO
Pyridoxine supplementation—2-5mg PO qd
PMS—40-500mg PO qd
Isoniazid adjunct—25-50mg PO qd to prevent associated neuropathy

NOTE: available in some areas combined with doxylamine (Diclectin) for the treatment of N/V during pregnancy; antagonizes ***levodopa.***

- **Contraindications**—hypersensitivity to drug or class, **levodopa** therapy
- **Caution**—unknown

Maternal Considerations .....

Pyridoxine is a coenzyme for several amino acid decarboxylases and transaminases. It reduces N/V of pregnancy, but does not reduce the side effects associated with oral contraceptive use. Recent study suggests the preemptive use of **pyridoxine** early in gestation decreases the prevalence of severe N/V in at-risk women. It also appears effective in reducing postoperative nausea after laparoscopy. **Pyridoxine** is used in combination with antituberculosis therapy to reduce the risk of neuropathy. There is not enough evidence to confirm clinical benefits of routine supplementation during pregnancy other than one trial suggesting protection against dental decay.
Side effects include numbness, unsteady gait, and paresthesias.

Fetal Considerations .....

Pyridoxine crosses the human placenta and is not teratogenic. **Pyridoxine** supplementation during pregnancy increases neonatal stores in a dose-dependent manner.

Breastfeeding Safety .....

Pyridoxine requirements are thought to increase during lactation. Maternal supplementation increases human breast milk content in a dose-dependent manner.

Drug Interactions .....

Antagonizes the action of **levodopa.** However, this vitamin may be used concurrently in patients receiving a preparation containing both **carbidopa** and **levodopa.**

References .....

Chang SJ. J Nutr Sci Vitaminol 1999; 45:449-58.
Chang SJ, Kirksey A. J Nutr Sci Vitaminol 2002; 48:10-17.
Jewell D, Young G. Cochrane Database Syst Rev 2002; (1):CD000145.
Koren G, Maltepe C. J Obstet Gynaecol 2004; 24:530-3.
Magee LA, Mazzotta P, Koren G. Am J Obstet Gynecol 2002; 185:S256-61.
Reeve BK, Cook DJ, Babineau D, et al. Can J Anaesth 2005; 52:55-61.

Sahakian V, Rouse D, Sipes S, et al. Obstet Gynecol 1991; 78:33-6.
Thaver D, Saeed MA, Bhutta ZA. Cochrane Database Syst Rev 2006; (2):CD000179.
Vutyavanich T, Wongtrangan S, Ruangsri R. Am J Obstet Gynecol 1995; 173:881-4.

Summary

Pregnancy Category: A
Lactation Category: S

- **Pyridoxine** reduces the severity of morning sickness.
- Routine supplementation during pregnancy and lactation is recommended.

Pyrimethamine—(Daraprim; Eraprelina; Malocide)

International Brand Name—Malocide (France)

Drug Class

Antiprotozoals

Indications

Malaria treatment and prophylaxis, toxoplasmosis, isosporiasis

Mechanism

Inhibits plasmodium dihydrofolate reductase

Dosage with Qualifiers

Malaria treatment—50mg PO qd ×2w in combination with **sulfadiazine** and **quinine;** use in **chloroquine**-resistant areas
Malaria prophylaxis—25mg PO qw ×10w after exposure; use in **chloroquine**-resistant areas
Toxoplasmosis—begin 50-75mg PO qd ×1-3w, then 25-50mg PO qd ×4-5w in combination with sulfadoxine and folinic acid
Toxoplasmosis with HIV—begin 200mg PO ×1, then 50-100mg PO qd ×4-8w, then maintenance
Isosporiasis—50-75mg PO qd

NOTE: may be combined with sulfadoxine (Fansidar).

- **Contraindications**—hypersensitivity to drug or class, folate deficiency
- **Caution**—hepatic or renal dysfunction, G6PD deficiency

Maternal Considerations

Severe anemia is a cause of maternal morbidity in endemic areas, and treatment leads to resolution. HIV infection during pregnancy is associated with an increased risk of malaria. **Pyrimethamine** has a long history of use during pregnancy, especially for the treatment of primary toxoplasmosis and malaria. Recent study suggests the use of intermittent preventative therapy in endemic areas.
Side effects include aplastic anemia, pancytopenia, thrombocytopenia, Stevens-Johnson syndrome, agranulocytosis, megaloblastic anemia, seizures, pulmonary eosinophilia, erythema multiforme, N/V, abdominal pain, dizziness, malaise, diarrhea, rash, fever, dry mouth, and increased skin pigmentation.

Fetal Considerations

Pyrimethamine crosses the human placenta with about 30% efficiency. While it has been long used for the treatment of toxoplasmosis during pregnancy, several recent studies conclude that antenatal therapy does not alter outcome, perhaps because fetal infection has already occurred. Other studies suggest **pyrimethamine** does not reduce transmission, but rather the sequelae of infection. Further research is required to define the role of prenatal screening and therapy. In contrast, the treatment

of pregnant women (in combination with sulfadoxine) in malaria-endemic areas is cost-effective, reducing the risk of prematurity and IUGR secondary to placental malaria. In rodents, **pyrimethamine** is associated with embryotoxicity and IUGR. **Pyrimethamine** was associated with an increased risk of cleft palate, micrognathia, and clubfoot in pigs.

Breastfeeding Safety

There are no adequate reports or well-controlled studies in nursing women. **Pyrimethamine** is excreted into human breast milk in low concentrations. It is estimated the breastfed neonate would ingest less than 10% of the maternal dose over 48h.

Drug Interactions

Concomitant use of other antifolic drugs or agents associated with myelosuppression, including sulfonamides or **trimethoprim-sulfamethoxazole** combinations, **proguanil, zidovudine,** or cytostatic agents (e.g., **methotrexate**), may increase the risk of bone marrow suppression. If signs of folate deficiency develop, **pyrimethamine** should be discontinued. Folinic acid should be administered until normal hematopoiesis is restored.
Mild hepatotoxicity has been reported in some patients also given **lorazepam.**

References

Foulon W, Villena I, Stray-Pedersen B, et al. Am J Obstet Gynecol 1999; 180:410-5.
Gilbert RE, Gras L, Wallon M, et al. Int J Epidemiol 2001; 30:1303-8.
Gras L, Gilbert RE, Ades AE, Dunn DT. Int J Epidemiol 2001; 30:1309-13.
Peytavin G, Leng JJ, Forestier F, et al. Biol Neonate 2000; 78:83-5.
Shulman CE. Ann Trop Med Parasitol 1999; 93:S59-66.
Shulman CE, Dorman EK, Cutts F, et al. Lancet 1999; 353:632-6.
Verhoeff FH, Brabin BJ, Hart CA, et al. Trop Med Int Health 1999; 4:5-12.
Wallon M, Liou C, Garner F, Peyron F. BMJ 1999; 318:1511-4.
Wolfe EB, Parise ME, Haddix AC, et al. Am J Trop Med Hyg 2001; 64:178-86.

Summary

Pregnancy Category: C
Lactation Category: S

- **Pyrimethamine** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Quetiapine—(Seroquel)

International Brand Name—Seroquel (Ecuador, England, Hong Kong, Hungary, Indonesia, Ireland, Israel, Korea, Malaysia, Netherlands, Philippines, Poland, Singapore, South Africa, Taiwan, Thailand); Socalm (India)

Drug Class — Antipsychotics

Indications — Psychosis

Mechanism — Unknown; antagonizes multiple neurotransmitter receptors

Dosage with Qualifiers — Psychosis—begin 25mg PO bid, increase by 25-50mg/dose q1-2d; max 800mg/d

NOTE: hepatic dosing.

- **Contraindications**—hypersensitivity to drug or class
- **Caution**—hepatic dysfunction, cardiac disease, CVD, seizures, hypotension, hypovolemia

Maternal Considerations — **Quetiapine** is a dibenzothiazepine derivative. The published experience during pregnancy is limited to case reports. A single case report suggests the t/2 is decreased by 25-30% throughout pregnancy
Side effects include hypotension, tardive dyskinesia, menstrual irregularities, hyperprolactinemia, hypothyroidism, diabetes mellitus, neuroleptic malignant syndrome, leukopenia, headache, somnolence, dizziness, constipation, tachycardia, dry mouth, asthenia, rash, hypercholesterolemia, hypertriglyceridemia, elevated LFTs, dyspepsia, abdominal pain, rhinitis, weight gain, and fever.

Fetal Considerations — There are no adequate reports or well-controlled studies in human fetuses. **Quetiapine** crosses the human placenta, achieving an F:M ratio of about 0.25. Only about 4% of the maternal dose is transferred across the isolated cotyledon. The pregnancy outcomes of women who contacted a teratogen information service after exposure to **quetiapine** appeared normal. Rodent studies are mostly reassuring, revealing no evidence of teratogenicity despite the use of doses higher than those used clinically. Embryotoxicity and IUGR were noted at the highest doses.

Breastfeeding Safety — There are no adequate reports or well-controlled studies in nursing women. Small amounts of **quetiapine** are excreted into human breast milk (but in one series only 50% of women had detectable levels in their milk). Detailed kinetics studies are scarce. In one report, the average milk concentration was 41mcg/L, the M:P ratio (measured using the average concentrations during the elimination phase) was 0.29, and the relative infant dose was 0.09% of the maternal weight-adjusted dose (7273mcg/kg/d). The infant plasma concentration of 1.4mcg/L was some 6% of the corresponding maternal plasma concentration. No adverse effects were noted in the infant.

Drug Interactions — Potentiates the cognitive and motor effects of ethanol.
May enhance certain antihypertensive agents.
May antagonize the effects of **levodopa** and dopamine agonists.
Phenytoin (100mg tid) increases the oral clearance of **quetiapine** by 5-fold, requiring an increased dose of **quetiapine** to maintain control of symptoms of schizophrenia in patients receiving both **quetiapine** and **phenytoin,** or other hepatic enzyme inducers (e.g., barbiturates, **carbamazepine,** glucocorticoids, **rifampin**).

Divalproex (500mg bid) increased the mean plasma concentration of **quetiapine** at steady-state by 17% without affecting either the absorption or oral clearance.
Thioridazine (200mg bid) increased the oral clearance of **quetiapine** (300mg bid) by 65%.
Ketoconazole (200mg qd ×4d), a potent inhibitor of CYP3A, reduced the oral clearance of **quetiapine** by 84%, resulting in a 335% increase in the maximum plasma concentration of **quetiapine**. Caution is indicated with **ketoconazole** and other CYP3A inhibitors (e.g., **erythromycin, fluconazole, itraconazole**).
The mean oral clearance of **lorazepam** (2mg, single dose) was reduced by 20%.

References

Klier CM, Mossaheb N, Saria A, et al. J Clin Psychopharmacol 2007; 27:720-2.
McKenna K, Koren G, Tetelbaum M, et al. J Clin Psychiatry 2005; 66:444-9.
Misri S, Corral M, Wardrop AA, Kendrick K. J Clin Psychopharmacol 2006; 26:508-11.
Newport DJ, Calamaras MR, DeVane CL, et al. Am J Psychiatry 2007; 164:1214-20.
Rahi M, Hekkinen T, Hartter S, et al. Psychopharmacol 2007; 21:751-6.
Rampono J, Kristensen JH, Ilett KF, et al. Ann Pharmacother 2007; 41:711-4.
Taylor TM, O'Toole MS, Ohlsen RI, et al. Am J Psychiatry 2003; 160:588-9.
Tenyi T, Trixler M, Keresztes Z. Am J Psychiatry 2002; 159:674.

Summary

Pregnancy Category: C
Lactation Category: S (likely)

- **Quetiapine** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.
- There are alternative agents for which there is more experience regarding use during pregnancy and lactation.

Quinapril—(Accupril)

International Brand Name—Accuprin (Italy); Accupro (Austria, Czech Republic, Denmark, England, Finland, Germany, Ireland, Sweden, Switzerland); Accupron (Greece); Acequin (Italy); Acuitel (France, Israel, Mauritius); Acuprel (Spain); Acupril (Mexico, Netherlands); Asig (Australia); Conan (Japan); Korec (France); Quinaten (Colombia); Quinazil (Italy)

Drug Class

ACEI/A2R-antagonists; Antihypertensives

Indications

Hypertension, CHF

Mechanism

ACEI

Dosage with Qualifiers

Hypertension—begin 10mg PO qd, adjust for effect q2w moving to bid if necessary; max 80mg/d
CHF—begin 5mg PO qd, adjust weekly for effect, moving to bid; max 40mg/d

NOTE: renal dosing.

- **Contraindications**—hypersensitivity to drug or class, angioedema
- **Caution**—renal dysfunction, renal artery stenosis, collagen vascular disease, hyponatremia, hypovolemia

Maternal Considerations

There are no adequate reports or well-controlled studies of **quinapril** in pregnant women. In general, ACEIs should be avoided during pregnancy. The lowest effective dose should be used when **quinapril** is required for BP control during pregnancy. ***Side effects*** include angioedema, hypotension, renal failure, cough, dizziness, fatigue, N/V, URI symptoms, myalgia, arthralgia, hyperkalemia, neutropenia, agranulocytosis, and elevated BUN/Cr.

Fetal Considerations

There is no published experience in human fetuses. **Quinapril** likely crosses the human placenta like other ACEIs. As a group, adverse fetal effects are reported across gestation. In contrast to conclusions based on earlier data, adverse fetal effects occur even after 1st trimester exposure to ACEIs, for which the relative risk is 2.7. Exposure is associated with CV and CNS disorders. Later exposure is associated with cranial hypoplasia, anuria, reversible or irreversible renal failure, death, oligohydramnios, prematurity, IUGR, and PDA. The mechanism of renal dysfunction is likely related to fetal hypotension and prolonged decreased glomerular filtration. There is inadequate study to determine whether the response to **quinapril** is typical of this group. The one published rodent study is reassuring. If oligohydramnios is detected, **quinapril** should be discontinued unless lifesaving for the mother. Antenatal surveillance should be initiated (e.g., BPP) if the fetus is potentially viable. Oligohydramnios may not appear until after the fetus has irreversible injury. Neonates exposed *in utero* to ACEIs should be observed closely for hypotension, oliguria, and hyperkalemia. If oliguria occurs despite adequate BP and renal perfusion, exchange transfusion or peritoneal dialysis may be required.

Breastfeeding Safety

There are no adequate reports or well-controlled studies in nursing women. **Quinapril** enters human breast milk with an M/P ratio of 0.12. No drug is detected more than 4h after maternal ingestion. It is unlikely the breastfed neonate would ingest clinically relevant amounts.

Drug Interactions

As with other ACEIs, patients on diuretics (especially those recently begun) occasionally may experience an excessive reduction of BP after starting **quinapril.** The risk of hypotension can be minimized by either discontinuing the diuretic or cautiously increasing salt intake prior to beginning **quinapril.** May attenuate potassium loss caused by thiazide diuretics and increase serum potassium even when used alone. Potassium supplements or potassium-containing salt substitutes should be used cautiously and with appropriate serum monitoring if used with potassium-sparing diuretics (e.g., **amiloride, spironolactone, triamterene**).

Tetracycline absorption is reduced by ⅓, possibly due to the high magnesium content in **quinapril** tablets.

Increased serum **lithium** levels and symptoms of **lithium** toxicity have been reported. These drugs should be used together with caution and frequent measurements of serum **lithium.**

References

Begg EJ, Robson RA, Gardiner SJ, et al. Br J Clin Pharmacol 2001; 51:478-81.

Dostal LA, Kim SN, Schardein JL, Anderson JA. Fundam Appl Toxicol 1991; 17:684-95.

Summary

Pregnancy Category: C (1st trimester), **D** (2nd and 3rd trimesters)

Lactation Category: S (likely)

- **Quinapril** and other ACEIs should be avoided during pregnancy if possible.
- When mother's disease requires treatment with **quinapril,** the lowest doses should be used followed by close monitoring of the fetus.

Quinidine gluconate-sulfate—(Quinaglute Dura-Tabs; Quinidex Extentabs; Quinora)

International Brand Name—Quinaglute Dura-tabs (South Africa)

Drug Class	Antiarrhythmics, class IA; Antiprotozoals
Indications	Atrial fibrillation, ventricular arrhythmia, SVT, malaria
Mechanism	Depresses phase 0 action potential; intraerythrocytic schizonticide
Dosage with Qualifiers	Atrial fibrillation—324-648mg PO q8-12h (gluconate), 200-300mg PO q4-6h (sulfate); adjust to therapeutic level of 2-6mcg/ml Ventricular arrhythmia—324-648mg PO q8-12h (gluconate), 200-300mg PO q4-6h (sulfate); adjust to therapeutic level of 2-6mcg/ml SVT—324-648mg PO q8-12h (gluconate), 200-300mg PO q4-6h (sulfate); adjust to therapeutic level of 2-6mcg/ml Life-threatening malaria—15mg/kg sulfate (or 24mg/kg gluconate) in 250ml 0.9 NS over 4h, then 7.5mg/kg sulfate (or 12mg/kg gluconate) 8h after the load given over 4h q8h ×7d • **Contraindications**—hypersensitivity to drug or class, myasthenia gravis, intraventricular conduction defects, complete AV block, history of TTP associated with **quinidine** or **quinine** • **Caution**—**succinylcholine,** incomplete AV block, sick sinus syndrome, digoxin toxicity, QT interval prolongation, CHF, hypomagnesemia, hypokalemia, G6PD deficiency, and hepatic or renal dysfunction
Maternal Considerations	There are no adequate reports or well-controlled studies of **quinidine** in pregnant women. All class IA agents should be administered with continuous cardiac monitoring in the hospital because of the risk of ventricular arrhythmia (torsades de pointes). **Quinidine** is a stereoisomer of quinine. It has a long record of safety during pregnancy, and is generally well tolerated. The clearance of **quinidine** is apparently unaffected by pregnancy. In women with severe *P. falciparum* malaria and hyperparasitemia, IV **quinidine** is often coupled with exchange transfusion, resulting in the clearing of the parasitemia and high survival rates. Therapeutic levels of **quinidine** inhibit pseudocholinesterase activity in pregnant women by 60-70%, necessitating caution if **succinylcholine** is to be used intraoperatively. ***Side effects*** include QT interval prolongation, torsades de pointes, AV block, cardiac arrest, respiratory arrest, ventricular arrhythmia, syncope, hypotension, hemolytic anemia, thrombocytopenia, thrombocytopenic purpura, agranulocytosis, SLE-like syndrome, optic neuritis, N/V, diarrhea, abdominal pain, dyspepsia, headache, fatigue, chest pain, blurred vision, rash, abnormal ECG, insomnia, tremor, and tinnitus.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. **Quinidine** crosses the human placenta, reaching an F:M ratio approaching unity over time. *In vitro*, it causes a dose-dependent relaxation of placental arteries and veins. **Quinidine** has been used successfully to correct fetal SVT and reverse hydrops. Elimination of maternal parasitemia does not necessarily mean elimination from the placenta. Rodent teratogenicity studies have not been performed.

Breastfeeding Safety

There are no adequate reports or well-controlled studies in nursing women. **Quinidine** is excreted into human milk with an M:P ratio near unity. It is estimated that the unsupplemented neonate would ingest 1.2mg/kg/d, or 1% of the total maternal daily dose. This is below the therapeutic dose prescribed to infants. Neonatal kinetics have not been studied.

Drug Interactions

Renal elimination is decreased by drugs that alkalinize the urine (carbonic anhydrase inhibitors, **sodium bicarbonate,** thiazide diuretics).

Levels are increased by use with **amiodarone** or **cimetidine.**

Very rarely, levels are decreased by use with **nifedipine.**

Hepatic elimination may be accelerated by use with drugs that induce CYP3A4 (e.g., **phenobarbital, phenytoin, rifampin**).

Levels rise when **ketaconazole** is given, perhaps because of CYP3A4 metabolic pathway competition.

Hepatic clearance is significantly reduced, with corresponding increases in serum levels and t/2, by **verapamil.**

Slows **digoxin** elimination and reduces the apparent volume of distribution. As a result, serum **digoxin** levels may double, requiring a decrease in the **digoxin** dose. Serum levels of **digitoxin** are also increased when used with **quinidine,** although the effect appears smaller.

Potentiates the anticoagulatory action of **warfarin,** and the anticoagulant dosage may need to be reduced.

Therapeutic serum levels of **quinidine** inhibit the action of CYP2D6, effectively converting extensive metabolizers into poor metabolizers. Caution must be exercised when **quinidine** is prescribed together with drugs metabolized by CYP2D6.

Increases serum levels of **procainamide.**

Increases serum **haloperidol** levels.

Perhaps because both are metabolized by CYP3A4, co-administration slows the metabolism of **nifedipine.** Interactions with other dihydropyridine calcium channel blockers (e.g., **felodipine, nicardipine, nimodipine**) have not been reported, but they are all dependent upon CYP3A4 for metabolism.

Quinidine's anticholinergic, vasodilating, and negative inotropic actions may be additive to those of other drugs with these effects, and antagonistic to those of drugs with cholinergic, vasoconstricting, and positive inotropic effects. For example, when **quinidine** and **verapamil** are used in doses that are each well tolerated as monotherapy, hypotension due to additive peripheral α blockade may occur.

Potentiates the actions of depolarizing neuromuscular blocking (e.g., **decamethonium, succinylcholine**) and nondepolarizing agents (e.g., **pancuronium,** *d*-**tubocurarine**). In addition, *in vitro* addition of **quinidine** to serum from pregnant women reduces the activity of pseudocholinesterase.

Diltiazem significantly decreases the clearance and increases the t/2 of **quinidine,** but **quinidine** does not alter the kinetics of **diltiazem.**

Grapefruit juice inhibits CYP3A4-mediated metabolism of **quinidine** to 3-hydroxyquinidine and should be avoided.

A decrease in dietary salt intake may lead to an increase in **quinidine.**

References

Hill LM, Malkasian GD Jr. Obstet Gynecol 1979; 54:366-8.
Joglar JA, Page RL. Drug Saf 1999; 20:85-94.
Kambam JR, Franks JJ, Smith BE. Am J Obstet Gynecol 1987; 157:897-9.
Omar HA, Rhodes LA, Ramirez R, et al. J Cardiovasc Electrophysiol 1996; 7:1197-203.
Procop GW, Jessen R, Hyde SR, Scheck DN. J Perinatol 2001; 21:128-30.
Spinnato JA, Shaver DC, Flinn GS, et al. Obstet Gynecol 1984; 64:730-5.

Summary

Pregnancy Category: C
Lactation Category: S (likely)
- **Quinidine** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Quinine—(Qm-260; Quin-Amino; Quinaminoph; Quinamm; Quinasul; Quindan; Quinite; Quiphile)

International Brand Name—Biquinate (Australia); Genin (Thailand); Kinin (Denmark, Sweden); Kininh (Germany); Myoquin (Australia); Q200 (New Zealand); Q300 (New Zealand); Quinate (Australia); Quinbisu (Australia); Quinimax (South Africa); Quinoctal (Australia); Quinsul (Australia)

Drug Class

Antimalarials; Antiprotozoals

Indications

Malaria

Mechanism

Unknown; schizontocidal

Dosage with Qualifiers

Malaria—650mg PO q8h ×3-7d

NOTE: use with other antimalarial agents.

- **Contraindications**—hypersensitivity to drug, class, or **mefloquine** or **quinidine;** G6PD deficiency, optic neuritis, tinnitus, thrombocytopenic purpura, hypoglycemia, myasthenia gravis
- **Caution**—arrhythmias

Maternal Considerations

Malaria is a major cause of maternal/perinatal morbidity and death in regions of the world. Treatment dramatically reduces those risks. **Quinine** is used extensively in developing countries for the treatment of malaria during pregnancy. Its metabolism and clearance are unaltered by pregnancy. It is one of a limited number of drugs used where multidrug-resistant *P. falciparum* is endemic. However, **quinine** has a higher treatment failure rate than **chloroquine. Quinine** toxicity is associated with abortion. ***Side effects*** include cinchonism, hemolysis, prolonged QT interval, edema, hypoglycemia, thrombocytopenia, agranulocytosis, optic nerve damage, N/V, diarrhea, headache, confusion, hypotension, altered color perception, photosensitivity, rash, pruritus, delirium, tinnitus, and mydriasis.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. **Quinine** crosses the placenta, achieving an F:M ratio of 0.32 ± 0.14. The risks of pregnancy loss, IUGR, or malformation are unchanged after 1st trimester exposure for malaria treatment. Congenital malformations reported in the human were associated with large doses (up to 30g) taken to trigger abortion. In about half of these reports, the abnormality was deafness related to auditory nerve hypoplasia. Other abnormalities reported included limb anomalies, visceral defects, and visual changes. Teratogenic effects are observed in rabbits and guinea pigs but not mice, rats, dogs, and monkeys. Congenital malaria is rare, but elimination of the maternal parasitemia does not guarantee elimination from the placenta. **Quinine** is used for the treatment of neonatal malaria. Considering the kinetics of placental transport, fetal toxicity seems a low probability at recommended doses.

Breastfeeding Safety

There are no adequate reports or well-controlled studies in nursing women. **Quinine** enters human breast milk, achieving an M:P ratio of 0.31 (range 0.11-0.53). The total daily dose ingested by the unsupplemented neonate is between 1 and 3mg/d. There are no reports of toxicity in breastfed newborns.

Drug Interactions

Antacids containing aluminum and/or magnesium may delay or decrease absorption and should be avoided.

The oral clearance of **quinine** decreases and the mean elimination t/2 increases when given with **cimetidine** but not with **ranitidine.** Should **quinine** be given with an H_2-receptor blocker, **ranitidine** is preferred over **cimetidine.**

Ketoconazole increases the mean **quinine** AUC by 45% and lowered oral clearance by 31%. Patients should be monitored closely for adverse reactions.

Erythromycin inhibits the metabolism of **quinine** *in vitro* and is thus likely to increase plasma quinine concentrations. It should be avoided.

Rifampin lowers the **quinine** AUC by 75%. Therefore the use of **rifampin** with **quinine** should be avoided.

Tetracycline increases the mean plasma **quinine** concentrations by 2-fold. Patients should be monitored closely for adverse reactions.

Troleandomycin increases the AUC by 87%, lowering oral clearance by 45%. **Troleandomycin** use should be avoided.

Urinary alkalinizing agents may increase plasma **quinine** concentrations.

Has the potential to inhibit the metabolism of drugs that are substrates of CYP3A4 and CYP2D6, as well as inhibit the biliary excretion of drugs such as **digoxin.**

Increases the plasma C_{max} and AUC of **carbamazepine** (56% and 104%, respectively) and **phenobarbital** (53% and 81%, respectively), but not **phenytoin.** If use with **carbamazepine** or **phenobarbital** cannot be avoided, frequent monitoring of the anticonvulsant drug concentrations is recommended. Patients should also be monitored closely for adverse reactions associated with these anticonvulsants. **Carbamazepine, phenobarbital,** and **phenytoin** are CYP3A4 inducers and may decrease **quinine** plasma concentrations.

Elevated plasma **astemizole** was reported in a subject who experienced torsades de pointes after receiving 3 doses of **quinine** for nocturnal leg cramps concomitantly with chronic **astemizole.** The use of **quinine** with **astemizole** and other CYP3A4 substrates with QT prolongation potential (e.g., **cisapride, halofantrine, pimozide, quinidine, terfenadine**) should also be avoided.

Decreased the metabolism of **desipramine** in patients who were extensive CYP2D6 metabolizers, but had no effect in patients who were poor CYP2D6 metabolizers. Although clinical drug interaction studies have not been conducted, antimalarial doses of **quinine** may inhibit the metabolism of other drugs that are CYP2D6 substrates (e.g., **flecainide, debrisoquine, dextromethorphan, metoprolol, paroxetine**).
Increased the **digoxin** AUC by 33%. Thus, **digoxin** concentrations should be closely monitored, and the **digoxin** dose adjusted, as necessary.
Increased the **mefloquine** AUC by 22% and significantly prolonged the QTc interval. The concomitant administration of **mefloquine** and **quinine** may produce ECG abnormalities (including QTc prolongation) and may increase the risk of seizures.
Cinchona alkaloids such as **quinine** have the potential to depress hepatic enzyme synthesis of vitamin K–dependent coagulation pathway proteins and enhance the action of **warfarin** and other oral anticoagulants. **Quinine** may also interfere with the anticoagulant effect of **heparin.** Thus, the PT, PTT, or INR should be closely monitored.
Quinine may produce an elevated value for urinary 17-ketogenic steroids when the Zimmerman method is used.

References

Abdelrahim II, Adam I, Elghazali G, et al. J Clin Pharm Ther 2007; 32:15-9.
McCready R, Thwai KL, Cho T, et al. Trans R Soc Trop Med Hyg 2002; 96:180-4.
Moran NF, Couper ID. S Afr Med J 1999; 89:943-6.
Phillips RE, Looareesuwan S, White NJ, et al. Br J Clin Pharmacol 1986; 21:677-83.
Phillips-Howard PA, Wood D. Drug Saf 1996; 14:131-45.
Zucker JR, Lackritz EM, Ruebush TK 2nd, et al. Am J Trop Med Hyg 1996; 55:655-60.

Summary

Pregnancy Category: X
Lactation Category: S (likely)

- Malaria is a major cause of maternal/perinatal illness.
- **Quinine** is an effective agent for the treatment of malaria.
- Except for the tetracyclines, there is no evidence that any of the antimalarial drugs in use are teratogenic at the recommended doses.
- **Quinine** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Rabeprazole—(Aciphex)

International Brand Name—Gastrodine (Chile); Pariet (Australia, Colombia, France, Germany, Indonesia, Mexico, Peru, Philippines, South Africa, Taiwan, Thailand); Rabec (Argentina); Rabeloc (India)

Drug Class

Antiulcer agents; Gastrointestinals; Proton pump inhibitors

Indications

GERD, esophagitis, duodenal ulcer, hypersecretory conditions, stress ulcer, ulcer prophylaxis

Mechanism

Hydrogen-potassium ATP-ase inhibitor

Dosage with Qualifiers

GERD—20mg PO qd or bid ×4-8w; may repeat for an additional 8w if needed
Erosive esophagitis—20mg PO qd or bid ×4-8w; may repeat for an additional 8w if needed
Duodenal ulcer—20mg PO qd or bid ×4w; may repeat for an additional 4w if needed
Hypersecretory conditions—60mg PO qd

NOTE: do not crush or chew.

- **Contraindications**—hypersensitivity to drug or class
- **Caution**—hepatic dysfunction, long-term use

Maternal Considerations

GERD and/or heartburn occur in 45-85% of women during pregnancy. The effect of estrogen and **progesterone** on lower esophageal sphincter tone is a recognized factor. The treatment for GERD is the reduction of gastric acidity. There is no published experience with **rabeprazole** during pregnancy. Other proton pump inhibitors are generally considered effective treatment for GERD during pregnancy. There are no reported adverse effects. Proton pump inhibitors are first-line agents for the prevention of "aspiration syndrome" during general anesthesia.
Side effects include hepatic failure, blood dyscrasias, headache, and diarrhea.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **rabeprazole** crosses the human placenta. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically.

Breastfeeding Safety

There is no published experience in nursing women. It is unknown whether **rabeprazole** enters human breast milk. It is concentrated in rodent breast milk.

Drug Interactions

May augment the INR and PT increase when used with **warfarin.** Produces sustained inhibition of gastric acid secretion. An interaction with compounds that are dependent on gastric pH for absorption may occur due to the magnitude of acid suppression. For example, it decreases by almost ⅓ the bioavailability of **ketoconazole** and increases the AUC and C_{max} for **digoxin** by 19% and 29%, respectively. Therefore, patients may need to be monitored when such drugs are taken concomitantly.
In a clinical study in patients categorized by CYP2C19 genotype (n = 6 per genotype category), gastric acid suppression was higher in poor metabolizers compared to extensive metabolizers. Use with **amoxicillin** and **clarithromycin** resulted in increased plasma levels of **rabeprazole** and 14-hydroxyclarithromycin. Use with **clarithromycin** or **pimozide** is contraindicated.

References	There is no published experience in pregnancy or during lactation.
Summary	**Pregnancy Category: B** **Lactation Category: U** • **Rabeprazole** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk. • Proton pump inhibitors are agents of choice for the treatment of GERD in nonpregnant patients. • Safety data are limited to animal studies and case reports. As a result, proton pump inhibitors are recommended during pregnancy only for the treatment of severe, intractable GERD. • There are alternative agents for which there is more experience during pregnancy and lactation.

Rabies immune globulin, human—(BayRab; Hyperab; Imogam rabies)

International Brand Name—Bayer Bayrab Rabies Immune Globulin (Philippines); Bayrab (Canada); Imogam (Australia); Imogan Rabia (Spain); Rabigam (South Africa); Rabuman Berna (Philippines, Thailand)

Drug Class	Antivirals; Immune globulins
Indications	Rabies exposure
Mechanism	Passive immunization
Dosage with Qualifiers	Rabies exposure—20IU/kg (0.133ml/kg) concurrent with the 1st vaccine dose; if feasible, up to ½ the dose should be thoroughly infiltrated in the area of the wound and the rest IM in the gluteus *NOTE: may also be given up to day 7 after 1st vaccine dose; never give in the same syringe or site as vaccine.* • **Contraindications**—none known • **Caution**—hypersensitivity to drug or class, asthma
Maternal Considerations	Over 50% of the rabies cases among Americans result from exposure to dogs outside the US. Prevention is key. Rabies is almost universally fatal once it occurs. **Rabies immune globulin** is prepared from the plasma of donors hyperimmunized with **rabies vaccine.** The product is standardized to an average potency of 150IU/ml. **Rabies vaccine** and **rabies immune globulin** should be given to all suspected of rabies exposure unless previously immunized with **rabies vaccine** and with confirmed adequate antirabies titers. It has been used successfully without complication during pregnancy. The reported adverse reaction rate is similar in pregnant and nonpregnant women. ***Side effects*** include injection site reaction and mild fever.
Fetal Considerations	There are no adequate reports or well-controlled studies of **rabies immune globulin** in human fetuses. Antirabies IgG likely crosses the human placenta. Fetal infection with rabies is reported. It is not known whether transfer provides any level of protection to the perinate. Animal reproduction studies have not been performed.
Breastfeeding Safety	There is no published experience in pregnancy. It is unknown whether **rabies immune globulin** enters human breast milk. However, other IgG antibodies are excreted into breast milk.

Drug Interactions

Repeated doses of **rabies immune globulin** should not be administered once vaccine treatment has been initiated as this could prevent the full expression of active immunity expected from the rabies vaccine.
Other antibodies in the **rabies immune globulin** preparation may interfere with the response to live vaccines such as measles, mumps, polio, or rubella. Immunization with live vaccines should not be given within 3mo after **rabies immune globulin** administration.

References

Chabala S, Williams M, Amenta R, Ognjan AF. Am J Med 1991; 91:423-4.
Chutivongse S, Wilde H, Benjavongkulchai M, et al. Clin Infect Dis 1995; 20:818-20.
Sipahioglu U, Alpaut S. Mikrobiyol Bul 1985; 19:95-9.
Sudarshan MK, Giri MS, Mahendra BJ, et al. Hum Vaccin 2007; 3:87-9.

Summary

Pregnancy Category: C
Lactation Category: S (likely)

- Rabies remains a problem in many locales; it is almost uniformly fatal once manifest.
- Postexposure prophylaxis with both immune globulin and vaccine reduces the risk of disease.
- Pregnant women respond to **rabies immune globulin.**

Rabies vaccine—(Imovax Rabies; RabAvert)

International Brand Name—Berirab P (Philippines); Imovax Rabbia (Italy); Lyssavac N Berna (Ecuador, Hong Kong, Malaysia, Peru, Philippines, Thailand); Rabies-Imovax (Finland, Sweden); Rabipur (Austria, Czech Republic, England, Germany, India, Ireland, Israel); Rabuman Berna (Ecuador); Rasilvax (Italy); Vacuna Antirrabica Humana (Colombia)

Drug Class

Vaccines

Indications

Rabies exposure

Mechanism

Active immunization

Dosage with Qualifiers

Rabies exposure, booster immunization—1ml IM on days 0, 7, 21, and 28 after exposure
Rabies exposure, immunization—1ml IM booster

NOTE: for IM use only.

- **Contraindications**—none known
- **Caution**—hypersensitivity to bovine gelatin, chicken protein, neomycin, chlortetracycline, amphotericin B

Maternal Considerations

Over 50% of the rabies cases among Americans result from exposure to dogs outside the US. It is almost universally fatal once manifest. **Rabies vaccine** is an inactivated vaccine grown in chicken fibroblasts. **Rabies vaccine** and **rabies immune globulin** should be given to all suspected of rabies exposure unless previously immunized with **rabies vaccine** producing confirmed adequate antirabies titers. There are no data on the interchangeable use of different rabies vaccines in a single pre- or postexposure series. Thus, vaccine from a single manufacturer should be used for the complete series if possible. The vaccine has been used successfully during pregnancy, and pregnant women respond immunologically at least as well as nonpregnant women.

The reported adverse reaction rate is similar in pregnant and nonpregnant women.
Side effects include anaphylaxis, paralysis, and muscular sclerosis.

Fetal Considerations

There are no adequate reports or well-controlled studies of **rabies vaccine** in human fetuses. Fetal rabies is reported. It is likely the IgG antibody produced in response to the vaccine crosses the placenta. It is not known whether transfer provides any level of perinatal protection. In one trial, intrauterine growth and pregnancy outcome were normal in women vaccinated for postexposure prophylaxis. There were no adverse vaccine effects reported in over 250 pregnancies.

Breastfeeding Safety

There is no published experience in nursing women. It is unknown whether **rabies vaccine** enters human breast milk. It is likely the antibodies produced in response to the vaccine are excreted into the milk. It is generally accepted that the woman can resume breastfeeding once the vaccination series has begun.

Drug Interactions

Corticosteroids, other immunosuppressive agents, antimalarials, and immunosuppressive illnesses interfere with the development of active immunity after vaccination, and may diminish the protective efficacy of the vaccine. Preexposure prophylaxis should be administered to such persons with the understanding their immune response may be inadequate.
Immunosuppressive agents should not be administered during postexposure therapy unless essential for the treatment of other conditions. When rabies postexposure prophylaxis is administered to persons receiving corticosteroids or other immunosuppressive therapy, or who are immunosuppressed, it is important that a serum sample be tested for rabies antibody to ensure that an acceptable antibody response has been induced.
Rabies immune globulin must not be administered at more than the recommended dose, since the response to active immunization may be impaired.

References

Chabala S, Williams M, Amenta R, Ognjan AF. Am J Med 1991; 91:423-4.
Chutivongse S, Wilde H, Benjavongkulchai M, et al. Clin Infect Dis 1995; 20:818-20.
Sipahioglu U, Alpaut S. Mikrobiyol Bul 1985; 19:95-9.
Sudarshan MK, Giri MS, Mahendra BJ, et al. Hum Vaccin 2007; 3:87-9.
Sudarshan MK, Madhusudana SN, Mahendra BJ. J Commun Dis 1999; 31:229-36.
Sudarshan MK, Madhusudana SN, Mahendra BJ, et al. Indian J Publ Health 1999; 43:76-8.
Toouey S. Travel Med Infect Dis 2007; 5:327-48.

Summary

Pregnancy Category: X
Lactation Category: U

- Rabies remains a problem in many locales; it is almost uniformly fatal.
- Postexposure prophylaxis with both immune globulin and vaccine reduces the risk of disease and may be lifesaving.
- **Rabies vaccine** is a heat-killed product and not contraindicated during pregnancy.
- Pregnant women respond to **rabies vaccine** at least as well as matched nonpregnant women.
- There is no evidence of fetal jeopardy from vaccination.

Raloxifene—(Evista)

International Brand Name—Bonmax (India); Celvista (Thailand); Evista (Hong Kong, Indonesia, Israel, Korea, Malaysia, Philippines, Singapore, Taiwan); Loxar (Uruguay); Loxifen (Paraguay); Raxeto (Argentina)

Drug Class	Calcium metabolism agents; SERMs
Indications	Postmenopausal osteoporosis, prophylaxis and treatment
Mechanism	Estrogen receptor modulator inhibiting bone resorption and turnover
Dosage with Qualifiers	Postmenopausal osteoporosis—60mg PO qd *NOTE: take with vitamin D (400U qd) and calcium.* • **Contraindications**—hypersensitivity to drug or class, pregnancy, DVT, HRT or OCP use • **Caution**—unknown
Maternal Considerations	The decline in estrogen after oophorectomy and menopause enhances bone resorption and accelerates bone loss. Osteoporosis is underdiagnosed and undertreated. SERMs are a new family of drugs for the management of estrogen-related pathology. **Raloxifene** decreases resorption of bone and reduces biochemical markers of bone turnover to the premenopausal range. **Raloxifene** does not stimulate the endometrium and may reduce the risk of ovarian cancer. It does not appear to affect the patient's interest in sex, desire for or frequency of sexual activity, or the frequency or intensity of orgasm. Nor does **raloxifene** interfere with estrogen and non-hormonal vaginal cream moisturizers in postmenopausal vaginal atrophy. Long-term effects are under study. There is no published experience during pregnancy. ***Side effects*** include PE, DVT, hot flashes, arthralgia, flu-like symptoms, sinusitis, nausea, weight gain, pharyngitis, depression, cough, leg cramps, insomnia, and dyspepsia.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. It is not known whether **raloxifene** crosses the human placenta. Studies in rodents reveal an increase in several types of defects, including heart, brain, and skeleton. Different from estrogen, **raloxifene** does not alter the organization of the neuronal system related to sexual receptivity in rodents.
Breastfeeding Safety	There is no published experience in nursing women. It is unknown whether **raloxifene** enters human breast milk.
Drug Interactions	Use with **cholestyramine** is not recommended. **Cholestyramine** is an anion exchange resin and causes a 60% reduction in the absorption and enterohepatic cycling of **raloxifene.** Use with **warfarin** was assessed in a single-dose study where it had no effect on the pharmacokinetics of **warfarin,** but decreased the PT some 10%. The PT should thus be monitored more closely when starting or stopping therapy with **raloxifene.** In the osteoporosis treatment trial, there were no clinically relevant effects of warfarin co-administration on plasma concentrations of raloxifene.
References	Modugno F, Ness RB, Ewing S, Causley JA. Obstet Gynecol 2003; 101:353-61. Parsons A, Merritt D, Rosen A, et al. Obstet Gynecol 2003; 101:346-52.

Pinilla L, Barreiro ML, Tena-Sempere M, Aguilar E. Neurosci Lett 2002; 329:285-8.
Vestergaard P, Rejnmark L, Mosekilde L. Osteoporos Int 2005; 16:134-41.

Summary

Pregnancy Category: X
Lactation Category: U

- There are no indications for **raloxifene** during pregnancy.

Ramipril—(Altace)

International Brand Name—Cardace (India); Corpril (Thailand); Delix (Germany); Hytren (Austria); Pramace (Sweden); Quark (Italy); Ramace (Australia, Belgium, Denmark, Finland, Korea, Mexico, Netherlands, Philippines, South Africa, Thailand); Triatec (Denmark, France, Greece, Indonesia, Ireland, Italy, Portugal, Sweden, Switzerland); Tritace (Austria, Belgium, Colombia, Costa Rica, Czech Republic, Denmark, Dominican Republic, Ecuador, El Salvador, England, Guatemala, Honduras, Hong Kong, Ireland, Korea, Mexico, Netherlands, New Zealand, Nicaragua, Panama, Philippines, Puerto Rico, Taiwan); Unipril (Italy); Vesdil (Germany)

Drug Class — ACEI/A2R-antagonists

Indications — Hypertension, post-MI CHF, CV risk reduction

Mechanism — ACE inhibition

Dosage with Qualifiers

Hypertension—begin 2.5mg PO qd; max 20mg PO qd
Post-MI CHF—begin 2.5mg PO bid ×7d, then 5mg PO bid
CV risk reduction—begin 2.5mg PO qd ×7d, then 10mg PO qd; indicated for patients >55y with either CAD, CVA, or PVD or with diabetes mellitus and at least 1 other risk factor

NOTE: renal dosing.

- **Contraindications**—hypersensitivity to drug or class, angioedema
- **Caution**—severe CHF, renal dysfunction, renal artery stenosis, collagen vascular disease, hyponatremia and volume depletion

Maternal Considerations

Some ACEIs decrease proteinuria and preserve renal function in patients with hypertension and diabetes mellitus to a greater extent than other antihypertensive agents. More recently, they were shown to decrease the progression of nephropathy in normotensive patients with type 2 diabetes mellitus. There are no adequate reports or well-controlled studies of **ramipril** in pregnant women. In general, ACEIs are avoided during pregnancy because of fetal risks. The lowest effective dose should be used if **ramipril** is required for BP control during pregnancy.
Side effects include angioedema, severe hypotension, hyperkalemia, hepatotoxicity, pancreatitis, agranulocytosis, neutropenia, cough, dizziness, fatigue, N/V, myalgias, arthralgias, and URI symptoms.

Fetal Considerations

There is no published experience in human fetuses. **Ramipril** likely crosses the human placenta as similar agents do. Transfer was described as low in one rodent study. In contrast to conclusions based on earlier data, adverse fetal effects occur even after 1st trimester exposure to ACEIs, for which the relative risk is 2.7. Exposure is associated with CV and CNS disorders.
No such increase is seen with other classes of antihypertensive agents. Later exposure is associated with cranial hypoplasia, anuria, reversible or irreversible renal failure, death, oligohydramnios, prematurity, IUGR, and PDA. The mechanism of renal

dysfunction is likely related to fetal hypotension associated with prolonged decreased glomerular filtration. There is inadequate study to decide whether **ramipril** is typical of ACEIs. However, the one published rodent study is reassuring. If oligohydramnios is detected, **ramipril** should be discontinued unless lifesaving for the mother. Antenatal surveillance should be initiated (e.g., BPP) if the fetus is potentially viable. Oligohydramnios may not appear until after the fetus has irreversible injury. Neonates exposed *in utero* to ACEIs should be observed closely for hypotension, oliguria, and hyperkalemia. If oliguria occurs despite adequate pressure and renal perfusion, exchange transfusion or peritoneal dialysis may be required.

Breastfeeding Safety

There is no published experience in nursing women. It is unknown whether **ramipril** enters human breast milk. It is described as low in rodents.

Drug Interactions

Use with NSAIDs has been associated with worsening of renal failure and an increased serum potassium.
May be associated with hypotension when used with diuretics, especially if the diuretic was recently intiated. The possibility can be minimized by either discontinuing the diuretic or increasing the salt intake prior to initiation of **ramipril.**
May attenuate potassium loss caused by thiazide diuretics. Potassium-sparing diuretics (e.g., **amiloride, spironolactone, triamterene**) or potassium supplements can increase the risk of hyperkalemia. The patient's serum potassium should be monitored frequently.
Increased serum **lithium** levels and symptoms of **lithium** toxicity have been reported in patients receiving ACEIs during therapy with **lithium.** These drugs should be used together with caution, and frequent monitoring of serum **lithium** levels.

References

Cooper WO, Hernandez-Diaz S, Arbogast PG, et al. N Engl J Med 2006; 354:2443-51.
Eckert HG, Badian MJ, Gantz D, et al. Arzneimittelforschung 1984; 34:1435-47.

Summary

Pregnancy Category: C (1st trimester), **D** (2nd and 3rd trimesters)
Lactation Category: U

- **Ramipril** and other ACEIs should be avoided throughout pregnancy if possible.
- 1st trimester exposure is likely associated with an increase in CV and CNS abnormalities.
- Neonatal skull hypoplasia and reversible or irreversible renal failure are the most frequent fetal consequences of ACEIs during late pregnancy.
- When the mother's disease requires treatment with **ramipril,** the lowest doses should be used followed by close monitoring of the fetus.

Ranitidine—(Ranitiget; Zantac)

International Brand Name—Azanplus (Colombia); Pylorid (Australia, Canada, Denmark, England, Hong Kong, Ireland, Israel, Netherlands, Thailand); Pylorid 400 (Philippines); Pylorisin (Austria)

Drug Class — Antihistamines, H_2; Antiulcer agents; Gastrointestinals

Indications — Duodenal or gastric ulcer, erosive esophagitis, GERD, dyspepsia

Mechanism — H_2 antagonist

Dosage with Qualifiers

Duodenal or gastric ulcer—150mg PO bid
Erosive esophagitis—150mg PO qid
GERD—150mg PO bid
Dyspepsia—75mg PO qd or bid

NOTE: renal dosing; may be combined with ***bismuth subsalicylate*** *(Tritec).*

- **Contraindications**—hypersensitivity to drug or class, porphyria
- **Caution**—hepatic or renal dysfunction

Maternal Considerations

Pregnant women with symptomatic GERD should be managed aggressively with lifestyle and dietary modification. Antacids are first-line therapy. Should they fail, **ranitidine** or **cimetidine** are second-line options effective during pregnancy. **Ranitidine** has also been used successfully during pregnancy for the treatment of Zollinger-Ellison syndrome. It is used in many labor wards every 6h to reduce the risk of acid aspiration.
Side effects include hepatotoxicity, thrombocytopenia, myalgia, headache, N/V, diarrhea, constipation, vertigo, dizziness, malaise, dry skin, rash, and confusion.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. **Ranitidine** crosses the human placenta, achieving in the isolated perfused cotyledon about 40% of the level of antipyrene. Epidemiologic study reveals no increased prevalence of adverse fetal outcomes following 1st trimester exposure. Rodent studies are reassuring, noting no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically. **Ranitidine** reduces fetal gastric pH when administered to pregnant rabbits, thus suggesting placental transfer.

Breastfeeding Safety

There is no published experience in nursing women. While **ranitidine** is concentrated in human breast milk, no adverse effects are reported. **Ranitidine** is approved for use in pediatric practice.

Drug Interactions

Clarithromycin increases plasma **ranitidine** concentrations by 50-60% and 14-hydroxyclarithromycin plasma concentrations by almost ⅓.

References

Aslan A, Karaguzel G, Uysal N, et al. Am J Perinatol 1999; 16:209-15.
Dicke JM, Johnson RF, Henderson GI, et al. Am J Med Sci 1988; 295:198-206.
Garbis H, Elefant E, Diav-Citrin O, et al. Reprod Toxicol 2005; 19:453-8.
Hagemann TM. J Hum Lact 1998; 14:259-62.
Kearns GL, McConnell RF Jr, Trang JM, Kluza RB. Clin Pharm 1985; 4:322-4.

Larson JD, Patatanian E, Miner PB Jr, et al. Obstet Gynecol 1997; 90:83-7.
Ruigomez A, Garcia Rodriguez LA, Cattaruzzi C, et al. Am J Epidemiol 1999; 150:476-81.
Stewart CA, Termanini B, Sutliff VE, et al. Am J Obstet Gynecol 1997; 176:224-33.

Summary

Pregnancy Category: B
Lactation Category: S (likely)
- **Ranitidine** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.
- Medications used for treating GERD are not routinely tested in randomized, controlled trials in pregnant women.

Remifentanil—(Ultiva)

International Brand Name—None identified.

Drug Class

Analgesics, narcotic

Indications

Anesthesia

Mechanism

Binds opiate receptors

Dosage with Qualifiers

Anesthesia:
Induction—0.5-1mcg/kg/min IV; anesthesia induced when given with a hypnotic and a muscle relaxant to avoid chest rigidity
Maintenance—0.05-2mcg/kg/min IV; usually given along with inhaled or IV anesthetic agent
Postoperative—0.025-0.2mcg/kg/min IV
Sedation—0.025-0.2mcg/kg/min IV; usually given with sedative-hypnotic (e.g., **propofol**)

NOTE: onset <1min, duration 5-10min, peak 1-5min.

- **Contraindications**—hypersensitivity to drug or class, epidural or intrathecal use
- **Caution**—respiratory depression

Maternal Considerations

Unlike other opioids, **remifentanil** undergoes rapid hydrolysis by nonspecific blood and tissue esterases. Even after a 4h infusion, the functional t/2 is only 4min. This characteristic suggests a potential for use in obstetrics. In a pilot study, **remifentanil** provided superior pain relief to laboring women when given by PCA compared to IM **meperidine.** However, **remifentanil** is difficult to titer in clinical practice, and produces high levels of sedation and excess rates of maternal oxygen desaturation. It is more often used as a supplement to neuraxial anesthesia during cesarean delivery.
Side effects include apnea, chest wall rigidity, ventricular arrhythmia, bradycardia, hypotension, dependency, seizures, N/V, shivering, fever, dizziness, constipation, headache, blurred vision, pruritus, oliguria, confusion, tachycardia, agitation, anxiety, and biliary spasm.

Fetal Considerations

Remifentanil crosses the human placenta, achieving an F:M ratio approximating 0.5. Mean clearance approximates 93 ml/min/kg. Thus, while **remifentanil** crosses the placenta, it appears to be rapidly metabolized, redistributed, or both. Neonatal sedation is reported. Rodent studies are reassuring, revealing no evidence of

teratogenicity or IUGR despite the use of doses higher than those used clinically.

Breastfeeding Safety

There is no published experience in nursing women. It is unknown whether **remifentanil** enters human breast milk. It is excreted into rodent breast milk. Considering the indication and t/2, one-time **remifentanil** use is unlikely to pose a clinically significant risk to the breastfeeding neonate.

Drug Interactions

Remifentanil may enhance the effect of other CNS depressants.

References

Kan RE, Hughes SC, Rosen MA, et al. Anesthesiology 1998; 88:1467-74.
Thurlow JA, Laxton CH, Dick A, et al. Br J Anaesth 2002; 88:374-8.
Volmanen P, Akural EI, Raudaskoski T, Alahuhta S. Anesth Analg 2002; 94:913-7.

Summary

Pregnancy Category: C
Lactation Category: S (likely)

- There are alternative agents with a higher safety profile for which there is more experience regarding use during pregnancy and lactation.

Repaglinide—(Prandin)

International Brand Name—GlucoNorm (Canada); NovoNorm (Argentina, Australia, Brazil, Chile, China, Colombia, Hong Kong, Indonesia, Korea, Malaysia, Mexico, Paraguay, Philippines, Singapore, Taiwan, Thailand, Uruguay); Prandin (Brazil); Rapilan (India); Sestrine (Argentina)

Drug Class

Adrenergic antagonists; Antidiabetic agents

Indications

Diabetes mellitus type 2

Mechanism

ATP-dependent potassium channel antagonist that stimulates islet cell insulin release in a glucose-dependent manner

Dosage with Qualifiers

Diabetes mellitus type 2—0.5-4mg PO 5-30min qac; max 16mg/d

NOTE: titer to glucose profile.

- **Contraindications**—hypersensitivity to drug or class, IDDM, ketoacidosis
- **Caution**—severe renal disease

Maternal Considerations

The published experience during pregnancy with **repaglinide** is limited to isolated case reports. Its clearance is lower in women than in men. **Insulin** remains the standard agent for the treatment of hyperglycemia during pregnancy. However, a growing body of research indicates that some oral hypoglycemic agents such as **glyburide** may be equally effective and safe, while more convenient.
Side effects include hypoglycemia, pancreatitis, Stevens-Johnson syndrome, hemolytic anemia, hepatic dysfunction, headache, URI symptoms, N/V, constipation, diarrhea, dyspepsia, myalgias, and chest pain.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **repaglinide** crosses the

human placenta. Rodent studies are reassuring, revealing no evidence of teratogenicity. However, an increased risk of IUGR may be secondary to chronic maternal hypoglycemia.

Breastfeeding Safety

There is no published experience in nursing women. It is unknown whether **repaglinide** enters human breast milk. It does enter rat milk and is associated with skeletal deformities in the feeding pups.

Drug Interactions

Metabolism may be inhibited by CYP3A4 inhibitors (e.g., **ketoconazole, miconazole**) and antibacterial agents (e.g., **clarithromycin, erythromycin**). Drugs that induce CYP3A4 (e.g., barbiturates, **carbamezapine, rifampin**) may increase **repaglinide** metabolism.

Use with **gemfibrozil** may significantly increase **repaglinide** levels. Patients taking **repaglinide** should not start taking **gemfibrozil;** patients taking **gemfibrozil** should not start taking **repaglinide.** Concomitant use may result in enhanced and prolonged blood glucose–lowering effects of **repaglinide.**

Rare post-marketing events of serious hypoglycemia have been reported.

The hypoglycemic action of oral blood glucose–lowering agents may be potentiated by certain drugs, including β-adrenergic blocking agents, **chloramphenicol,** coumarins, MAOIs, NSAIDs and other drugs that are highly protein bound, **probenecid,** salicylates, and sulfonamides. The patient should be observed closely for hypoglycemia. When such drugs are withdrawn, the patient should be observed closely for loss of glycemic control.

Certain drugs tend to produce hyperglycemia and may lead to loss of glycemic control. These drugs include the calcium channel blocking drugs, corticosteroids, estrogens, **isoniazid,** nicotinic acid, oral contraceptives, phenothiazines, **phenytoin,** thiazides and other diuretics, sympathomimetics, and thyroid products. When these drugs are withdrawn, the patient should be observed closely for hypoglycemia.

References

Mollar-Puchades MA, Martin-Cortes A, Perez-Calvo A, Diaz-Garcia C. Diabetes Obes Metab 2007; 9:146-7.

Napoli A, Ciampa F, Colatrella A, Fallucca F. Diabetes Care 2006; 29:2326-7.

Viertel B, Guttner J. Arzneimittelforschung 2000; 50:425-40.

Summary

Pregnancy Category: C
Lactation Category: U

- **Repaglinide** should be avoided during pregnancy and lactation until additional research supports its use.

Reserpine—(Reserpaneed; Serpalan; Serpasil; Serpatabs; Serpate; Serpivite)

International Brand Name—Maviserpin (Mexico); Rauserpine (Taiwan); Rauverid (Philippines); Serpasil (Canada, Indonesia); Serpasol (Spain)

Drug Class	Adrenergic antagonists, other; Antihypertensives
Indications	Hypertension, adjunct for psychosis
Mechanism	Depletes catecholamine and 5-HT stores
Dosage with Qualifiers	Hypertension—begin 0.5mg PO qd ×1-2w, then 0.1-0.25mg PO qd Psychiatric disorders—begin 0.5mg PO qd *NOTE: discontinue with first signs of depression.* • **Contraindications**—hypersensitivity to drug or class, depression (especially with suicidal tendencies), active peptic ulcer, active ulcerative colitis, electroconvulsive therapy • **Caution**—history of either peptic ulcer or ulcerative colitis; gallstones; renal insufficiency; anesthesia; use of **digoxin** or **quinidine,** or other antihypertensives
Maternal Considerations	**Reserpine** is a pure crystalline alkaloid of rauwolfia. It is a second-line agent for the treatment of hypertension. **Reserpine** is also used for the treatment of cerebral vasospasm, migraines, Raynaud's syndrome, refractory depression, tardive dyskinesia, and thyrotoxic crisis. There is only limited study during pregnancy. ***Side effects*** include N/V, diarrhea, anorexia, dryness of mouth, hypersecretion, arrhythmias, syncope, angina-like symptoms, bradycardia, edema, dyspnea, epistaxis, nasal congestion, dizziness, headache, paradoxical anxiety, depression, nervousness, nightmares, drowsiness, myalgias, weight gain, deafness, and pruritus.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. **Reserpine** crosses the human placenta. It can increase neonatal respiratory tract secretions, and cause nasal congestion, cyanosis, and anorexia. While it is unclear whether **reserpine** is a human teratogen, rodent studies reveal evidence of teratogenicity and embryotoxicity. It is also tumorigenic.
Breastfeeding Safety	**Reserpine** is excreted in human breast milk. Increased respiratory tract secretions, nasal congestion, cyanosis, and anorexia can occur in breastfed infants.
Drug Interactions	MAOIs should be avoided or used with extreme caution. Should be used cautiously with **digitalis** and **quinidine,** since cardiac arrhythmias have occurred with rauwolfia preparations. Use with other antihypertensive agents necessitates careful titration of dosage with each agent. Use with TCAs may decrease the antihypertensive effect of **reserpine.** The action of direct-acting amines (e.g., **epinephrine, isoproterenol, metaraminol, phenylephrine**) may be prolonged. The action of indirect acting amines (e.g., amphetamines, **ephedrine, tyramine**) is inhibited.

References	Southern African Hypertension Society Executive Committee 2000. S Afr Med J 2001; 91:163-72. Mirmiran M, Swaab DF. Neurotoxicology 1986; 7:95-102.
Summary	**Pregnancy Category: C** **Lactation Category: NS** • **Reserpine** should probably be avoided during pregnancy and lactation unless there is no other option. • There are alternative agents for which there is more experience regarding use during pregnancy and lactation.

Reteplase—(Rapilysin; Retavase)

International Brand Name—None identified.

Drug Class	Anticoagulants
Indications	Acute MI
Mechanism	Promotes fibrinolysis by converting plasminogen to plasmin
Dosage with Qualifiers	Acute MI—10U IV over 2min; repeat 2nd dose 30min later if no complications • **Contraindications**—hypersensitivity to drug or class, history of stroke or recent surgery or trauma, active bleeding, intracranial mass, AVM, aneurysm, severe hypertension • **Caution**—unknown
Maternal Considerations	**Reteplase** is recombinant plasminogen activator. There are no adequate reports or well-controlled studies of **reteplase** in pregnant women. The published experience is limited to 2 case reports associated with life-threatening thrombosis. There were no reported adverse effects. There is a real risk of uterine hemorrhage if administered in the puerperium. ***Side effects*** include intracranial hemorrhage, ventricular arrhythmia, pulmonary edema, cholesterol embolization, anemia, GI and GU bleeding, and N/V.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **reteplase** crosses the human placenta. Rodent studies showed no evidence of teratogenicity, but there was an increased risk of genital hemorrhage and abortion.
Breastfeeding Safety	There is no published experience in nursing women. It is unknown whether **reteplase** enters human breast milk. However, considering the indication and dosing, one-time **reteplase** use is unlikely to pose a clinically significant risk to the breastfeeding neonate.
Drug Interactions	Interaction with other cardioactive drugs has not been studied. In addition to bleeding associated with **heparin** and vitamin K antagonists, drugs that alter platelet function (e.g., **abciximab, aspirin, dipyridamole**) may increase the risk of bleeding if administered prior to or after **reteplase.**
References	Rinaldi JP, Yassine M, Aboujaoude F, et al. Arch Mal Coeur Vaiss 1999; 92:427-30. Yap LB, Alp NJ, Forfar JC. Int J Cardiol 2002; 82:193-4.

■ **Summary** ·····

Pregnancy Category: C
Lactation Category: U

- **Reteplase** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

$Rh_o(D)$ immune globulin—(Gamulin Rh; HypRho-D; Mini-Gamulin Rh; Rhesonativ; WinRho SDF)

International Brand Name—Anti Rh_O (D) (Mexico); Bay Rh_O-D (Israel); Cutter Hyperab (Hong Kong); Cutter Hyprho-D (Hong Kong); IGRHO (Israel); Natead (France); Partobulin (Czech Republic, Hong Kong, Italy, Korea); Partogloman (Austria); Probi RHO (D) (Mexico); Rhesogam (Germany); Rhesogamma (Sweden); Rhesugam (South Africa); Rhesuman (Belgium, Greece, India, Italy, Spain, Switzerland); Rhesuman Berna (Colombia, Hong Kong, Israel, Malaysia, Peru, Thailand); Rhogam (Belgium, Hong Kong); WinRho SDF (New Zealand)

■ **Drug Class** ····· Immune globulins

■ **Indications** ····· Risk for D alloimmunization

■ **Mechanism** ····· Passive immunization

■ **Dosage with Qualifiers** ·····

Delivery >12w gestation—300mcg IM within 72h covers transplacental hemorrhage up to 15ml PRBCs
Pregnancy termination (spontaneous or iatrogenic) <12w—120-150mcg IM
Antenatal prophylaxis at 28w or after placental bleeding or instrumentation—300mcg IM; repeat for each bleeding episode >72h apart
Transfusion accident—Multiply the volume (in ml) of Rh^+ whole blood administered by the hematocrit of the donor unit. This equals the volume of PRBCs transfused. Divide the volume (in ml) of PRBCs by 15 to obtain the number of vials or syringes of Rh IgG to be administered.

NOTE: available as a pooled plasma or engineered product, in "indication specific" doses.

- **Contraindications**—hypersensitivity to drug or class, Rh^+ status
- **Caution**—none identified

■ **Maternal Considerations** ·····

Rh alloimmunization remains a perinatal health problem even in countries with a developed program of prophylaxis. Patient or medical error is the most common cause of failed prophylaxis. Anti-D human immunoglobulin has been in clinical use for more than 30y. Its assessment is based more on experience than on well-designed comparative trials, but is estimated to have reduced perinatal mortality by about 10,000 cases/y in the US alone. A meta-analysis of 6 trials involving more than 10,000 women demonstrated efficacy of prophylaxis after delivery of a $Rh_o(D)$-positive infant to a $Rh_o(D)$-negative woman, reducing sensitization from 10% to 1.5%. The addition of antenatal prophylaxis reduces the rate of sensitization further, down to <0.5%. However, the optimal dosing regimen and route of administration remain unclear. Some data favor the use of **$Rh_o(D)$ immune globulin** after abortion, as it appears to reduce immunization rates from about 3-4% to 0.4%. **$Rh_o(D)$ immune globulin** is also likely effective antenatally in circumstances or procedures carrying a risk of maternal exposure to fetal RBCs, although this has not been proved in comparative trials.

Criteria for an Rh-incompatible pregnancy requiring treatment includes: mother $Rh_o(D)$-negative, not previously sensitized to the $Rh_o(D)$ factor; neonate $Rh_o(D)$-positive and direct antiglobulin negative. It is generally recommended that **$Rh_o(D)$ immune globulin** should be administered to all nonsensitized Rh^- women after spontaneous or induced abortion, ruptured tubal pregnancy, chorionic villus sampling, amniocentesis, abdominal trauma, or any occurrence of transplacental hemorrhage unless the fetus is known to be $Rh_o(D)$-negative. However, there is minimal evidence that administering **Rh immune globulin** for 1st trimester vaginal bleeding prevents maternal sensitization or development of hemolytic disease of the newborn. The practice is based on expert opinion and extrapolation from experience with fetomaternal hemorrhage in late pregnancy. Its use for 1st trimester bleeding is not evidence-based. If **$Rh_o(D)$ immune globulin** is given antenatally, it is essential the mother receive another dose after delivery of a $Rh_o(D)$-positive infant. If the father is known and $Rh_o(D)$-negative, **$Rh_o(D)$ immune globulin** is unnecessary. **$Rh_o(D)$ immune globulin** should be given within 72h of delivery or abortion (spontaneous or iatrogenic). Passively acquired anti-$Rh_o(D)$ may be detected after delivery following antenatal treatment; however, the woman should be treated again postpartum if the neonate is $Rh_o(D)$-positive. One 300mcg vial or syringe is sufficient to prevent maternal sensitization if the transferred fetal PRBC volume is <15ml (30ml whole blood). More than one vial or syringe of **$Rh_o(D)$ immune globulin** must be given when the fetomaternal hemorrhage >15ml PRBCs or 30ml whole blood. The number of vials required is calculated by taking the volume of PRBCs determined by an approved laboratory assay, divided by 2 to get the volume of packed fetal RBCs in the maternal blood, and dividing that number by 15 to get the number of syringes or vials. More recently, it has been suggested that **$Rh_o(D)$ immune globulin** might be helpful in women with ITP unresponsive to corticosteroids and nonspecific types of immune globulin.

Side effects include injection site reaction and fever.

Fetal Considerations

There is no evidence of fetal harm after extensive clinical experience. Babies born of women given **$Rh_o(D)$ immune globulin** antepartum may have a weakly positive antiglobulin test at birth. There is no credible evidence that the risk of autism is increased by antenatal exposure.

Breastfeeding Safety

There are no adequate reports or well-controlled studies in nursing women. **$Rh_o(D)$ immune globulin** is excreted into human breast milk, but the amount of intact antibody detectable in the neonate is too low to cause clinically relevant hemolysis.

Drug Interactions

Other antibodies contained in **$Rh_o(D)$ immune globulin** may interfere with the response to live virus vaccines such as measles, mumps, polio, or rubella. Therefore, immunization with live vaccines should not be given within 3mo.

References

Bowman JM, Chown B. Can Med J 1968; 99:385-8.
Bowman JM, Pollock JM. Can Med J 1978; 118:627-30.
Croen LA, Matevia M, Yoshida CK, Grether JK. Am J Obstet Gynecol 2008; 199:234.e1-6.
Crowther C, Middleton P. Cochrane Database Syst Rev 2000; (2):CD000021.
Grimes DA, Ross WC, Hatcher RA. Obstet Gynecol 1977; 50:261-3.
Hannafin B, Lovecchio F, Blackburn P. Am J Emerg Med 2006; 24:487-9.

Maayan-Metzger A, Schwartz T, Sulkes J, Merlob P. Arch Dis Child Fetal Neonatal Ed 2001; 84:F60-2.
Miles JH, Takahashi TN. Am J Med Genet A 2007; 143:1397-407.
Sieunarine K, Shapiro S, Al Obaidi MJ, Girling J. BJOG 2007; 114:505-7.
Weinberg L. Emerg Med J 2001; 18:444-7.

Summary

Pregnancy Category: C
Lactation Category: S

- **Rh_o(D) immune globulin** is safe and likely effective for each of the listed indications.
- Antenatal and postnatal prophylaxis is cost-effective in most developed countries.

Ribavirin—(Rebetol; Viramid; Virazid; Virazole)

International Brand Name—Cotronak (Germany); Desiken (Mexico); Virazin (Korea)

Drug Class

Antivirals

Indications

Chronic HCV infection

Mechanism

Unknown

Dosage with Qualifiers

Chronic HCV infection—400mg PO qam and 600mg qpm if <75kg; 600mg PO bid if >74.9kg

*NOTE: may be combined with **interferon alfa-2b** (Rebetron); report treated pregnant women to The Ribavirin Pregnancy Registry (1-800-593-2214).*

- **Contraindications**—hypersensitivity to drug or class, male partners of pregnant women, significant cardiac disease, autoimmune hepatitis, hemoglobinopathy, CrCl <50ml/min
- **Caution**—psychiatric disorder, myelosuppression, pulmonary or cardiac disease, diabetes mellitus

Maternal Considerations

Hepatitis C is a growing problem worldwide. Perhaps ⅓ of patients with HIV also have hepatitis C. Liver disease due to chronic HCV infection is now the 2nd leading cause of death in some HIV-infected populations. It is the most common cause of chronic liver disease and liver transplantation. The application of blood product screening has virtually eliminated transfusion-related viral transmission. As a result, maternal-fetal transmission is now one of the most important modes of transmission. HCV transmission is 2- to 4-fold higher in women co-infected with HIV. Cesarean delivery has not been shown to decrease perinatal transmission. The published experience with **ribavirin** during pregnancy is limited to case reports. No adverse effects are reported. Considering the risk of viral transmission to the perinate is increased by co-infection, it seems likely future trials will address treatment of hepatitis C in HIV-infected pregnant women. The CDC does not recommend **ribavirin** for postexposure prophylaxis. Patients with chronic hepatitis whose therapy can be delayed should not be treated until controlled studies are available. However, women exposed to **ribavirin** inadvertently during pregnancy may be encouraged to continue pregnancy. In patients with acute hepatitis C during pregnancy, the use of **ribavirin** therapy should be considered with close monitoring. The Ribavirin Pregnancy Registry was initiated in January 2004.

Side effects include hemolytic anemia, thrombocytopenia, neutropenia, marrow suppression, MI, suicidal ideation, N/V, autoimmune disorders, pulmonary toxicity, pancreatitis, diabetes mellitus, headache, fatigue, myalgia, arthralgia, fever, insomnia, depression, alopecia, irritability, anorexia, rash, pruritus, dyspnea, dyspepsia, and loss of concentration.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **ribavirin** crosses the human placenta. There are only limited case reports of its use during pregnancy. Rodent studies reveal an increased prevalence of limb, eye, and brain defects. The incidence and severity is proportional to drug dose. Teratogenicity was not seen at doses approximating the recommended human dose. **Ribavirin** is often used in the pediatric population for the treatment of RSV. The prevalence of hepatitis C in children is between 0.05% and 0.4%. The major mode of acquisition has shifted from parenteral to maternal-infant transmission. While the actual rate of maternal-infant transmission is low, HIV increases the rate of transmission.

Breastfeeding Safety

There is no published experience in nursing women. It is unknown whether **ribavirin** enters human breast milk. **Ribavirin** is toxic to lactating rats and their offspring.

Drug Interactions

Use with **didanosine** is not recommended. There are reports of fatal hepatic failure, as well as peripheral neuropathy, pancreatitis, and symptomatic hyperlactatemia/lactic acidosis.
May antagonize the *in vitro* antiviral activity of **stavudine** and **zidovudine** against HIV. Therefore, use with either of these drugs should be undertaken with caution.
In Study NR15961 among chronic HCV/HIV co-infected cirrhotic patients receiving NRTIs, hepatic decompensation (some fatal) was observed. Patients receiving Pegasys/Copegus and NRTIs should be closely monitored for treatment-associated toxicities. Physicians should refer to prescribing information for the respective NRTIs for guidance regarding toxicity management.
In Study NR15961, use with **zidovudine** was associated with severe neutropenia (ANC <500) and severe anemia (Hb <8g/dl) more frequently than similar patients not receiving zidovudine (neutropenia 15% vs. 9%; anemia 5% vs. 1%).

References

Ferm VH, Willhite C, Kilham L. Teratology 1978; 17:93-101.
Hegenbarth K, Maurer U, Kroisel PM, et al. Am J Gastroenterol 2001; 96:2286-7.
Labarga P, Pinilla J, Cachorro I, del Prado YR. Reprod Toxicol 2007; 24:414-6.
Prows CA, Shortridge L, Kenner C, Lemasters G. J Pediatr Nurs 1993; 8:370-5.
Rezvani M, Koren G. Reprod Toxicol 2006; 21:113-5.
U.S. Public Health Service. MMWR Recomm Rep 2001; 50(RR-11):1-52.

Summary

Pregnancy Category: X
Lactation Category: U

- **Ribavirin** is a teratogen in rodents; there is inadequate experience to conclude it is or is not a teratogen in humans. It is used clinically for the treatment of small children.
- **Ribavirin** should be used during pregnancy and lactation only if the benefit justifies the potential risk.
- Physicians are encouraged to register pregnant women with The Ribavirin Pregnancy Registry (1-800-593-2214) for a better follow-up of the outcome while under treatment with **ribavirin.**

Riboflavin

International Brand Name—None identified.

Drug Class	Vitamins/minerals
Indications	Replacement, supplementation
Mechanism	Unknown
Dosage with Qualifiers	Replacement—5-25mg PO qd Supplementation—1.7mg PO qd (MDR) **Contraindications**—hypersensitivity to drug or class **Caution**—unknown
Maternal Considerations	**Riboflavin** is an important nutrient contained in virtually all multivitamin supplements. Contrary to conventional wisdom, the maternal concentration of **riboflavin** does not decline during normal, unsupplemented pregnancy. However, maternal supplementation does generate supraphysiologic levels. Epidemiologic studies suggest multivitamin supplementation during the pregnancy of HIV-infected women improves maternal weight gain. ***Side effects*** include bright yellow urine.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. **Riboflavin** is actively transported across the human placenta with a transfer index (clearance **riboflavin**:clearance L-glucose) in the isolated cotelydon of 3.4 ± 0.95. Observational studies note a positive relationship between maternal **riboflavin** levels and fetal size. This finding also applies to women who abuse tobacco. There is no substantative evidence **riboflavin** is a teratogen, though epidemiological study suggests low intake may be associated with congenital heart disease. In some animal models, **riboflavin** supplementation reduces the incidence of NTDs.
Breastfeeding Safety	**Riboflavin** is excreted into human breast milk, and the concentration is proportional to the maternal concentration. Women who do not drink milk are more likely to have low concentrations of **riboflavin** in their breast milk.
Drug Interactions	No clinically relevant interactions identified.
References	Badart-Smook A, van Houwelingen AC, Kester AD, Hornstra G. J Am Diet Assoc 1997; 97:867-70. Baker H, DeAngelis B, Holland B, et al. J Am Coll Nutr 2002; 21:33-7. Cikot RJ, Steegers-Theunissen RP, Thomas CM, et al. Br J Nutr 2001; 85:49-58. Dancis J, Levitz M, Katz J, et al. Pediatr Res 1992; 32:195-9. Faron G, Drouin R, Pedneault L, et al. Teratology 2001; 63:161-3. Mannion CA, Gray-Donald K, Johnson-Down L, Koski KG. J Am Coll Nutr 2007; 26:149-55. Ortega RM, Quintas ME, Martinez RM, et al. J Am Coll Nutr 1999; 18:324-9. Seller MJ. Ciba Found Symp 1994; 181:161-73; discussion 173-9. Smedts HP, Rakhshandehroo M, Verkleij-Hagoort AC, et al. Eur J Nutr 2008; 47:357-65. Villamor E, Msamanga G, Spiegelman D, et al. Am J Clin Nutr 2002; 76:1082-90.

Summary

Pregnancy Category: A
Lactation Category: S

- The maternal concentration of **riboflavin** does not change during normal pregnancy.
- Prenatal multivitamin supplements successfully increase the maternal concentration.

Rifabutin—(Ansamycin; Mycobutin)

International Brand Name—Alfacid (Germany); Ansatidine (France); Ansatipin (Finland, Spain); Ansatipine (France); Mycobutin (Austria, Belgium, Bulgaria, Canada, England, Germany, Hong Kong, Hungary, Ireland, Israel, Italy, Netherlands, South Africa, Switzerland, Taiwan)

Drug Class

Antimycobacterials

Indications

Prevention of disseminated MAC disease in women with advanced HIV infection

Mechanism

Unknown; inhibits bacterial DNA-dependent RNA polymerase

Dosage with Qualifiers

MAC prevention—300mg PO qd

NOTE: renal dosing.

- **Contraindications**—hypersensitivity to drug or class, active TB
- **Caution**—neutropenia, thrombocytopenia

Maternal Considerations

Rifabutin is an alternative to **rifampin** for the treatment of *Mycobacterium* TB in HIV-infected women taking certain antiretroviral agents concomitantly. It is also recommended by the U.S. Public Health Service/Infectious Diseases Society of America Prevention of Opportunistic Infections in Persons Infected with HIV Working Group as an alternative agent to **rifampin** for chemoprophylaxis of tuberculosis. There is no experience with **rifabutin** during pregnancy. In healthy nonpregnant women, **rifabutin** and **rifampin** significantly increase the clearance of **ethinyl estradiol,** suggesting women who use low-dose oral contraceptives should either switch to a higher dose or use a backup contraceptive method while taking **rifabutin.**
Side effects include thrombocytopenia, neutropenia, leukopenia, uveitis, rash, N/V, abdominal pain, headache, dyspepsia, diarrhea, belching, discolored urine, taste changes, fever, anorexia, myalgias, asthenia, flatus, chest pain, and insomnia.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **rifabutin** crosses the human placenta. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically.

Breastfeeding Safety

There are no adequate reports or well-controlled studies in nursing women. It is unknown whether **rifabutin** enters human breast milk. Breastfeeding is contraindicated in HIV-infected nursing women where formula is available to reduce the risk of neonatal transmission.

Drug Interactions

Decreases steady-state plasma levels of **zidovudine,** an antiretroviral metabolized mainly through glucuronidation; the mean decreases in C_{max} and AUC were 48% and 32%, respectively.

The related drug **rifampin** is known to reduce the activity of a number of other drugs, including analgesics, anticoagulants, cardiac glycoside preparations, corticosteroids, **cyclosporine, dapsone,** narcotics (including **methadone**), oral contraceptives, oral hypoglycemic agents (sulfonylureas), and **quinidine. Rifampin** has also been reported to decrease the effects of anticonvulsants, barbiturates, β-adrenergic blockers, **chloramphenicol, clofibrate, diazepam, disopyramide, ketoconazole, mexiletine,** progestins, **theophylline,** and **verapamil.** However, unlike **rifampin, rifabutin** appears not to affect the acetylation of **isoniazid.** When **rifabutin** was compared with **rifampin** in a study with 8 healthy normal volunteers, **rifabutin** appeared to be a less potent enzyme inducer than **rifampin.** Patients using oral contraceptives should consider changing to non-hormonal methods of birth control.

References

LeBel M, Masson E, Guilbert E, et al. J Clin Pharmacol 1998; 38:1042-50.

Summary

Pregnancy Category: B
Lactation Category: U

- **Rifabutin** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Rifampin—(Abrifam; Aptecin; Corifam; Fenampicin; Rifadin; Rifamate; Rifamed; Rifampicin; Rifamycin; Rifarad; Rifocina; Rifumycin; Rimactane; Rimpacin; Syntaxil; Syntoren; Tibirim; Visedan)

International Brand Name—Eremfat (Germany); Finamicina (Mexico); Kalrifam (Indonesia); Manorifcin (Thailand); Medifam (Philippines); Prolung (Indonesia); Ramfin (Malaysia, Thailand); Ramicin (Indonesia); Rifa (Germany); Rifacilin (India); Rifadine (Belgium, France); Rifagen (Spain); Rifaldin (Spain); Rifamax (Philippines); Rifapiam (Italy); Rifarad (Israel, South Africa); Rifasynt (Hong Kong); Rifcin (South Africa); Rifodex (Korea); Rifoldin (Austria, Switzerland); Rimactan (Austria, Belgium, Bulgaria, Colombia, Denmark, Ecuador, France, Germany, Israel, Italy, Mexico, Netherlands, Norway, Peru, Spain, Sweden, Switzerland); Rimpacin (Israel, South Africa); Rimpin (India); Rimycin (Australia); Ripin (Taiwan); Ripolin (Taiwan); Rofact (Canada)

Drug Class

Antimycobacterials

Indications

TB, meningococcal prophylaxis

Mechanism

Bactericidal—inhibits DNA-dependent RNA polymerase

Dosage with Qualifiers

TB—10-20mg/kg PO qd on an empty stomach (not to exceed 600mg/d)
Meningococcal prophylaxis (not treatment)—600mg PO bid ×2d

NOTE: may be combined with ***isoniazid*** *±* ***pyrazinamide*** *and* ***ethambutol*** *or* ***streptomycin.***

- **Contraindications**—hypersensitivity to drug or class
- **Caution**—hepatic dysfunction or use of a hepatic enzyme inducer

Maternal Considerations

Untreated TB poses a significant threat to the mother, fetus, and family. A 3-drug regimen of **rifampin, isoniazid,** and **pyrazinamide** is recommended for the initial 2mo treatment phase. All pregnant women taking **isoniazid** should also take **pyridoxine**

to reduce the chance of a 'chemical' hepatitis. The CDC recommends that either **streptomycin** or **ethambutol** be added during the initial treatment unless the likelihood of **isoniazid** resistance is low. However, **streptomycin** is contraindicated in pregnancy. **Ciprofloxacin** has the best safety profile of second-line drugs for the treatment of drug-resistant TB. After the initial phase, treatment is continued with **rifampin** and **isoniazid** for 4mo, or longer if the sputum or culture is positive, resistant organisms are present, or patient is HIV positive. There are no adequate reports or well-controlled studies of **rifampin** in pregnant women. A long clinical experience suggests pregnancy does not increase the risk of an adverse effect. **Rifampin** may cause hemorrhage in the mother and neonate when administered during the 3rd trimester. Treatment with **vitamin K** may be indicated. **Rifampin** impairs the effectiveness of OCPs. Women using a low-dose OCP should consider a higher dose preparation or a backup method of contraception.

Side effects include renal failure, shock, hepatotoxicity, hemolytic anemia, thrombocytopenia, leukopenia, elevated LFTs, interstitial nephritis, N/V, diarrhea, anorexia, headache, fatigue, dizziness, abdominal pain, pruritus, rash, dyspnea, ataxia, visual changes, and urticaria.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. **Rifampin** crosses the human placenta, but the kinetics have not been detailed. There is no substantative evidence of teratogenicity in humans. **Rifampin** does cross the rodent placenta, and is teratogenic at oral doses 15-25× the MRHD, affecting bone, spine, and palate, depending upon the species. Congenital TB does occur on occasion, especially in association with miliary TB. **Rifampin** is used to treat children in the first few months of life.

Breastfeeding Safety

There are no adequate reports or well-controlled studies in nursing women. Only trace amounts of **rifampin** are excreted into human breast milk.

Drug Interactions

May accelerate the metabolism of the following drugs: antiarrhythmics (e.g., **disopyramide, mexiletine, quinidine, tocainide**), anticonvulsants (e.g., **phenytoin**), antifungals (e.g., **fluconazole, itraconazole, ketoconazole**), barbiturates, β-blockers, calcium channel blockers (e.g., **diltiazem, nifedipine, verapamil**), cardiac glycoside preparations, **chloramphenicol, clofibrate,** corticosteroids, **cyclosporine, dapsone, diazepam, doxycycline,** fluoroquinolones (e.g., **ciprofloxacin**), **haloperidol, levothyroxine, methadone,** narcotic analgesics, **nortriptyline,** oral anticoagulants, oral hypoglycemic agents (sulfonylureas), oral or other systemic hormonal contraceptives, progestins, **quinine, tacrolimus,** TCAs (e.g., **amitriptyline, nortriptyline**), **theophylline,** and **zidovudine.** It may be necessary to adjust the dosages of these drugs.

Women using oral or other systemic hormonal contraceptives should be advised to change to non-hormonal methods of birth control.

May increase the requirements for coumarin-type anticoagulant drugs. It is recommended that a PT or INR be performed frequently.

Ketoconazole and **rifampin** decrease the serum concentrations of both.

Enalapril decreases concentrations of enalaprilat, the active metabolite of **enalapril.** Dosage adjustments are to be based on the patient's clinical response.

Antacid use may reduce the absorption of **rifampin.** The daily dose of **rifampin** should be given at least 1h before the antacid. **Probenecid** and cotrimoxazole may increase the blood level of **rifampin.**
The potential for hepatotoxicity is increased when use with either **halothane** or **isoniazid.** Their combined use should be avoided. Monitor the patient closely for hepatotoxicity if **isoniazid** must be used.

References

Bothamley G. Drug Saf 2001; 24:553-65.
Centers for Disease Control and Prevention. JAMA 1993; 270:694-8.
Dickinson BD, Altman RD, Nielsen NH, Sterling ML. Obstet Gynecol 2001; 98:853-60.
Holdiness MR. Early Hum Dev 1987; 15:61-74.
Pillet P, Grill J, Rakotonirina G, et al. Arch Pediatr 1999; 6:635-9.
Termine A, Santuari E. Ann Ist Carlo Forlanini 1968; 28:431-9.
Tran JH, Montakantikul P. J Hum Lact 1998; 14:337-40.

Summary

Pregnancy Category: C
Lactation Category: S

- **Rifampin** and the core group of antituberculosis drugs appear safe and effective during pregnancy when given as recommended.

Rifapentine—(Priftin)

International Brand Name—None identified.

Drug Class

Antimycobacterials

Indications

TB

Mechanism

Bactericidal—inhibits DNA-dependent RNA polymerase

Dosage with Qualifiers

TB—begin 600mg PO with food 2×/w ×2mo; then 600mg PO qw ×2mo

NOTE: not for monotherapy; take with meals to improve bioavailability.

- **Contraindications**—hypersensitivity to drug or class
- **Caution**—hepatic dysfunction, nephrotoxic drug use

Maternal Considerations

Rifapentine is similar to **rifampin,** but has a more convenient dosing protocol. It must be taken in tandem with at least one other antituberculosis drug to which the isolate is susceptible. There are no adequate reports or well-controlled studies of **rifapentine** in pregnant women. The published experience is limited to isolated case reports.
Side effects include thrombocytopenia, neutropenia, leukopenia, elevated LFTs, hyperbilirubinemia, proteinuria, hematuria, pancreatitis, pseudomembranous colitis, interstitial nephritis, hepatotoxicity, urinary casts, rash, pruritus, acne, anorexia, arthralgia, pain, and N/V.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. **Rifapentine** is teratogenic in rodents when given

at doses similar to human, affecting bone, heart, spine, and palate (species-dependent). There is also evidence of embryotoxicity.

Breastfeeding Safety

There is no published experience in nursing women. It is unknown whether **rifapentine** enters human breast milk.

Drug Interactions

Decreased the **indinavir** C_{max} by 55% and the AUC by 70%. The clearance of **indinavir** increased by 3-fold in the presence of **rifapentine** while t/2 did not change. **Rifapentine** should be used with extreme caution, if at all, in patients who are also taking protease inhibitors.

Patients using oral or other systemic hormonal contraceptives should be advised to change to non-hormonal methods of birth control.

Induces CYP3A4 and 2C8/9. Thus, it may increase the metabolism of drugs metabolized by these enzymes. Enzyme induction occurs within 4d and return to baseline 14d after discontinuing **rifapentine.** The magnitude of enzyme induction by **rifapentine** is dose and dosing frequency dependent.

Dose adjustments of the following drugs may be necessary: antiarrhythmics (e.g., **disopyramide, mexiletine, quinidine, tocainide**), antibiotics (e.g., **chloramphenicol, clarithromycin, dapsone, doxycycline**), anticonvulsants (e.g., **phenytoin**), antifungals (e.g., **fluconazole, itraconazole, ketoconazole**), barbiturates, benzodiazepines (e.g., **diazepam**), β-blockers, calcium channel blockers (e.g., **diltiazem, nifedipine, verapamil**), corticosteroids, cardiac glycosides, **clofibrate,** fluoroquinolones (e.g., **ciprofloxacin**); haloperidol, HIV protease inhibitors (e.g., **indinavir, nelfinavir, ritonavir, saquinavir**), immunosuppressants (e.g., **cyclosporine, tacrolimus**), **levothyroxine,** narcotic analgesics (e.g., **methadone**), oral anticoagulants (e.g., **warfarin**), oral hypoglycemic agents (e.g., sulfonylureas), oral or other systemic hormonal contraceptives, progestins, **quinine,** reverse transcriptase inhibitors (e.g., **delavirdine, zidovudine**), **sildenafil,** TCAs (e.g., **amitriptyline, nortriptyline**), and **theophylline.**

References

Temple ME, Nahata MC. Ann Pharmacother 1999; 33:1203-10.

Summary

Pregnancy Category: C
Lactation Category: U

- **Rifapentine** has no significant clinical advantage over **rifampin** that would justify its use during pregnancy and lactation.

Riluzole—(Rilutek)

International Brand Name—None identified.

Drug Class	Neurologics; Neuroprotectives
Indications	ALS
Mechanism	Unknown
Dosage with Qualifiers	ALS—50mg PO q12h taken on an empty stomach • **Contraindications**—hypersensitivity to drug or class • **Caution**—hepatic or renal dysfunction, hypertension, history of neutropenia
Maternal Considerations	ALS is the most common progressive motor neuron disease, but is rare in the obstetric population. There are no published reports of **riluzole** use during pregnancy. ***Side effects*** include hepatotoxicity, asthenia, N/V, diarrhea, rhinitis, headache, abdominal pain, weight loss, tachycardia, worsening of spasticity, insomnia, cough, paresthesias, edema, and depression.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **riluzole** crosses the human placenta. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically. Maternal and embryo toxicity were seen.
Breastfeeding Safety	There are no adequate reports or well-controlled studies in nursing women. It is unknown whether **riluzole** enters human breast milk.
Drug Interactions	*In vitro* studies suggest that CYP1A2 is the principal isozyme involved in the initial oxidative metabolism of **riluzole** and, therefore, interactions may occur when **riluzole** is given with agents that affect CYP1A2 activity. Potential inhibitors of CYP1A2 (e.g., **amitriptyline, caffeine,** phenacetin, quinolones, **theophylline**) could decrease the riluzole elimination rate, while inducers of CYP1A2 (e.g., charcoal-broiled food, cigarette smoke, **omeprazole, rifampicin**) could increase the **riluzole** elimination rate.
References	There are no current relevant references.
Summary	**Pregnancy Category: C** **Lactation Category: U** • **Riluzole** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Rimantadine—(Flumadine)

International Brand Name—Gabirol (Mexico); Germic (Argentina)

Drug Class	Antivirals
Indications	Influenza A treatment and prophylaxis
Mechanism	Unknown
Dosage with Qualifiers	Influenza A treatment—100mg PO bid ×7d Influenza prophylaxis—100mg PO bid *NOTE: renal dosing.* • **Contraindications**—hypersensitivity to drug or class • **Caution**—hepatic or renal dysfunction
Maternal Considerations	Pregnant women suffered a higher mortality rate during the influenza pandemics of the last century and should be vaccinated prior to each influenza season. Prophylaxis is not a substitute for vaccination, although it is an important adjunct. **Rimantadine** is 70-90% effective in preventing influenza A. When used for prophylaxis, antiviral agents can prevent illness while permitting subclinical infection and the genesis of protective antibodies. **Rimantadine** reduces the duration of the illness if administered within 2d of symptom onset should an unprotected woman contract influenza A. To reduce the emergence of antiviral drug–resistant viruses, **rimantadine** therapy is discontinued as soon as clinically warranted, typically after 3-5d, or within 24-48h from resolution of signs and symptoms. There is no published experience with **rimantadine** in pregnant women. ***Side effects*** include CHF, AV block, bronchospasm, seizures, N/V, insomnia, dizziness, anorexia, dry mouth, abdominal pain, nervousness, and fatigue.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **rimantadine** crosses the human placenta. It does cross the rodent placenta and is initially concentrated in the fetal liver. The elimination t/2 is less than 3h. Rodent studies are generally reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically. Embryo and maternal toxicity occur at the highest doses. There is also an increase in pup death during the first 2-4d postpartum, and decreased fertility of the F_1 generation. **Rimantadine** has not been tested in children under 1y.
Breastfeeding Safety	There is no published experience in nursing women. It is unknown whether **rimantadine** enters human breast milk. **Rimantadine** is concentrated in rat milk in a dose-dependent fashion, achieving twice plasma levels 2-3h after dosing. Until further study, breastfeeding women who choose to take **rimantadine** should probably stop feeding and pump until 48h after discontinuing the drug.
Drug Interactions	No clinically relevant interactions identified.
References	Pravdina NF, Shobukhov VM, Petrova IG, et al. Biull Eksp Biol Med 1985; 99:74-6.

Summary	**Pregnancy Category: C** **Lactation Category: U** • **Rimantadine** should be used during pregnancy only if the benefit justifies the potential perinatal risk.

Risedronate—(Actonel)

International Brand Name—Actonel (Australia, England, France, Germany, Hong Kong, Indonesia, Ireland, Israel, Korea, Malaysia, Philippines, Singapore, Thailand); Actonel Once A Week (Israel, South Africa); Ribastamin (Argentina)

Drug Class	Bisphosphonates; Calcium metabolism agents
Indications	Postmenopausal osteoporosis, steroid-induced osteoporosis, Paget's disease
Mechanism	Inhibits osteoclast bone resorption
Dosage with Qualifiers	Postmenopausal osteoporosis—5mg PO with water qd Steroid-induced osteoporosis—5mg PO qd with water for women on **prednisone** 7.5mg/d or more Paget's disease—30mg PO qd with water before breakfast ×2mo; supplement calcium and vitamin D • **Contraindications**—hypersensitivity to drug or class • **Caution**—unknown
Maternal Considerations	There is no published experience with **risedronate** during pregnancy. ***Side effects*** include headache, irritability, nervousness, menstrual irregularities, sweating, increased bowel motility, shock, insomnia, tremor, tachycardia, arrhythmia, weight loss, heat intolerance, and diaphoresis.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **risedronate** crosses the human placenta. In one study, placental transport was not confirmed in the mouse. Rodent studies are generally reassuring, revealing no clear evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically. Pregnancy wastage was increased with maternal toxicity.
Breastfeeding Safety	There is no published experience in nursing women. It is unknown whether **risedronate** enters human breast milk. Small amounts are excreted into rodent milk.
Drug Interactions	Use with calcium, antacids, or oral medications containing divalent cations will interfere with the absorption of **risedronate.**
References	Richardson AC, Tinling SP, Chole RA. Otolaryngol Head Neck Surg 1993; 109:623-33.
Summary	**Pregnancy Category: C** **Lactation Category: U** • **Risedronate** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Risperidone—(Risperdal)

International Brand Name—Neripros (Indonesia); Noprenia (Indonesia); Riperidon (Korea); Rispen (Korea); Risperdal Consta (England, Germany, Hong Kong, Ireland, Israel, New Zealand, Philippines, Thailand); Risperdalconsta LP (France); Risperdal Quicklet (England, Germany, Hong Kong, Ireland); Rispid (India); Rispolet (Poland); Rizodal (Indonesia); Sequinan (Argentina); Tractal (Colombia); Zargus (Brazil); Zofredal (Indonesia)

Drug Class	Antipsychotics
Indications	Psychosis
Mechanism	Unknown; antagonizes dopamine D_2 and 5-HT_2 receptors
Dosage with Qualifiers	Psychosis—begin 1mg PO bid; increase by 1-2mg/d qw *NOTE: hepatic and renal dosing; avoid **caffeine**-containing products such as colas and tea.* • **Contraindications**—hypersensitivity to drug or class, prolonged QT interval • **Caution**—hepatic or renal dysfunction, seizures, cardiac or cerebrovascular disease, hypotension, hypovolemia, dehydration, agents that prolong the QT interval, aspiration pneumonia risk
Maternal Considerations	There are no adequate reports or well-controlled studies of **risperidone** in pregnant women. The published experience is limited to several case reports. ***Side effects*** include neuroleptic malignant syndrome, menstrual irregularities, hypotension, extrapyramidal signs, tardive dyskinesia, hyperglycemia, diabetes mellitus, seizures, QT interval prolongation, insomnia, agitation, headache, anxiety, rhinitis, constipation, N/V, diarrhea, dyspepsia, dizziness, tachycardia, somnolence, increased REM sleep, and hyperprolactinemia.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **risperidone** crosses the human placenta. The pregnancy outcomes of women who contacted a teratogen information service and the manufacturer's data after exposure to **risperidone** appeared normal. It does cross the rodent placenta. Rodent studies are generally reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically. The observed increased neonatal mortality may relate to either the drug or maternal toxicity.
Breastfeeding Safety	There are no adequate reports or well-controlled studies in nursing women. **Risperidone** enters human breast milk. In one woman taking 6mg PO qd, the peak milk levels of **risperidone** and its active metabolite were 12mcg/L and 40mcg/L, respectively. Thus, the estimated infant dose is 7.8mcg/kg/d, or 4.3% of the weight-adjusted maternal dose. There are case reports of its use in breastfeeding women without apparent adverse effect.
Drug Interactions	Given the primary CNS effects of **risperidone,** apply caution when using other centrally acting drugs or ethanol. May enhance the hypotensive effects of other hypotensive agents. May antagonize the effects of **levodopa** and dopamine agonists. Chronic administration of **clozapine** with **risperidone** may decrease the clearance of **risperidone.** **Carbamazepine** may decrease the plasma concentrations of **risperidone** and its pharmacologically active metabolite 9-hydroxyrisperidone by about 50%. Plasma concentrations

of **carbamazepine** did not appear to be affected. Use with other known enzyme inducers (e.g., **phenobarbital, phenytoin, rifampin**) may cause similar decreases, which could lower the therapeutic efficacy of **risperidone.** Patients should be monitored closely during the first 4-8w. On discontinuation of **carbamazepine** or other hepatic enzyme inducers, the dose of **risperidone** should be re-evaluated.
Fluoxetine and **paroxetine,** which inhibit CYP2D6, increase the plasma concentration of **risperidone** 2.5- to 2.8-fold and 3- to 9-fold, respectively. In addition, paroxetine lowered the concentration of 9-hydroxyrisperidone an average of 13%. When either **fluoxetine** or **paroxetine** is initiated or discontinued, the dose of **risperidone** should be re-evaluated.
May increase the peak **valproate** C_{max} by as much as 20%.

References

Coppda D, Russo LJ, Kwarta RF, et al. Drugs Saf 2007; 30:247-64.
Hill RC, McIvor RJ, Wojnar-Horton RE, et al. J Clin Psychopharmacol 2000; 20:285-6.
McKenna K, Koren G, Tetelbaum M, et al. J Clin Psychiatry 2005; 66:444-9.
Ratnayake T, Libretto SE. J Clin Psychiatry 2002; 63:76-7.
Rodriguez-Salgado B. Actas Esp Psiquiatr 2008; 36:366-8.

Summary

Pregnancy Category: C
Lactation Category: U
- **Risperidone** should be used during pregnancy and lactation only if the benefit justifies the potential risk.

Ritodrine—(No longer marketed in the US.)

International Brand Name—Anpo (Taiwan); Fetodrin (Taiwan); Lavopa SR (Korea); Materlac (Chile, Peru); Miodrina (Brazil); Miolene (Costa Rica, Dominican Republic, El Salvador, Guatemala, Honduras, Italy, Nicaragua, Panama); Pre-Par (Belgium, Czech Republic, Germany, Netherlands, Spain); Ritopar (Argentina); Utemerin (Japan); Utopar (Denmark, Finland, Norway); Yutopar (China, England, Greece, India, Indonesia, Ireland, Israel, Malaysia, South Africa, Taiwan)

Drug Class — Adrenergic agonists; β-Agonists; Tocolytics

Indications — Preterm labor

Mechanism — β_2-Agonist

Dosage with Qualifiers — Preterm labor—begin 0.05mg/min, increase by 0.05mg/min q10min (unless maternal HR >130bpm) until contractions stop; continue that dose for 12h after contractions end; max 0.35mg/min

- **Contraindications**—hypersensitivity to drug or class, sulfite allergy, indication for delivery (e.g., chorioamnionitis, severe preeclampsia), fetal demise, pulmonary hypertension, maternal hyperthyroidism, uncontrolled diabetes mellitus
- **Caution**—diabetes mellitus, maternal infection, CAD

Maternal Considerations

Preterm delivery is the leading cause of perinatal morbidity and death. There is no tocolytic agent known to change pregnancy outcome short of allowing corticosteroid administration.
Ritodrine decreases the intensity and frequency of uterine contractions, but does not alter in a clinically relevant fashion the

gestational age at delivery compared to placebo. Though the first drug approved as a tocolytic in the US, it was withdrawn from the market by its manufacturer. It is inferior to either **nifedipine** or atosiban in terms of both delivery delay and maternal morbidity. **Ritodrine** produces an immediate dose-related elevation of HR with maximum mean increase of 19-40bpm. The pulse pressure widens, the average systolic pressure increases 4.0mmHg, and the average diastolic pressure decreases 12.3mmHg. IV infusion transiently elevates glucose, insulin, and free fatty acids, while serum potassium declines. Maternal pulse rate and BP and FHR should be closely monitored. The effectiveness of parenteral **ritodrine** for tocolysis is limited to short-range prolongation of gestation. The effectiveness of maintenance tocolytic therapy with oral **ritodrine** is not proved. Maternal signs and symptoms of pulmonary edema should be sought constantly. A persistent tachycardia (>140bpm) may be a sign of impending pulmonary edema. Occult cardiac disease may be unmasked by **ritodrine.** If the patient complains of chest pain or tightness of chest, the drug should be temporarily discontinued. A baseline ECG is not cost-effective. **Ritodrine** has also been used to facilitate external version of a breech fetus.
Side effects include pulmonary edema, agranulocytosis, hypotension, palpitations, tachycardia, N/V, paradoxical hypertension, flushing, hyperglycemia, tremor, headache, nervousness, and chest pain.

Fetal Considerations

Ritodrine crosses the human placenta. There is no evidence of teratogenicity in humans. Rodent studies are reassuring. It has been suggested that **ritodrine** and other β-mimetics might promote fetal growth. This hypothesis cannot be confirmed. **Ritodrine** increases the FHR and left cardiac output, and has been used to treat fetal complete heart block.

Breastfeeding Safety

There is no published experience with **ritodrine** in pregnancy. However, considering the indication and clearance, it is unlikely the breastfed neonate would ingest clinically relevant amounts.

Drug Interactions

Corticosteroids may enhance the risk of pulmonary edema.
CV effects of parenteral **ritodrine** (especially cardiac arrhythmia or hypotension) may be potentiated by use with **magnesium sulfate, diazoxide, meperidine,** and general anesthetic agents.
Systemic hypertension may be exaggerated in the presence of parasympatholytic agents such as **atropine.**
The effects of other sympathomimetic amines may be potentiated. A sufficient time interval should elapse prior to administration of another sympathomimetic drug. With IV administration, 90% of the excretion of **ritodrine** is completed within 24h.
β-Adrenergic blocking drugs inhibit the action of **ritodrine;** use of these drugs should be avoided.
May potentiate the hypotensive effects of anesthetics used in surgery.

References

Berkman ND, Thorp JM Jr, Lohr KN, et al. Am J Obstet Gynecol 2003; 188:1648-59.
Chung T, Neale E, Lau TK, Rogers M. Acta Obstet Gynecol Scand 1996; 75:720-4.
Ezra Y, Elram T, Plotkin V, Elchalal U. Eur J Obstet Gynecol Reprod Biol 2000; 90:63-6.
Gulmezoglu AM, Hofmeyr GJ. Cochrane Database Syst Rev 2001; (4):CD000036.
Matsushita H, Higashino M, Sekizuka N, et al. Arch Gynecol Obstet 2002; 267:51-3.

Papatsonis DN, Van Geijn HP, Ader HJ, et al. Obstet Gynecol 1997; 90:230-4.
Sanchez-Ramos L, Kaunitz AM, Gaudier FL, Delke I. Am J Obstet Gynecol 1999; 181:484-90.
Shim JY, Park YW, Yoon BH, et al. BJOG 2006; 113:1228-34.
Weiner CP, Renk K, Klugman M. Am J Obstet Gynecol 1988; 159:216-22.

Summary

Pregnancy Category: B
Lactation Category: S

- **Ritodrine** should be used during pregnancy only if the benefit justifies the potential perinatal risk.
- The primary clinical goal of **ritodrine** administration is to delay delivery until there is maximal effect of corticosteroids; thereafter, its continued use provides risk but no benefit.
- The diagnosis of preterm labor requires cervical change and should not be based solely on the uterine contractions.
- **Ritodrine** and other β-mimetics have not changed pregnancy outcome. There are superior alternative agents such as **nifedipine, indomethacin,** and atosiban.

Ritonavir—(Norvir)

International Brand Name—Norvir (Australia, Hong Kong, Indonesia, Malaysia, South Africa, Taiwan, Thailand); Ritovir (India)

Drug Class

Antivirals; Protease inhibitors

Indications

HIV infection

Mechanism

Binds to active site of HIV protease

Dosage with Qualifiers

HIV infection—begin 300mg PO bid ×1d, then 400mg PO bid ×2d, then 500mg PO bid ×1d, then 600mg PO bid

NOTE: multiple drug interactions, including antiarrhythmics, antihistamines, ergot derivatives, GI mobility agents, neuroleptics, and hypnotics; check before prescribing.

- **Contraindications**—hypersensitivity to drug or class, use of a potent CYP3A4 inhibitor
- **Caution**—hepatic dysfunction

Maternal Considerations

There are few well-controlled studies of **ritonavir** in pregnant women. Published cohort studies and case reports do not suggest an increased risk of an adverse outcome during pregnancy. Many commonly used drugs alter the clearance of **ritonavir.** The patient should be questioned closely about concurrent drug use before prescribing.
Side effects include seizures, diabetes mellitus, thrombocytopenia, neutropenia, hyperlipidemia, elevated LFTs, N/V, diarrhea, asthenia, taste changes, paresthesias, vasodilation, anxiety, anorexia, pharyngitis, abdominal pain, myalgias, neuralgias, and rash.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. Placental transport of **ritonavir** is very low; most umbilical cord samples studied are below the level of detection. Limited transfer for most protease inhibitors reflects both their

high degree of plasma protein binding and their backward transport by P-glycoprotein in the placenta. Rodent studies are generally reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically. Combination therapy may enhance toxicity. Maternal toxicity from high doses leads to embryo toxicity.

Breastfeeding Safety

There are no adequate reports or well-controlled studies in nursing women. It is unknown whether **ritonavir** enters human breast milk. Breastfeeding is contraindicated in HIV-infected nursing women where formula is available to reduce the risk of neonatal transmission.

Drug Interactions

Inhibits CYP3A; agents that are extensively metabolized by CYP3A and have high first pass metabolism are especially susceptible to large increases in their AUC (>3-fold). It also inhibits CYP2D6 to a lesser extent. Use with CYP2D6 substrates may result in increases in the AUC (up to 2-fold) of the other agent, possibly requiring a dose reduction. **Ritonavir** can also induce CYP3A and other enzymes, including glucuronosyl transferase, CYP1A2, and possibly CYP2C9.

α-Adrenergic antagonists such as **alfuzosin** are contraindicated due to the potential for hypotension.

Antiarrhythmics (e.g., **amiodarone, bepridil, flecainide, propafenone, quinidine**) antihistamines (e.g., **astemizole, terfenadine**), **cisapride,** and **pimozide** are contraindicated due to the potential for serious and/or life-threatening cardiac arrhythmias.

Significant decreases in plasma concentrations of antifungals such as **voriconazole** may lead to a loss of antifungal activity and are contraindicated.

Ergot derivatives (e.g., **dihydroergotamine, ergonovine, ergotamine, methylergonovine**) are contraindicated due to the potential for serious and/or life-threatening acute ergot toxicity characterized by vasospasm and ischemia of the extremities and other tissues including the CNS.

Herbal products such as **St. John's wort** *(Hypericum perforatum)* may lead to loss of virologic response and possible resistance to **ritonavir** or to this class of protease inhibitors.

HMG-CoA reductase inhibitors such as **lovastatin** and **simvastatin** increase the risk of myopathy, including rhabdomyolysis. Use with **lovastatin** and **simvastatin** is not recommended. Use the lowest possible dose of **atorvastatin** with careful monitoring or, alternatively, consider an HMG-CoA reductase inhibitor such as **pravastatin** or **fluvastatin.**

Sedative-hypnotics such as **midazolam** and **triazolam** are contraindicated due to the potential for serious and/or life-threatening sedation or respiratory depression. **Ritonavir** increases the concentrations of **buspirone, clorazepate, diazepam, estazolam, flurazepam,** and **zolpidem.** A dose decrease may be needed.

Increases **indinavir** concentration (decreases C_{max} and increases C_{min}) and **saquinavir** concentration (increases AUC, C_{max}, and C_{min}).

The dosing of **didanosine** and **ritonavir** should be separated by 2.5h to avoid formulation incompatibility.

A decreased dose of either **tramadol** or **propoxyphene** may be needed.

Decreases the concentration of **meperidine** while increasing normeperidine concentration (a metabolite).

Increases the concentrations of **carbamazepine, clonazepam,** and **ethosuximide.**

Decreases the concentrations of **divalproex, lamotrigine,** and **phenytoin.**
May increase concentrations of **bupropion, nefazodone,** SSRIs, and TCAs, requiring a dose reduction in the antidepressant.
May increase **desipramine** levels, necessitating a dose reduction.
Use with **trazodone** increases the plasma concentrations of **trazodone.** Adverse events of nausea, dizziness, hypotension, and syncope have been observed. A lower dose of **trazodone** should be considered.
Increases **dronabinol** levels, requiring a decreased dose of **dronabinol.**
Increases **ketoconazole** and **itraconazole** levels; avoid **ketoconazole** or **itraconazole** >200 mg/day.
Increases **clarithromycin** levels; reduce the dose of **clarithromycin** by 50% for patients with CrCl 30-60ml/min, and by 75% for a CrCl <30ml/min.
Increases **rifabutin** and **rifabutin** metabolites, requiring a dose reduction of **rifabutin** by at least ¾ of the usual dose of 300 mg/d (e.g., 150mg qod or 3×/w). Further dose reduction may be necessary.
Decreases the concentration of **ritonavir,** potentially leading to a loss of virologic response. Alternate antimycobacterial agents such as **rifabutin** should be considered.
Decreases **atovaquone** levels; an increase in the **atovaquone** dose may be needed.
Increases **quinine** levels, possibly requiring a dose reduction of **quinine.**
Increases the concentrations of the β-blockers **metoprolol** and **timolol** and the calcium channel blockers **diltiazem, nifedipine,** and **verapamil.** Caution and clinical monitoring of patients are recommended. A dose decrease of these drugs may be needed.
Decreases **theophylline** levels, possibly requiring an increased dose of **theophylline.**
May increase **digoxin** levels. Caution should be exercised with appropriate monitoring of serum **digoxin** levels.
Increases **sildenafil**, **tadalafil**, and **vardenafil** concentrations. Use with **sildenafil** requires special caution as the AUC may increase more than 10-fold and result in an increase in adverse events, including hypotension, syncope, visual changes, and prolonged erection. The starting dose should not, in any case, exceed 25mg in a 48h period. The **tadalafil** dose should not exceed 10mg every 72h. The dose of **vardenafil** should not exceed 2.5mg every 72h.
Increases the levels of **cyclosporine, tacrolimus,** and **sirolimus**. Therapeutic concentration monitoring is recommended.
May increase the plasma levels of **fluticasone,** resulting in significantly reduced serum cortisol concentrations. Use with **fluticasone** is not recommended unless the potential benefit outweighs the risk of systemic corticosteroid side effects.
Decreases **methadone** concentration, possibly requiring a lower dose.
Increases the concentrations of **perphenazine, risperidone,** and **thioridazine.** A dose decrease may be needed.
The concomitant administration of **ritonavir** 500mg q12h and a fixed-combination oral contraceptive resulted in reductions of the **ethinyl estradiol** mean C_{max} and mean AUC by 32% and 40%, respectively. Alternate methods of contraception should be considered
A decreased dose of **dexamethasone, fluticasone,** and **prednisone** may be needed.
Increases **methamphetamine** concentration. Use with caution and consider a dose reduction.

References

Casey BM, Bawdon RE. Am J Obstet Gynecol 1998; 179:758-61.
Ghosn J, De Montgolfier I, Cornélie C, et al. Antimicrob Agents Chemother 2008; 52:1542-4.
Gingelmaier A, Kurowski M, Kästner R, et al. AIDS 2006; 20:1737-43.
Marzolini C, Rudin C, Decosterd LA, et al. AIDS 2002; 16:889-93.
Mirochnick M, Dorenbaum A, Holland D, et al. Pediatr Infect Dis J 2002; 21:835-8.
Pinelli JM, Symington AJ, Cunningham KA, Paes BA. Am J Obstet Gynecol 2002; 187:245-9.

Summary

Pregnancy Category: B
Lactation Category: NS

- **Ritonavir** is a protease inhibitor widely used during pregnancy as part of several treatment "cocktails."
- Breastfeeding is contraindicated in HIV-infected nursing women where formula is available to reduce the risk of neonatal transmission.
- Physicians are encouraged to register pregnant women under the Antiretroviral Pregnancy Registry (1-800-258-4263) for a better follow-up of the outcome while under treatment with **ritonavir.**

Rivastigmine—(Exelon)

International Brand Name—Exelon (Colombia, Hong Kong, India, Indonesia, Israel, Mexico, Peru, Philippines, South Africa, Taiwan, Thailand)

Drug Class

Cholinesterase inhibitors

Indications

Alzheimer's disease

Mechanism

Reversibly binds and inactivates acetylcholinesterase

Dosage with Qualifiers

Alzheimer's dementia—begin 1.5mg PO bid; increase gradually by 1.5mg/dose q2w as tolerated (6mg PO bid max)

NOTE: take with food.

- **Contraindications—**hypersensitivity to drug or class, sick sinus syndrome, bradycardia
- **Caution—**asthma, CV disease, COPD, peptic ulcer

Maternal Considerations

Rivastigmine is believed to enhance cholinergic function by increasing ACh concentration in the intact cholinergic nerves, keeping them functionally intact. There is no evidence that **rivastigmine** alters the course of the underlying disease. Clearance is altered by renal disease, though it is unclear whether the dose needs to be adjusted in response. There is no published experience with **rivastigmine** during pregnancy.
Side effects include seizures, hypotension, respiratory depression, and bradycardia.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **rivastigmine** crosses the human placenta. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than that used clinically. In pregnant rabbits receiving multiple PO doses, the fetus:placental tissue ratio of radioactivity averaged 0.5.

Breastfeeding Safety	There is no published experience in nursing women. It is unknown whether **rivastigmine** enters human breast milk. Only metabolites of the active drug were found in rabbit breast milk.
Drug Interactions	Because of their mechanism of action, cholinesterase inhibitors may interfere with the activity of anticholinergic medications. A synergistic effect may be expected when cholinesterase inhibitors are given with **succinylcholine,** similar neuromuscular blocking agents, or cholinergic agonists such as **bethanechol.**
References	Habucky K, Tse FL. Biopharm Drug Dispos 1998; 19:285-90.
Summary	**Pregnancy Category: B** **Lactation Category: S** • **Rivastigmine** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Rizatriptan—(Maxalt; Rizalt)

International Brand Name—Maxalt (Brazil, Canada, Chile, Costa Rica, El Salvador, England, Germany, Guatemala, Ireland, Mexico, Netherlands, New Zealand, Panama, Peru, Poland); Maxalt RPD (Canada, Chile, Peru, Venezuela); Rizalt (Israel)

Drug Class	Migraines; Serotonin receptor agonists
Indications	Migraine headache
Mechanism	5-HT_1 agonist
Dosage with Qualifiers	Migraine headache—5-10mg PO ×1, may repeat in 2h; max 24mg/d *NOTE: max 5mg/dose, 3 doses/24h if taking* ***propranolol.*** • **Contraindications**—hypersensitivity to drug or class, CAD, MI, uncontrolled hypertension, 5-HT_1 agonist <24h, MAOI <14d, ergot derivative <24h, basilar migraine, hemiplegic migraine • **Caution**—peripheral or cerebrovascular disease, cardiac risk factors, hepatic dysfunction
Maternal Considerations	There is no published experience with **rizatriptan** during pregnancy. Clearance is slower in nonpregnant women compared to men. ***Side effects*** include acute MI, arrhythmia, coronary spasm, palpitations, hypertensive crisis, cerebral hemorrhage, stroke, bowel or peripheral vascular ischemia, angioedema, somnolence, chest pain, neck tightness, dizziness, paresthesias, flushing, N/V, diarrhea, dyspnea, decreased mental acuity, tremor, and euphoria.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **rizatriptan** crosses the human placenta. A review of the outcomes of 25 prospective reports in the Pregnancy Registry and other sources does not suggest **rizatriptan** predisposes to either spontaneous abortions or congenital anomalies. Rodent studies are generally reassuring, revealing no evidence of teratogenicity. However, embryo toxicity and IUGR were noted unrelated to maternal toxicity.

Breastfeeding Safety	There is no published experience in nursing women. It is unknown whether **rizatriptan** enters human breast milk.
Drug Interactions	**Propranolol** increased the plasma concentrations of **rizatriptan** by 70%. Ergot-containing drugs have been reported to cause prolonged vasospastic reactions. Because there is a theoretical basis that these effects may be additive, use of ergotamine-containing or ergot-type medications (e.g., **dihydroergotamine, methysergide**) and **rizatriptan** within 24h is contraindicated. Because their vasospastic effects may be additive, use with other 5-HT_1 agonists within 24h of each other is not recommended. SSRIs (e.g., **fluoxetine, fluvoxamine, paroxetine, sertraline**) have been reported rarely to cause weakness, hyperreflexia, and incoordination when co-administered with 5-HT_1 agonists. Should not be used with MAO-A inhibitors and nonselective MAOIs; it has been shown that moclobemide (a specific MAO-A inhibitor) increased the systemic exposure of **rizatriptan** and its metabolite.
References	Fiore M, Shields KE, Santanello N, Goldberg MR. Cephalalgia 2005; 25:685-8.
Summary	**Pregnancy Category: C** **Lactation Category: U** • **Rizatriptan** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk. • There are alternative agents for which there is more experience regarding use during pregnancy and lactation. • Health care workers are urged to report prenatal exposures to **rizatriptan** to the manufacturer's Pregnancy Registry (1-800-986-8999).

Rocuronium—(Zemuron)

International Brand Name—None identified.

Drug Class	Neuromuscular blockers, nondepolarizing
Indications	Anesthetic paralysis
Mechanism	Nondepolarizing neuromuscular blocker
Dosage with Qualifiers	Anesthetic, neuromuscular paralysis—0.6-1.2mg/kg IV for induction, 0.1-0.2mg/kg IV q12min based on train-of-4 response to peripheral nerve stimulation *NOTE: onset 1min, duration 30min.* • **Contraindications**—hypersensitivity to drug or class • **Caution**—obesity, respiratory or hepatic dysfunction
Maternal Considerations	There are no adequate reports or well-controlled studies of **rocuronium** in pregnant women, though it has been used for cesarean delivery as part of rapid-sequence general anesthesia in patients who have a contraindication to **succinylcholine** (e.g., suspected malignant hyperthermia, upper-motor neuron lesion). However, the manufacturer notes that tracheal intubation can be problematic 60sec after administration, and does not recommend

its use (i.e., replacing **succinylcholine**) for rapid-sequence induction of general anesthesia for cesarean delivery. **Rocuronium** neuromuscular blockade may be prolonged by **magnesium sulfate** infusion or in the postpartum period if dosing is based on total rather than lean body weight. ***Side effects*** include arrhythmia, bronchospasm, hypotension, hypertension, and injection site pain.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. **Rocuronium** crosses the human placenta. In women undergoing rapid-sequence induction of general anesthesia, the F:M ratio approximates 0.18 at delivery. No clinical sequelae are noted. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically, assuming the mother was properly oxygenated.

Breastfeeding Safety

There is no published experience in nursing women. However, considering the indication and dosing, limited use of **rocuronium** is unlikely to pose a clinically significant risk to the breastfeeding neonate.

Drug Interactions

If used after **succinylcholine,** it should not be given until recovery from the **succinylcholine** is observed. The median duration of action of **rocuronium** 0.6mg/kg administered after a 1mg/kg dose of **succinylcholine** when T_1 returned to 75% of control was 36min (range 14-57, n = 12) vs. 28min (17-51, n = 12) without **succinylcholine.**

Use of inhalation anesthetics enhances the activity of other neuromuscular blocking agents (**enflurane** > **isoflurane** > **halothane**). **Isoflurane** and **enflurane** may also prolong the duration of action of the initial and maintenance doses of **rocuronium** and decrease the average dose of **rocuronium** required by 40% compared to opioid/nitrous oxide/oxygen anesthesia. In one study, use of **enflurane** in 10 patients resulted in a 20% increase in mean clinical duration of the initial intubating dose, and a 37% increase in the duration of subsequent maintenance doses, when compared to 10 patients under opioid/nitrous oxide/oxygen anesthesia. The duration of maintenance doses was affected to a greater extent, increasing by 30-50% under either **enflurane** or **isoflurane** anesthesia.

Potentiation by these agents is also observed with respect to the infusion rates of **rocuronium** required to maintain approximately 95% neuromuscular block. Under **isoflurane** and **enflurane** anesthesia, the infusion rates are decreased by approximately 40% compared to opioid/nitrous oxide/oxygen anesthesia. The median spontaneous recovery time (from 25% to 75% of control T_1) is not affected by **halothane,** but is prolonged by **enflurane** (15% longer) and **isoflurane** (62% longer). Reversal-induced recovery of **rocuronium** neuromuscular block is minimally affected by anesthetic technique.

In 2 of 4 patients receiving chronic anticonvulsant therapy, apparent resistance to the effects of **rocuronium** was observed in the form of diminished magnitude of neuromuscular block, or shortened clinical duration. As with other nondepolarizing neuromuscular blocking drugs, use with **carbamazepine** or **phenytoin** shortens the duration of neuromuscular blockade and may require a higher infusion rate due to the development of resistance to nondepolarizing muscle relaxants.

Drugs that may enhance the neuromuscular blocking action of nondepolarizing agents such as **rocuronium** include certain antibiotics (e.g., aminoglycosides, **bacitracin, colistin,** polymyxins, sodium colistimethate, tetracyclines, **vancomycin**).

Recurrent paralysis may occur when injecting **quinidine** during the recovery from other muscle relaxants.
Magnesium sulfate administered for the management of preeclampsia or preterm labor may enhance neuromuscular blockade.

References

Gaiser RR, Seem EH. Br J Anesth 1996; 77:669-71.
Gin T, Chan MT, Chan KL, Yuen PM. Anesth Analg 2002; 94:686-9.
Puhringer FK, Sparr HJ, Mitterschiffthaler G, et al. Anesth Analg 1997; 84:352-4.

Summary

Pregnancy Category: C
Lactation Category: S

- **Rocuronium** should be used during pregnancy and lactation only if the potential benefit justifies the perinatal risk.
- There are alternative agents for which there is more experience regarding use during pregnancy and lactation.

Rofecoxib—(NOTE: This drug has been withdrawn from the market.)

Drug Class

Analgesics, non-narcotic; COX-2 inhibitors; NSAID

Indications

Dysmenorrhea, rheumatoid and osteoarthritis, mild to moderate pain

Mechanism

Specific COX-2 inhibitor

Dosage with Qualifiers

*NOTE: Merck & Co voluntarily withdrew **rofecoxib** from the worldwide market in 2004 after evidence emerged from several trials of an increased risk of CV death compared to placebo after 18mo of therapy.*
Dysmenorrhea—50mg PO qd for a max of 5d
Rheumatoid arthritis—begin 12.5mg PO qd; max 25mg/d
Osteoarthritis—25mg/d; max 25mg/d
Mild to moderate pain—50mg PO qd for a max of 5d

NOTE: hepatic dosing.

- **Contraindications**—hypersensitivity to drug or class, NSAID-induced asthma or urticaria, hepatic failure, severe renal dysfunction, aspirin triad
- **Caution**—GI bleeding, nasal polyps, hepatic or renal dysfunction, CHF, hypertension, ischemic heart disease, hypovolemia, asthma

Maternal Considerations

Rofecoxib was withdrawn from the market in 2004. It is a COX-2 inhibitor that has analgesic, anti-inflammatory, and antipyretic properties. Because of its lack of *platelet* effects, **rofecoxib** is not a substitute for **aspirin** for CV *prophylaxis*. It is no more effective than **diclofenac** and **ibuprofen** for the relief of mild to moderate pain when used at maximal doses. Further, it only modestly reduces the risk of GI reactions (1.3% vs. 1.8% after 1y of treatment). There are no adequate reports or well-controlled studies of **rofecoxib** in pregnant women. Though **rofecoxib** inhibits spontaneous contractions of isolated rat myometrium at lower concentrations than **indomethacin,** it has no effect on either the onset or duration of labor in rodents.

Side effects include GI bleeding or ulcer, esophagitis, bronchospasm, hypertension, CHF, MI, hepatotoxicity, renal failure, renal papillary necrosis, anemia, blood dyscrasias, epigastric pain, N/V, edema, dyspepsia, fatigue, and dizziness.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. **Rofecoxib** crosses the human placenta. Fetal levels are dependent on maternal, as NSAID agents are not metabolized by the fetal kidney. Similar to other NSAIDs, **rofecoxib** is associated with oligohydramnios and constriction of the ductus arteriosus. The latter reverses with cessation, and the long-term impact of in utero ductal constriction on the otherwise healthy fetus is currently unknown. Rodent studies are generally reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically. Embryotoxicity was noted at higher doses.

Breastfeeding Safety

Rofecoxib (25mg) was given to 6 women at weaning. Blood and milk were sampled up to 72h postdose. The median (range) M:P ratio and infant "dose" were 0.25 (0.16-0.32) and 2.1% (1.8-3.2%), respectively. Thus, the use of **rofecoxib** during breastfeeding is unlikely to pose harm based on the low transfer into human milk.

Drug Interactions

NSAIDs may diminish the antihypertensive effect of ACEIs.
Use with low-dose **aspirin** may result in an increased rate of GI ulceration or other complications.
Clinical studies, as well as post-marketing observations, have shown that NSAIDs can reduce the natriuretic effect of **furosemide** and thiazides in some patients. This response has been attributed to inhibition of renal prostaglandin synthesis.
NSAIDs may increase plasma **lithium** levels and reduce renal **lithium** clearance. Patients should be observed carefully for signs of **lithium** toxicity.
Use with **rifampin**, a potent inducer of hepatic metabolism, produced an approximate 50% decrease in **rofecoxib** plasma levels. A starting daily dose of 25mg of **rofecoxib** should be considered for the treatment of osteoarthritis when used with potent inducers of hepatic metabolism.
Increases the plasma **theophylline** concentrations ($AUC_{(0\text{-}8)}$) by 38-60% in healthy subjects. Adequate monitoring of **theophylline** plasma levels should be considered when **rofecoxib** is initiated or changed in patients receiving **theophylline.** This suggests that **rofecoxib** is a modest inhibitor of CYP1A2. Therefore, there is a potential for an interaction with other drugs that are metabolized by CYP1A2 (e.g., **amitriptyline, tacrine, zileuton**).
Anticoagulant activity should be monitored, particularly in the first few days after initiating or changing **rofecoxib** therapy, in patients receiving **warfarin** or similar agents.

References

Gardiner SJ, Begg EJ, Zhang M, Hughes RC. Eur J Clin Pharmacol 2005; 61:405-8.
http://www.fda.gov/cder/drug/infopage/vioxx/default.htm
Editorial. Prescrire Int 2000; 9:166-7.
Dore M, Mellier G, Benchaib M, et al. BJOG 2002; 109:983-8.

Summary

Pregnancy Category: C
Lactation Category: U

- Merck & Co withdrew **rofecoxib** from the worldwide market in 2004 after evidence emerged from several trials of an increased risk of CV death

- Health care practitioners are urged to report any prenatal exposure to **rofecoxib** by calling the manufacturer's Pregnancy Registry (1-800-986-8999).
- There are numerous alternative agents on the market.

Ropinirole—(Requip)

International Brand Name—Requip (Argentina, Canada, Chile, England, France, Germany, Hong Kong, Ireland, Israel, Korea, Malaysia, New Zealand, Singapore)

Drug Class	Antiparkinson agents; Dopaminergics
Indications	Parkinson's disease
Mechanism	Dopamine agonist
Dosage with Qualifiers	Parkinson's disease—begin 0.25mg PO tid; increase 0.25mg PO tid/w; max 24mg/d • **Contraindications**—hypersensitivity to drug or class • **Caution**—unknown
Maternal Considerations	There is no published experience with **ropinirole** during pregnancy. ***Side effects*** include somnolence, atrial fibrillation, syncope, hypotension, N/V, hallucinations, dizziness, fatigue, dyspepsia, malaise, edema, chest or abdominal pain, sweating, pharyngitis, anorexia, and visual changes.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **ropinirole** crosses the human placenta. Rodent teratogenicity studies reveal IUGR and digit abnormalities at doses that are multiples of the MRHD.
Breastfeeding Safety	There is no published experience in nursing women. It is unknown whether **ropinirole** enters human breast milk. **Ropinirole** inhibits prolactin secretion in humans and could interfere with establishment of the milk reflex.
Drug Interactions	CYP1A2 is the major enzyme responsible for the metabolism of **ropinirole.** An adjustment of the **ropinirole** dose may be required if therapy with a known potent inhibitor of CYP1A2 is stopped or started. Oral administration of **ropinirole** increased the mean steady-state C_{max} of **levodopa** by 20%, but its AUC was unaffected. Use with **ciprofloxacin,** an inhibitor of CYP1A2, increased the **ropinirole** AUC by 84% on average, and C_{max} by 60%. Population pharmacokinetic analysis studies reveal that estrogens (mainly **ethinyl estradiol**) reduce the oral clearance of **ropinirole** by ⅓. However, a dose adjustment may not be needed for **ropinirole** because patients must be carefully titrated with **ropinirole** to tolerance or adequate effect. A dose adjustment may be required if the estrogen therapy is stopped or started. Since **ropinirole** is a dopamine agonist, it is possible that dopamine antagonists, such as neuroleptics (phenothiazines, butyrophenones, thioxanthenes) or **metoclopramide,** may diminish the effectiveness of **ropinirole.** Patients with major psychotic disorders treated with neuroleptics should only be treated with dopamine agonists if the potential benefits outweigh the risks.

References	There is no published experience in pregnancy or during lactation.
Summary	**Pregnancy Category: C** **Lactation Category: U** • **Ropinirole** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Rosiglitazone—(Avandia)

International Brand Name—Avandia (Hong Kong, Israel, Malaysia, Philippines, Singapore, Taiwan, Thailand); Rezult (India); Rosi (Israel); Rossini (Israel)

Drug Class	Antidiabetic agents; Thiazolidinediones
Indications	Diabetes mellitus, type 2
Mechanism	Increases insulin sensitivity
Dosage with Qualifiers	Diabetes mellitus, type 2—begin 4PO qd; max 8mg/d, adjust for glucose control *NOTE: check AST/ALT at baseline and then q2mo ×12mo.* • **Contraindications**—hypersensitivity to drug or class, type 1 diabetes mellitus, diabetic ketoacidosis, concurrent insulin use, CHF (NYHA Class III and IV) • **Caution**—CHF (NYHA Class I and II), hypertension, hepatic dysfunction, edema
Maternal Considerations	**Rosiglitazone** may be used alone or in combination with **metformin** or a sulfonylurea. The short-term use of **rosiglitazone** and **clomiphene** is more efficacious than **metformin** and **clomiphene** for ovulation induction in women with **clomiphene**-resistant PCOS. Improved glucose control may also lead to ovulation in premenopausal, anovulatory women and increase the risk of an unplanned pregnancy. Paradoxically, it may interfere with ovulation in spontaneously cycling women. Concern that **rosiglitazone** may increase the risk of adverse cardiac events remains controversial. The published experience with **rosiglitazone** during pregnancy is limited to case reports and small series. ***Side effects*** include hepatotoxicity, hepatitis, elevated LFTs, anemia, CHF, URI, fluid retention, edema, headache, weight gain, and hypoglycemia.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. **Rosiglitazone** crosses the human placenta. In a study of women undergoing elective abortion, drug transfer increased after 10w, achieving roughly a 2:1 M:F concentration gradient. Minimal amounts of **rosiglitazone** in AF suggest fetal metabolism. In another study employing the dual perfused isolated placental cotelydon, the clearance indices for low and high concentrations of **rosiglitazone** were 0.14 ± 0.04 and 0.20 ± 0.08, suggesting the drug crosses the placenta at a relatively low rate. Fetal accumulation occurred in only 1/5 placentas at 16.4ng/ml (5%) for an 8mg dose and in 2/5 placentas ranging from 0 to 74ng/ml (5% to 8%) at higher concentrations. Rodent studies are generally reassuring, revealing no evidence of teratogenicity despite the use of doses higher than those used clinically. High doses were associated with fetal losses and IUGR, possibly reflecting sustained hypoglycemia.

Breastfeeding Safety ..... There is no published experience in nursing women. It is unknown whether **rosiglitazone** enters human breast milk. It is excreted into rat milk.

Drug Interactions ..... An inhibitor of CYP2C8 (e.g., **gemfibrozil**) might increase the AUC for **rosiglitazone,** while an inducer of CYP2C8 (e.g., **rifampin**) might decrease the AUC. Changes in diabetes treatment may be needed based upon clinical response.

References .....

Cataldo NA, Abbasi F, McLaughlin TL, et al. Fertil Steril 2001; 76:1057-9.
Chan LY, Yeung JH, Lau TK. Fertil Steril 2005; 83:955-8.
Choi JS, Han JY, Ahn HK, et al. Diabetes Care 2006; 29:2176.
FDA (May 21, 2007). "FDA Issues Safety Alert on Avandia."
Haddad GF, Jodicke C, Thomas MA, et al. Reprod Toxicol 2008; 26:183-4.
Holmes HJ, Casey BM, Bawdon RE. Am J Obstet Gynecol 2006; 195:1715-9.
Rouzi AA, Ardawi MS. Fertil Steril 2006; 85:428-35.

Summary .....

Pregnancy Category: C
Lactation Category: U

- **Rosiglitazone** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.
- Insulin is the drug of choice for the treatment of diabetes during pregnancy.

Rubella virus vaccine, live—(Meruvax II)

International Brand Name—Cendevax (South Africa); Ervevax (Australia, Austria, Bulgaria, Czech Republic, England, Germany, Italy, Malaysia, Netherlands, Philippines, Switzerland, Taiwan, Thailand); Gunevax (Philippines, Thailand); Meruvax II (Australia); Rubavax (England); Rubeaten (Austria, Czech Republic, Greece, Italy, Spain, Switzerland); Rubeaten Berna (Malaysia, Philippines, South Africa, Taiwan, Thailand); Rudivax (Malaysia, Taiwan)

Drug Class ..... Vaccines

Indications ..... Rubella susceptibility

Mechanism ..... Active immunization

Dosage with Qualifiers ..... Susceptible women of childbearing age—0.5ml SC

- **Contraindications**—hypersensitivity to drug or class, allergy to **neomycin,** any active febrile infection, untreated TB, immunosuppressive therapy (except replacement corticosteroids), blood dyscrasias, lymphoma, primary or acquired immunodeficiency (including AIDS)
- **Caution**—do not give with immunoglobulin

Maternal Considerations ..... The **rubella virus vaccine** produces a modified, noncommunicable rubella infection in susceptible persons. Vaccine-induced immunity persists for at least 10y without significant decline. Vaccinating susceptible women confers individual protection against rubella during a subsequent pregnancy, thus preventing congenital rubella. Yet, only about half the world's countries vaccinate for rubella. Outbreaks continue to occur in countries with national immunization programs, typically involving women born in other countries.

Perhaps the most convenient time to vaccinate is immediately postpartum while the patient is still hospitalized. In that instance, conception should be delayed 1mo. Unfortunately, the opportunity is often missed because of physician/hospital oversight. Rubella susceptibility should be confirmed serologically before vaccinating.
Side effects include injection site reaction, mild regional lymphadenopathy, urticaria, rash, malaise, sore throat, fever, headache, N/V, diarrhea, polyneuritis, syncope, and thrombocytopenia.

Fetal Considerations

Rubella vaccine virus has been found in the products of conception in women undergoing termination and in the offspring of vaccinated women. Similar to natural viral infections, newborns may shed virus for an extended time.
The manufacturer reports that in over 700 women inadvertently vaccinated within 3mo before or after conception, no newborn had stigmas of congenital rubella syndrome. Pregnancy termination is not recommended solely because of inadvertent vaccination.

Breastfeeding Safety

Rubella vaccine virus is excreted into human breast milk, and neonatal infection is reported. However, the risk is generally considered small and immunization not a reason to avoid breastfeeding.

Drug Interactions

Use with immune globulins may interfere with the expected immune response.

References

Bath SK, Singleton JA, Strikas RA, et al. Am J Infect 2000; 28:327-32.
Buimovici-Klein E, Hite RL, Byrne T, Cooper LZ. J Pediatr 1977; 91:939-41.
Centers for Disease Control and Prevention. MMWR Morb Mortal Wkly Rep 2001; 50:1117.
Hofmann J, Kortung M, Pustowoit B, et al. J Med Virol 2000; 61:155-8.
Landes RD, Bass JW, Millunchick EW, Oetgen WJ. J Pediatr 1980; 97:465-7.

Summary

Pregnancy Category: C
Lactation Category: U

- **Rubella virus vaccine** prevents congenital rubella.
- Inadvertent vaccination during pregnancy is not associated with an adverse outcome.
- The immediate postpartum period is an excellent opportunity to vaccinate susceptible women, an opportunity overlooked too often.

Salmeterol inhaled—(Serevent; Serevent Diskus)

International Brand Name—Aeromax (Germany); Salmeter (India); Seretide (Philippines); Serevent (Hong Kong, Indonesia, Japan, Malaysia, New Zealand, Philippines, Taiwan, Thailand); Serevent Inhaler and Disks (Australia); Serobid (India); Zamitrel (Mexico)

Drug Class	Adrenergic agonists; β-Agonists; Bronchodilators
Indications	Asthma prophylaxis, exercise-induced asthma, COPD
Mechanism	Selective β_2-adrenergic agonist
Dosage with Qualifiers	Asthma prophylaxis—2 puffs INH q12h Exercise-induced asthma—2 puffs INH ×1 COPD—2 puffs INH q12h *NOTE: 21mcg/spray MDI.* • **Contraindications**—hypersensitivity to drug or class, acute asthma, arrhythmia • **Caution**—hypertension, CV disease, diabetes mellitus, seizures, hyperthyroidism, hypokalemia
Maternal Considerations	Asthma is estimated to affect up to 4% of pregnancies. For pregnant women with persistent asthma, inhaled **cromolyn** is generally considered the first-line therapy, followed by inhaled **budesonide** if symptoms worsen. **Salmeterol** is a long-acting β-adrenergic agonist. It also is a potent inhibitor of mast cell release of histamine, leukotrienes, and prostaglandin D_2. Systemic levels of **salmeterol** are low or undetectable after inhalation. It has also been used for the treatment of altitude sickness. There are no published trials of its use during pregnancy, and recommendations are based on "expert" opinion. It is typically used as a secondary agent. ***Side effects*** include angioedema, paradoxical bronchospasm, laryngospasm, arrhythmia, hypertension, headache, nasal congestion, rhinitis, pharyngitis, urticaria, palpitations, tachycardia, tremor, and nervousness.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **salmeterol** crosses the human placenta. Transfer across the rat placenta is low. Considering the low systemic levels achieved and the poor placental transport, it is unlikely the fetus is exposed to a clinically relevant concentration. When given orally at doses 50-100× greater than those inhaled, **salmeterol** is associated with cleft palate and abnormal ossification. These studies do not seem relevant to clinical practice.
Breastfeeding Safety	There is no published experience with **salmeterol** in breastfeeding women. However, considering the dose and route, it is unlikely the breastfed neonate would ingest clinically relevant amounts. The transfer into rodent milk is limited.
Drug Interactions	MAOIs or TCAs may potentiate the CV actions of **salmeterol;** use with extreme caution if the patient is being treated with or within 2w of these agents. β-Adrenergic receptor blocking agents not only block the pulmonary effect of β-agonists, but may also produce severe bronchospasm in asthmatic patients. Patients with asthma should not normally be treated with β-blockers. Under certain circumstances (e.g., as prophylaxis after MI), there may be no

acceptable alternative to the β-adrenergic blocker. In this setting, cardioselective β-blockers can be considered, although they should be administered with caution.
ECG changes and/or hypokalemia secondary to non–potassium-sparing diuretics (such as loop or thiazide diuretics) can be acutely worsened by β-agonists, especially when the recommended dose of the β-agonist is exceeded.

References

Blaiss MS; National Institute of Health. Allergy Asthma Proc 2004; 25:375-9.
Manchee GR, Barrow A, Kulkarni S, et al. Drug Metab Dispos 1993; 21:1022-8.

Summary

Pregnancy Category: C
Lactation Category: S

- **Salmeterol** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.
- It seems unlikely that it poses any significant risk to fetus or neonate when used as directed.

Salsalate—(Amigesic; Anaflex 750; Artha-G; Carsalate; Diagen; Disalcid; Marthritic; Mono-Gesic; Nobegyl; Ro-Salcid; Salflex; Salgesic; Salicylsalicylic acid; Salsitab)

International Brand Name—Atisuril (Spain); Disal (Korea, Taiwan); Disalgesic (Germany); Salina (Japan); Saril (Korea); Umbradol (Spain)

Drug Class

Analgesics, non-narcotic; Salicylates

Indications

Arthritis

Mechanism

Unknown; prostaglandin synthesis inhibitor

Dosage with Qualifiers

Arthritis—1000mg PO tid

- **Contraindications**—hypersensitivity to drug or class, NSAID/ASA-induced asthma history, flu-like symptoms or varicella, peptic ulcer disease
- **Caution**—renal dysfunction

Maternal Considerations

Salsalate is a dimer of salicylic acid and absorbed in the intestine. Unlike **aspirin, salsalate** does not inhibit platelet aggregation, and there is no increase in GI bleeding over placebo. There is no published experience during pregnancy.
Side effects include hepatic or nephrotoxicity, Reye's syndrome, N/V, epigastric pain, fatigue, rash, and dizziness.

Fetal Considerations

There is no published experience in human fetuses. It is unknown whether **salsalate** crosses the human placenta. **Salsalate** and salicylic acid are teratogenic and embryocidal in rats when given in doses 4-5× the usual human dose; teratogenicity is not seen when given at twice the usual human dose.

Breastfeeding Safety

There is no published experience in nursing women. It is unknown whether **salsalate** enters human breast milk. Salicylic acid, the primary metabolite, reaches an M:P ratio approximating unity.

Drug Interactions

Salicylates antagonize the uricosuric action of drugs used to treat gout.
Aspirin and other salicylates will be additive to **salsalate** and may lead to salicylate toxicity.
Drugs and foods that raise urine pH will increase renal clearance and urinary excretion of salicylic acid, thus lowering plasma levels; acidifying drugs or foods will decrease urinary excretion and increase plasma levels.
Use with anticoagulant drugs may predispose to systemic bleeding.
May enhance the hypoglycemic effect of sulfonylurea oral antidiabetic drugs.
Salicylate competes with a number of drugs for protein binding sites, notably **methotrexate, naproxen,** penicillin, **phenytoin,** sulfinpyrazone, **thiopental,** thyroxine, triiodothyronine, **warfarin,** and possibly corticosteroids.

References

There is no published experience in pregnancy or during lactation.

Summary

Pregnancy Category: C
Lactation Category: U

- **Salsalate** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.
- There are alternative agents for which there is more experience regarding use during pregnancy and lactation.

Saquinavir—(Fortovase; Invirase)

International Brand Name—Fortovase (Argentina, Australia, Brazil, Canada, Chile, Colombia, Ecuador, Hong Kong, Israel, Mexico, Peru, Philippines, Taiwan, Thailand, Uruguay, Venezuela)

Drug Class

Antivirals; Protease inhibitors

Indications

HIV adjunct treatment

Mechanism

HIV protease inhibitor

Dosage with Qualifiers

HIV adjunct treatment—600mg PO tid (Invirase) or 1200mg tid PO (Fortovase) within 2h of eating

- **Contraindications**—hypersensitivity to drug or class; **astemizole, cisapride,** ergot, **midazolam, terfenadine,** or **triazolam** use
- **Caution**—hepatic dysfunction, use of **lovastatin** or **simvastatin**

Maternal Considerations

Saquinavir is well-tolerated during pregnancy and is part of several treatment regimens. Its clearance is increased by pregnancy, and the usually recommended dose may be inadequate. **Ritonavir** significantly increases **saquinavir** concentration, and the combination during pregnancy may have some advantage.
Side effects include N/V, diarrhea, diabetes mellitus, hyperglycemia, peripheral neuropathy, headache, buccal ulceration, rash, dyspepsia, abdominal pain, and eczema.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. **Saquinavir,** like many protease inhibitors, does not significantly cross the human placenta probably because of reverse placental P-glycoprotein transport whose expression

it enhances. Unbound concentrations of **saquinavir** are likely to be substantially lower in umbilical cord than maternal plasma. It is unlikely to pose a significant risk to the fetus. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR.

Breastfeeding Safety

There is no published experience in nursing women. It is unknown whether **saquinavir** enters human breast milk. Breastfeeding is contraindicated in HIV-infected nursing women where formula is available to reduce the risk of neonatal transmission.

Drug Interactions

The metabolism of **saquinavir** is mediated by CYP3A4 (90% of the hepatic metabolism) and it is a substrate for P-glycoprotein (Pgp). Drugs that affect CYP3A4 and/or Pgp may modify the pharmacokinetics of **saquinavir.** Similarly, **saquinavir** might also modify the pharmacokinetics of other drugs that are substrates for CYP3A4 or Pgp.

*Drugs that should not be used with **saquinavir** include:*
Antiarrhythmics (e.g., **amiodarone, bepridil, flecainide, propafenone, quinidine**) and antihistamines (e.g., **astemizole, terfenadine**), which may cause serious and/or life-threatening reactions.
Ergot derivatives (e.g., **dihydroergotamine, ergonovine, ergotamine, methylergonovine**), which may cause serious and life-threatening acute ergot toxicity characterized by peripheral vasospasm and ischemia of the extremities and other tissues.
Garlic capsules decrease **saquinavir** plasma levels and should not be used while taking **saquinavir** as the sole protease inhibitor.
Cisapride is contraindicated due to the potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
Rifampin decreases the concentration of **saquinavir** and should be avoided if possible.
Herbal products such as **St. John's wort** *(Hypericum perforatum)* may lead to the loss of virologic response and possible resistance to **saquinavir** or to this class of protease inhibitors.
Sedative-hypnotic agents (e.g., **midazolam, triazolam**) may result in prolonged or increased sedation or respiratory depression

An alteration in the dose or regimen may be necessary when used with:
NNRTIs (e.g., **delavirdine, efavirenz, nevirapine**), which may decrease **saquinavir** levels. **Saquinavir** should not be given as the sole protease inhibitor.
HIV protease inhibitors (e.g., **indinavir, nelfinavir, ritonavir**), which can increase **saquinavir** concentrations. **Saquinavir** 1200mg bid with **nelfinavir** 1250mg bid results in adequate drug concentrations of both protease inhibitors. The **lopinavir/ritonavir** coformulated capsule increases **saquinavir.**
Increases the antiarrhythmic effects of **lidocaine;** monitor the levels.
May increase the anticoagulant effect of **warfarin;** monitor the INR.
Anticonvulsant drugs (e.g., **carbamazepine, phenobarbital, phenytoin**) decrease the concentration of **saquinavir.** Use with caution.
Clarithromycin increases **saquinavir** and **clarithromycin** levels. No dose adjustment is required when the two drugs are co-administered for <7-10d and there is normal renal function. However, the **clarithromycin** dose should be reduced by 50% in patients with CrCl 30-60ml/min, and by 75% if <30ml/min.
Ketoconazole and potentially **itraconazole** increase the **saquinavir** level with no change in the **ketoconazole** concentration.

Rifabutin and **rifampin** decrease the **saquinavir** level while increasing the **rifabutin** level. **Saquinavir** should not be given as the sole protease inhibitor.
Increases the levels of benzodiazepines (e.g., **alprazolam, clorazepate, diazepam, flurazepam**), perhaps necessitating a decrease in the benzodiazepine dose.
Increases the levels of calcium channel blockers (e.g., **amlodipine, diltiazem, felodipine, isradipine, nicardipine, nifedipine, nimodipine, nisoldipine, verapamil**), perhaps necessitating a decrease in the dose of the calcium channel blocker.
Dexamethasone decreases the **saquinavir** level, perhaps decreasing efficacy.
Increases the level and effect of some HMG-CoA reductase inhibitors (e.g., **atorvastatin, lovastatin, simvastatin**). Use the lowest possible dose with careful monitoring or consider other HMG-CoA reductase inhibitors (e.g., **fluvastatin, pravastatin, rosuvastatin**).
Increases the levels of some immunosuppressants (e.g., **cyclosporine,** rapamycin, **tacrolimus**).
The dose of **methadone** may need to be increased.
Alternative or additional contraceptive measures should be used when estrogen-based oral contraceptives and **saquinavir** are co-administered.
Increases levels of PDE5 inhibitors (e.g., **sildenafil, tadalafil, vardenafil**). Use with caution at reduced doses (**sildenafil:** 25mg q48h; **tadalafil:** ≤10mg q72h; **vardenafil:** ≤2.5mg q72h) with increased monitoring of adverse events.
Increases the levels of TCAs such as **amitriptyline** and **imipramine**. Therapeutic concentration monitoring is recommended.

References

Acosta EP, Zorrilla C, Van Dyke R, et al. HIV Clin Trials 2001; 2:460-5.
Huisman MT, Smit JW, Wiltshire HR, et al. Mol Pharmacol 2001; 59:806-13.
Lopez-Cortes LF, Ruiz-Valderas R, Rivero A, et al. Ther Drug Monit 2007; 29:171-6.
Mirochnick M, Dorenbaum A, Holland D, et al. Pediatr Infect Dis J 2002; 21:835-8.
Mölsä M, Heikkinen T, Hakkola J, et al. Clin Pharmacol Ther 2005; 78:123-31.
Parry S, Zhang J. Am J Obstet Gynecol 2007; 196:476.e1-6.
Sudhakaran S, Rayner CR, Li J, et al. Br J Clin Pharmacol 2007; 63:315-21.
Vithayasai V, Moyle GJ, Supajatura V, et al. J Acquir Immune Defic Syndr 2002; 30:410-2.

Summary

Pregnancy Category: B
Lactation Category: NS

- **Saquinavir** is an effective protease inhibitor when used in conjunction with other retroviral agents.
- It should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.
- Breastfeeding is contraindicated in HIV-infected nursing women where formula is available to reduce the risk of neonatal transmission.
- Physicians are encouraged to register pregnant women under the Antiretroviral Pregnancy Registry (1-800-258-4263) for a better follow-up of the outcome while under treatment with **saquinavir.**

Sargramostim—(GM-CSF; Granulocyte Macrophage-Colony Stimulating Factor; Leukine; Prokine)

International Brand Name—Leucogen (Korea)

Drug Class	Hematopoietic agents
Indications	Neutropenia post bone marrow transplant, post-AML chemotherapy, progenitor mobilization, bone marrow transplant failure
Mechanism	Stimulates granulocyte and macrophage proliferation and differentiation
Dosage with Qualifiers	Neutropenia post bone marrow transplant—250mcg/m^2 IV qd over 2h beginning 2-4h after transplant and >24h post chemotherapy Neutropenia post-AML chemotherapy—250mcg/m^2 IV qd over 4h beginning day 11 post chemotherapy; continue until ANC >1500 ×3d, max 42d Progenitor mobilization—250mcg/m^2 IV qd over 24h Bone marrow transplant failure—250mcg/m^2 IV qd over 2h ×14d; may repeat in 7d • **Contraindications**—hypersensitivity to drug or class, leukemic myeloid blast cells >10%, current chemotherapy, current radiation therapy • **Caution**—arrhythmia, CHF, pericardial effusion, pleural effusion
Maternal Considerations	**Sargramostim** is a recombinant human granulocyte-macrophage colony-stimulating factor. There is no published experience with **sargramostim** during pregnancy. ***Side effects*** include arrhythmias, anaphylaxis, pleural or pericardial effusion, capillary leak syndrome, RDS, fever, chills, headache, N/V, diarrhea, myalgias, asthenia, bone pain, edema, rash, pruritus, dyspnea, flushing, hypotension, tachycardia, and syncope.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **sargramostim** crosses the human placenta. Rodent teratogenicity studies have not been conducted.
Breastfeeding Safety	There is no reported experience in nursing women. It is unknown whether **sargramostim** enters human breast milk.
Drug Interactions	Drugs that may potentiate the myeloproliferative effects of **sargramostim,** such as **lithium** and corticosteroids, should be used with caution.
References	There is no published experience in pregnancy or during lactation.
Summary	**Pregnancy Category: C** **Lactation Category: U** • **Sargramostim** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Scopolamine—(Isopto Hyoscine; Minims Hyoscine Hydrobromide; Scopoderm; Transderm Scop)

International Brand Name—Kimite-patch (Korea); Scopoderm Depotplast (Norway); Scopoderm TTS (Austria, Bulgaria, China, England, France, Germany, Netherlands, New Zealand, Switzerland, Taiwan); Transcop (Italy); Transderm-V (Canada)

Drug Class	Anesthetics, adjunct; Anticholinergics; Antiemetics; Cycloplegics; Gastrointestinals; Motion sickness agents; Mydriatics; Ophthalmics; Vertigo agents
Indications	Motion sickness, obstetric amnesia, preoperative sedation, intraoperative amnesia
Mechanism	Anticholinergic
Dosage with Qualifiers	Motion sickness—1 patch behind the ear 4h prior to need; may replace in 3d Obstetric amnesia or preoperative sedation—0.32-0.65 mg SC/IM Intraoperative amnesia—0.4mg IV • **Contraindications**—hypersensitivity to drug or class, narrow-angle glaucoma • **Caution**—intestinal obstruction, history of seizures or psychosis, impaired metabolic function, hepatic or renal dysfunction
Maternal Considerations	**Scopolamine** differs only quantitatively in antimuscarinic actions from **atropine.** It is ineffective for the prevention of postoperative N/V. At one time popular for "twilight sleep" during labor, **scopolamine** has appropriately fallen out of favor. A recent study suggests it is effective in reducing the duration of the first stage of labor, and was not associated with any obvious adverse outcomes. It may reduce the post–cesarean section N/V associated with epidural **morphine,** but with an increase in drowsiness and dry mouth. **Scopolamine** is rapidly cleared, but there is no significant relationship between HR changes, sedative effects, and antisialagogue effects and serum concentration. ***Side effects*** include narrow-angle glaucoma, drowsiness, blurred vision, disorientation, dizziness, dilated pupils, hallucinations, confusion, psychosis, bronchospasm, respiratory depression, rash, muscle weakness, and red eyes.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. **Scopolamine** rapidly crosses the human placenta and may cause tachycardia and decreased beat-to-beat and long-term variability. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically.
Breastfeeding Safety	There are no adequate reports or well-controlled studies in nursing women. **Scopolamine** enters human breast milk, but the kinetics remain to be elucidated. The long clinical experience is reassuring.
Drug Interactions	Other drugs that have weak antimuscarinic activity (e.g., certain antihistamines, **meperidine,** phenothiazines, TCAs) may intensify the effects of antimuscarinic drugs. Aluminum- and magnesium trisillicate–containing antacids decrease the absorption of some antimuscarinic drugs and may do so with all of them.

Scopolamine should be used with care in patients taking drugs, including ethanol, capable of causing CNS effects. Special attention should be given to drugs having anticholinergic properties, such as **belladonna** alkaloids, antihistamines (including **meclizine**), and antidepressants.
Scopolamine may decrease the absorption of oral medications because of decreased gastric motility and delayed gastric emptying.

References

Ayromlooi J, Tobias M, Berg P. J Reprod Med 1980; 25:323-6.
Harnett MJ, O'Rourke N, Walsh M, et al. Anesth Analg 2007; 105:764-9.
Kanto J, Kentala E, Kaila T, Pihlajamaki K. Acta Anaesthesiol Scand 1989; 33:482-6.
Koski EM, Mattila MA, Knapik D, et al. Br J Anaesth 1990; 64:16-20.
Kotelko DM, Rottman RL, Wright WC, et al. Anesthesiology 1989; 71:675-8.
Samuels LA, Christie L, Roberts-Gittens B, et al. BJOG 2007; 114:1542-6.

Summary

Pregnancy Category: C
Lactation Category: S (likely)
- **Scopolamine** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Secobarbital—(Immenoctal; Novosecobarb; Secanal; Seconal)

International Brand Name—Quinalbarbitone (United Kingdom)

Drug Class

Anesthetics, adjunct; Anxiolytics; Barbiturates; Hypnotics

Indications

Short-term insomnia

Mechanism

Nonselective CNS depressant

Dosage with Qualifiers

Short-term insomnia—100mg PO qd

- **Contraindications**—hypersensitivity to drug or class, respiratory depression, porphyria
- **Caution**—unknown

Maternal Considerations

Barbiturates are dangerous drugs, with a narrow therapeutic index between the level required for sedation and that causing coma and death. **Secobarbital** is used by patients to self-treat the unpleasant effects of illicit stimulants, to reduce anxiety, and to get "high." It is physiologically addicting if taken in high doses for 1mo or more, and the abstinence syndrome can be life-threatening. There are no adequate reports or well-controlled studies of **secobarbital** in pregnant women. As a short-acting agent, **secobarbital** was used for decades as a short-term sleeping aid for pregnant women. Unfortunately, the sleep produced is not restful, characterized by a low percentage of REM stage. Hypnotic doses of barbiturates do not impair uterine activity significantly during labor. Anesthetic doses of barbiturates decrease the force and frequency of uterine contractions.

Side effects include respiratory depression, dependency, hepatotoxicity, Stevens-Johnson syndrome, angioedema, lethargy, and drowsiness.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. It is likely **secobarbital** rapidly crosses the human placenta. There is no substantative evidence **secobarbital** is a human teratogen. Administration during labor may cause respiratory depression in the newborn. Premature infants are particularly susceptible to the depressant effects of barbiturates. Withdrawal symptoms occur in infants of women who receive **secobarbital** throughout the 3rd trimester.

Breastfeeding Safety

There is no published experience in nursing women. Small amounts of **secobarbital** are excreted into human breast milk, but its occasional use is generally considered compatible with breastfeeding.

Drug Interactions

Most reports of significant drug interactions with the barbiturates have involved **phenobarbital.** The application of these data to other barbiturates appears valid.

Barbiturates induce hepatic microsomal enzymes, resulting in increased metabolism and decreased anticoagulant response to oral anticoagulants (e.g., **acenocoumarol, dicumarol, phenprocoumon, warfarin**). Patients on anticoagulant therapy may require a dose adjustment if barbiturates are added or withdrawn.

Barbiturates may enhance the metabolism of exogenous corticosteroids. Patients on corticosteroid therapy may require a dose adjustment if barbiturates are added or withdrawn.

Phenobarbital appears to interfere with the absorption of oral **griseofulvin.** It is preferable to avoid concomitant administration. Shortens the t/2 of doxycycline for as long as 2w after barbiturate therapy is discontinued.

The effect of barbiturates on the metabolism of **phenytoin** appears to be variable.

Sodium valproate and **valproic acid** increase **secobarbital** blood levels; thus, **secobarbital** levels should be monitored closely and appropriate dose adjustments made.

Use of other CNS depressants, including other sedatives or hypnotics, antihistamines, tranquilizers, or ethanol, may produce additive depressant effects.

MAOIs prolong the effects of barbiturates, probably because metabolism of the barbiturate is inhibited.

May decrease the effect of **estradiol** by increasing its metabolism. There have been reports of patients treated with AEDs (e.g., **phenobarbital**) who become pregnant while taking oral contraceptives. An alternate contraceptive method might be suggested to women taking barbiturates.

References

There are no current relevant references.

Summary

Pregnancy Category: D
Lactation Category: S

- **Secobarbital** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.
- There are alternative agents with greater safety and efficacy for the same indications during pregnancy and lactation

Selegiline—(Alzene; Carbex; Deprenyl; Eldeprine; Eldepryl; Selgene)

International Brand Name—Apo-Selegiline (New Zealand); Elegelin (Thailand); Julab (Hong Kong, Thailand); Julegil (Malaysia); Jumex (Austria, China, Hong Kong, Hungary, Indonesia, Israel, Italy, Korea, Malaysia, Philippines, Thailand); Jumexal (Costa Rica, El Salvador, Guatemala, Honduras, Nicaragua, Panama, Switzerland, Taiwan); Kinline (Thailand); MAO-B (Korea); MAOtil (Germany); Movergan (Germany); Niar (Mexico); Otrasel (France); Plurimen (Spain); Procythol (Greece); Sedicel (Colombia); Sefmex (Hong Kong); Selegil (Colombia, Peru); Selegos (Hong Kong, Singapore); Selgene (Thailand); Selgin (India); Xilopar (Germany); Zelapar (Philippines)

Drug Class	Antiparkinson agents
Indications	Parkinsonism
Mechanism	Selective MAO-B antagonist
Dosage with Qualifiers	Parkinsonism—5mg PO qam and qnoon *NOTE: death may occur if combined with* ***meperidine.*** • **Contraindications**—hypersensitivity to drug or class, opiate use • **Caution**—unknown
Maternal Considerations	**Selegiline** is a derivative of phenethylamine. It has also been used for the treatment of Alzheimer's dementia and narcolepsy. There are no adequate reports or well-controlled studies of **selegiline** in pregnant women. The literature consists of case reports involving 30-40 women in total with Parkinson's disease. ***Side effects*** include ventricular arrhythmia, N/V, diarrhea, dizziness, confusion, hallucinations, vivid dreams, headache, anxiety, anemia, hair loss, fatigue, and low back pain.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **selegiline** crosses the human placenta. Monoamine neurotransmitters are important for the development of the immature brain. Their endogenous levels are highly regulated by MAO, and any change in enzyme activity could have a profound effect on brain development. Some recommend discontinuing MAOIs before conception. Unfortunately, there is little scientific information on which to base such decisions. Rodent studies are generally reassuring, revealing no evidence of teratogenicity at doses higher than those used clinically. There was evidence of embryotoxicity at high doses.
Breastfeeding Safety	There are no adequate reports or well-controlled studies in nursing women. It is unknown whether **selegiline** enters human breast milk.
Drug Interactions	**Carbamazepine** slightly increases levels of **selegiline** and its metabolites. Changes in plasma concentrations are nearly 2-fold but variable across the subject population. **Carbamazepine** is contraindicated with MAOIs, including **selegiline.** Use with **phenylpropanolamine** was associated with a higher incidence of significant BP elevations than with **phenylpropanolamine** alone, suggesting a possible pharmacodynamic interaction. There were no clinically significant changes in BP with **pseudoephedrine** use, but hypertension has been reported with **ephedrine.** It is prudent to avoid the concomitant use of sympathomimetic agents with **selegiline.**

Has greater affinity for MAO-B; this selectivity is lost as its concentration increases. In addition to their role in the catabolism of CNS monoamines, MAOs are also important in the catabolism of exogenous amines found in foods and drugs. MAO in the GI tract (primarily type A) protects from exogenous amines with vasopressor actions, such as tyramine, which if absorbed intact can cause a hypertensive crisis (the so-called cheese reaction). If a large amount of tyramine is absorbed, it is taken up by adrenergic neurons and causes hypertension secondary to NE release from neuronal storage sites. While most foods contain negligible amounts or no tyramine, a few food products may contain large amounts that represent a potential risk for patients with significant inhibition of GI MAO-A. Studies suggest **selegiline** 6mg/24h does not require a modified diet. Due to the more limited data available for 9mg/24h and 12mg/24h, patients taking these doses should follow a modified diet.
Stupor, muscular rigidity, severe agitation, and elevated temperature have been reported when used with **meperidine.** Symptoms usually resolve over days when the combination is discontinued. This is typical of the interaction of meperidine and MAOIs. Other serious reactions (including severe agitation, hallucinations, and death) have been reported in patients receiving this combination. Severe toxicity has also been reported when used with TCAs and SSRIs.
Use with **dextromethorphan** has been reported to cause brief episodes of psychosis or bizarre behavior. Therefore, **dextromethorphan** should not be used with **selegiline.**

■ **References**

Golbe LI. Neurol Clin 1994; 12:497-508.
Hagell P, Odin P, Vinge E. Mov Disord 1998; 13:34-8.

■ **Summary**

Pregnancy Category: C
Lactation Category: U

- **Selegiline** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Selenium sulfide topical—(Abbottselsun; Exsel; Glo-Sel; Lenium; Micalon; Sebo-Lenium; Sel-Pen; Selsum; Selsun; Selukos; Versel)

International Brand Name—Abbottselsun (Spain); Sebo-Lenium (Switzerland); Sebosel (Thailand); Selson (Korea); Selsun 1.0 (Hong Kong); Selsun 2.5 (Hong Kong); Selsun Blue (Finland, Hong Kong, Indonesia, Israel, Norway, Sweden, Switzerland); Selsun R (Netherlands); Selukos (Austria, Finland, Germany, Norway, Sweden); Versel (Canada)

■ **Drug Class** — Antidermatophytes; Antifungals; Dermatologics

■ **Indications** — Dandruff, seborrhea, tinea versicolor

■ **Mechanism** — Reduces epidermal and follicular epithelial corneocyte production

■ **Dosage with Qualifiers**

Dandruff, seborrhea—massage 5-10ml on wet scalp 2×/w, rinse after 2-3min
Tinea versicolor—apply 2.5% lotion qd ×7d, then monthly ×3mo

NOTE: wash hands, avoid contact with jewelry.

- **Contraindications**—hypersensitivity to drug or class, inflamed skin
- **Caution**—unknown

Maternal Considerations	There is no published experience with **selenium sulfide** during pregnancy. Systemic absorption is scant whether measured after shampooing or lotion application. ***Side effects*** include skin irritation, hair loss, hair discoloration, and oily or dry scalp.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **selenium sulfide** crosses the human placenta. Elemental selenium does cross passively. Considering the dose and route, it is unlikely the maternal systemic concentration will reach a clinically relevant level.
Breastfeeding Safety	There is no published experience in nursing women. It is unknown whether **selenium sulfide** enters human breast milk. However, the concentration of elemental selenium in milk is the same as maternal plasma. Considering the indication and dosing, **selenium sulfide** use is unlikely to pose a clinically significant risk to the breastfeeding neonate.
Drug Interactions	No clinically relevant interactions identified.
References	Nandakumaran M, Dashti HM, Al-Saleh E, Al-Zaid NS. Mol Cell Biochem 2003; 252:91-6. Ozdemir HS, Karadas F, Pappas AC, et al. Biol Trace Elem Res 2008; 122:206-15.
Summary	**Pregnancy Category: C** **Lactation Category: S** (likely) • **Selenium sulfide** is unlikely to pose a risk when used as indicated.

Senna—(Ex-lax; Senna-Gen; Sennokot)

International Brand Name—None identified.

Drug Class	Laxatives
Indications	Constipation
Mechanism	Cathartic; increases peristalsis
Dosage with Qualifiers	Constipation—2-4 tabs PO qd or bid • **Contraindications**—hypersensitivity to drug or class, bowel obstruction, undiagnosed abdominal pain • **Caution**—unknown
Maternal Considerations	Despite a long clinical experience, there are no adequate reports or well-controlled studies of **senna** in pregnant women. **Senna** is absorbed across the GI tract only to a limited degree. Some believe **senna** is the purgative of choice during pregnancy and lactation. It effectively relieves postpartum constipation. It does not affect the myometrial activity of the pregnant ewe. ***Side effects*** include laxative abuse, nausea, bloating, cramps, flatulence, diarrhea, melanosis coli, and discolored urine.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **senna** crosses the human placenta.

Breastfeeding Safety — Less than 1% of the maternal dose of **senna** enters human breast milk. This amount is inadequate for a clinical effect.

Drug Interactions — No clinically relevant interactions identified.

References

Faber P, Strenge-Hesse A. Pharmacology 1988; 36(Suppl 1):212-20.
Garcia-Villar R. Pharmacology 1988; 36(Suppl 1):203-11.
[No authors]. Pharmacology 1992; 44(Suppl 1):20-2.
[No authors]. Pharmacology 1992; 44(Suppl 1):23-5.
Shelton MG. S Afr Med J 1980; 57:78-80.

Summary

Pregnancy Category: C
Lactation Category: S

- **Senna** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.
- Occasional use for the relief of constipation should be safe during pregnancy and lactation.

Sertraline—(Lustral; Zoloft)

International Brand Name—Altruline (Mexico); Aremis (Spain); Atruline (Costa Rica, El Salvador, Guatemala, Honduras, Nicaragua, Panama); Besitran (Spain); Deprax (Chile); Dominum (Colombia, Peru); Doxime (Paraguay); Fatral (Indonesia); Fridep (Indonesia); Gladem (Austria, Germany); Lesefer (Colombia); Lustral (England, Ireland, Israel); Nudep (Indonesia); Seltra (Korea); Sercerin (Brazil); Serlain (Belgium); Serlift (Malaysia); Sertranex (Colombia); Sertranquil (Colombia); Sosser (Colombia); Traline (Korea); Zolof (Colombia); Zoloft (Argentina, Brazil, Bulgaria, Canada, China, Czech Republic, Denmark, Finland, France, Germany, Hong Kong, Hungary, Indonesia, Italy, Korea, Malaysia, Netherlands, Peru, Philippines, Poland, Sweden, Switzerland, Taiwan, Thailand, Uruguay, Venezuela); Zosert (India)

Drug Class — Antidepressants; SSRIs, type 1

Indications — Depression, postpartum depression, OCD, premenopausal dysphoric disorder, post-traumatic stress disorder, panic disorder

Mechanism — Selective serotonin reuptake inhibitor

Dosage with Qualifiers

Depression—begin 50mg PO qd; max 200mg PO qd
OCD—begin 50mg PO qd; max 200mg PO qd
Premenopausal dysphoric disorder—begin either 50mg PO qd or cycle days 15-28, may increase 50mg/d per cycle, max 150mg/d
Post-traumatic stress disorder—begin 25mg PO qd ×7d before increasing 25-50mg/d; max 200mg/d
Panic disorder—begin 25mg PO qd; max 200mg PO qd

NOTE: discontinue slowly.

- **Contraindications**—hypersensitivity to drug or class, MAOI <14d
- **Caution**—renal dysfunction

Maternal Considerations — Depression is common during and after pregnancy, but typically goes unrecognized. Pregnancy is not a reason *a priori* to discontinue psychotropic drugs. There are no adequate reports or well-controlled studies of **sertraline** in pregnant women, though there is growing experience with its use for the treatment of postpartum depression. However, **sertraline** is not recommended for prophylactic use. In general, women taking SSRIs during pregnancy for depression require an increased dose to maintain euthymia. Yet in the one longitudinal study clearance was unaltered during pregnancy.

Side effects include serotonin withdrawal syndrome, withdrawal syndrome, N/V, diarrhea, insomnia, headache, dry mouth, somnolence, dizziness, fatigue, tremor, dyspepsia, constipation, decreased libido, sweating, anorexia, nervousness, agitation, anxiety, and visual disturbances.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. **Sertraline** crosses the human placenta and enters the AF. Limited study suggests a low F:M ratio approximating 0.30-0.67, lower than **citalopram, fluoxetine,** and **paroxetine.** Maternal doses predict the umbilical cord concentration. Though there remains controversy, the most recent epidemiologic analyses reveal a significant association with omphalocele (OR, 5.7; 95% CI, 1.6-20.7; 3 exposed subjects) and septal defects (OR, 2.0; 95% CI, 1.2-4.0; 13 exposed subjects). An increased prevalence of IUGR cannot be excluded. Neonatal abstinence syndrome may occur in up to ⅓ of exposed neonates. There is some concern that the impact of antenatal exposure continues for at least a few months. Newborns chronically exposed to SSRIs have reduced responses to pain. Rodent studies are generally reassuring, though a delay in ossification was noted in rabbits. Further, the fetal loss rate is increased by late pregnancy exposure. The mechanism and significance are unclear. The exposure of mouse embryos in culture to **sertraline** at a high concentration (10μM) causes craniofacial malformations without evidence of general embryotoxicity, consistent with a direct action at 5-HT uptake sites.

Breastfeeding Safety

Sertraline and desmethylsertraline are present in human breast milk. The concentrations are affected by the fraction of milk sampled, the time after maternal dose (max 7-10h), and daily dose. The mean maximum calculated nursing infant doses of **sertraline** (0.67mg/d) and desmethylsertraline (1.44mg/d) represent 0.54% of the maternal daily dose. Neonatal serum concentration is usually below the detection limit of most commercial laboratories. If breastfed, the infant should be monitored for possible adverse effects, the drug given at the lowest effective dose, and breastfeeding avoided at times of peak drug levels.

Drug Interactions

Tightly bound to plasma protein; its use with other drugs tightly bound to protein (e.g., **digitoxin, warfarin**) may cause a shift in plasma levels. Conversely, adverse effects may result from displacement of protein-bound **sertraline** by other tightly bound drugs.

Cimetidine significantly increased the **sertraline** mean AUC (50%), C_{max} (24%), and t/2 (26%) compared to placebo. The clinical significance is unknown.

Sertraline decreases **diazepam** clearance by ⅓; the clinical significance is unknown.

Increases the **pimozide** AUC and C_{max} by about 40%, but is not associated with any changes in ECG. Since the highest recommended **pimozide** dose (10mg) has not been evaluated in combination with **sertraline,** the effect on QT interval and pharmacokinetic parameters at doses higher than 2mg are not known. While the mechanism of this interaction is unknown, concomitant administration of **sertraline** and **pimozide** is contraindicated due to the narrow therapeutic index of **pimozide.**

The duration of an appropriate washout period that should intervene before switching from one SSRI to another has not been established.

Many drugs effective in the treatment of major depressive disorder (e.g., the SSRIs, including **sertraline,** and most TCAs)

inhibit the biochemical activity of CYP2D6 (debrisoquin hydroxylase), and, thus, may increase the plasma concentrations of co-administered drugs that are metabolized by CYP2D6. The drugs for which this potential interaction is of greatest concern are those metabolized primarily by 2D6 and that have a narrow therapeutic index (e.g., the TCAs and the class 1C antiarrhythmics **flecainide** and **propafenone**). There is variability among the drugs effective in the treatment of major depressive disorder in the extent of clinically important 2D6 inhibition, and in fact **sertraline** at lower doses has a less prominent inhibitory effect on 2D6 than some others in the class. Nevertheless, even **sertraline** has the potential for clinically important 2D6 inhibition, and use with a drug metabolized by CYP2D6 may require lower doses than usual. Furthermore, an increased dose of the co-administered drug may be required whenever **sertraline** is withdrawn.

There are rare post-marketing reports describing patients with weakness, hyperreflexia, and incoordination following the use of an SSRI and **sumatriptan.** If concomitant treatment with **sumatriptan** and an SSRI (e.g., **citalopram, fluoxetine, fluvoxamine, paroxetine, sertraline**) is warranted, appropriate patient observation is advised.

The extent to which SSRI-TCA interactions may pose clinical problems will depend on the degree of inhibition and the pharmacokinetics of the SSRI involved. Nevertheless, caution is indicated as **sertraline** may inhibit TCA metabolism. Plasma TCA concentrations may need to be monitored and the dose of TCA reduced.

Serotonin release by platelets plays an important role in hemostasis. Studies reveal an association between the use of psychotropic drugs that interfere with serotonin reuptake and the occurrence of upper GI bleeding when used with nonselective NSAIDs. Patients should be cautioned about the use of such drugs with **sertraline.**

References

Bellantuono C, Migliarese G, Gentile S. Hum Psychopharmacol 2007; 22:121-8.

Freeman MP, Nolan PE, Davis MF, et al. J Clin Psychopharmacol 2008; 28:646-53.

Hendrick V, Smith LM, Suri R, et al. Am J Obstet Gynecol 2003; 188:812-5.

Hendrick V, Stowe ZN, Altshuler LL, et al. Am J Psychiatry 2003; 160:993-6.

Hostetter A, Ritchie JC, Stowe ZN. Biol Psychiatry 2000; 48:1032-4.

Hostetter A, Stowe ZN, Strader JR Jr, et al. Depress Anxiety 2000; 11:51-7.

Howard LM, Hoffbrand S, Henshaw C, et al. Cochrane Database Syst Rev 2005; (2):CD004363.

Kulin NA, Pastuszak A, Sage SR, et al. JAMA 1998; 279:609-10.

Levinson-Castiel R, Merlob P, Linder N, et al. Arch Pediatr Adolesc Med 2006; 160:173-6.

Louik C, Lin AE, Werler MM, et al. N Engl J Med 2007; 356:2675-83.

Oberlander TF, Eckstein Grunau R, et al. Pediatr Res 2002; 51:443-53.

Rampono J, Proud S, Hackett LP, et al.
Int J Neuropsychopharmacol 2004; 7:329-34.

Shuey DL, Sadler TW, Lauder JM. Teratology 1992; 46:367-78.

Stowe ZN, Hostetter AL, Owens MJ, et al. J Clin Psychiatry 2003; 64:73-80.

Stowe ZN, Owens MJ, Landry JC, et al. Am J Psychiatry 1997; 154:1255-60.

Summary

Pregnancy Category: C
Lactation Category: S (likely)

- Depression is common during pregnancy and the puerperium and should not be ignored if treatment is otherwise indicated.
- **Sertraline** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.
- Limited study suggests placental transfer of **sertraline** is lower than that for **citalopram, fluoxetine,** and **paroxetine.**

Sevoflurane—(Sevorane; Ultane)

International Brand Name—Elidiur (Italy); Sevofrane (China, Japan); Sevorane (Austria, Czech Republic, Denmark, France, Hong Kong, Hungary, Indonesia, Ireland, Israel, Italy, Malaysia, Netherlands, Philippines, Poland, Singapore, Thailand); Ultane (South Africa)

Drug Class

Anesthesia, general

Indications

Induction and maintenance of anesthesia

Mechanism

Unknown

Dosage with Qualifiers

Induction of anesthesia—titrate inhalation to effect; a technique used mainly in children
Maintenance of anesthesia—titrate inhalation to anesthetic effect, typically inspired concentration of 0.5-3%

NOTE: consult anesthesia specialty text.

- **Contraindications**—hypersensitivity to drug or class, malignant hyperthermia
- **Caution**—hepatitis, hepatic or renal dysfunction, aortic stenosis, mitral valve disease, head injury, myasthenia gravis, increased ICP

Maternal Considerations

There are no adequate reports or well-controlled studies of **sevoflurane** in pregnant women. It is popular for cesarean delivery when general anesthesia is elected, producing an intraoperative course and neonatal outcome similar to that of either **isoflurane** or a subarachnoid block. Like the other volatile anesthetics (**halothane** and **isoflurane**), **sevoflurane** reduces oxytocin-induced contraction of pregnant rat myometrium mediated, at least in part, by activation of Ca^{2+}-activated K^+ channels. *In vitro*, it is a vasodilator of chorionic plate vessels. A limited number of case reports in the 1st trimester do not report adverse outcomes.
Side effects include malignant hyperthermia, arrhythmias, hepatitis, increased ICP, N/V, agitation, cough, hypotension, shivering, laryngospasm, breath holding, increased salivation, bradycardia, dizziness, tachycardia, hypertension, and apnea.

Fetal Considerations

Sevoflurane rapidly crosses the human placenta. It has been used for fetal anesthesia during the EXIT procedure. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR. Neonatal adaptive capacity may be reduced during the first 24h compared to **desflurane**.

Breastfeeding Safety

There are no adequate reports or well-controlled studies in nursing women. It is unknown whether **sevoflurane** enters human breast milk. However, considering the indication and

dosing, one-time **sevoflurane** use is unlikely to pose a clinically significant risk to the breastfeeding neonate.

Drug Interactions

Benzodiazepines and opioids would be expected to decrease the MAC of **sevoflurane** in the same manner as with other inhalational anesthetics. **Sevoflurane** administration is compatible with benzodiazepines and opioids as commonly used in surgical practice. The anesthetic requirement for **sevoflurane** is decreased when administered in combination with nitrous oxide. Using 50% N_2O, the MAC equivalent dose requirement is reduced approximately 50% in adults.
Increases both the intensity and duration of neuromuscular blockade induced by nondepolarizing muscle relaxants. When used to supplement **alfentanil**-N_2O anesthesia, **sevoflurane** and **isoflurane** equally potentiate neuromuscular block induced with **atracurium, pancuronium,** or **vecuronium.**
Potentiation of neuromuscular blocking agents requires equilibration of muscle with delivered partial pressure of **sevoflurane.** Reduced doses of neuromuscular blocking agents during induction of anesthesia may result in delayed onset of conditions suitable for endotracheal intubation or inadequate muscle relaxation.

References

Aydin GB, Coskun F, Sahin A, Aypan U. Saudi Med J 2008; 29:841-6.
Farragher R, Maharaj CH, Higgins BD, et al. Anesth Analg 2008; 107:171-7.
Gambling DR, Sharma SK, White PF, et al. Anesth Analg 1995; 81:90-5.
Kanazawa M, Kinefuchi Y, Suzuki T, et al. Tokai J Exp Clin Med 1999; 24:53-5.
Yamakage M, Tsujiguchi N, Chen X, et al. Can J Anaesth 2002; 49:62-6.

Summary

Pregnancy Category: B
Lactation Category: S
- **Sevoflurane** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Sibutramine—(Meridia)

International Brand Name—Adisar (Peru); Atenix (Chile); Ectiva (Mexico); Meridia (Canada, Poland); Plenty (Colombia); Raductil (Argentina, Costa Rica, Dominican Republic, El Salvador, Guatemala, Honduras, Mexico, Nicaragua, Panama); Reductil (Colombia, England, Germany, Hong Kong, Ireland, Israel, Korea, Mexico, Peru, Philippines, Singapore, South Africa, Thailand); Reduten (Chile); Sacietyl (Argentina); Sibutral (France); Sibutrex (India)

Drug Class

Anorexiants; CNS stimulants

Indications

Obesity

Mechanism

Inhibits NE, serotonin, and dopamine reuptake

Dosage with Qualifiers

Obesity—begin 10mg PO qd, increase to 15mg PO qd after 4w; max 15mg/d

- **Contraindications**—hypersensitivity to drug or class, MAOI <14d, CAD, CHF, arrhythmias, stroke, severe hepatic or renal dysfunction, anorexia nervosa
- **Caution**—unknown

Maternal Considerations

Obesity is a major epidemic in the industrialized countries. Observational studies confirm a relationship between obesity and CV disease, type 2 diabetes mellitus, certain forms of cancer, gallstones, certain respiratory disorders, and an increase in overall mortality rate. These studies suggest that weight loss, if maintained, may produce health benefits for patients with chronic obesity. **Sibutramine** leads to dose-dependent weight loss. Maintenance therapy enhances the likelihood of maintaining the loss. The published experience during pregnancy is limited to case reports and small series. Clearance is modestly decreased in women.
Side effects include menstrual irregularities, dysmenorrhea, tachycardia, severe hypertension, seizures, headache, dry mouth, insomnia, rhinitis, anorexia, constipation, increased appetite, dizziness, anxiety, dyspepsia, nausea, rash, and sinusitis.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **sibutramine** crosses the human placenta. Case reports and small series are reassuring. Rodent studies are generally reassuring, with dysmorphology noted only at the highest doses concurrent with maternal toxicity and only in rabbits. Transport across the rodent placenta is limited.

Breastfeeding Safety

There is no published experience in nursing women. It is unknown whether **sibutramine** enters human breast milk.

Drug Interactions

There are reports of serious, sometimes fatal, reactions ("serotonin syndrome") in patients using MAOIs (e.g., **phenelzine, selegiline**) in combination with serotonergic agents (e.g., **fluoxetine, fluvoxamine, paroxetine, sertraline, venlafaxine**). Because **sibutramine** inhibits serotonin reuptake, it should not be used within 2w of using an MAOI. Similarly, there should be at least 2w between discontinuation of **sibutramine** and initiation of an MAOI.
Serotonin syndrome has also been reported when SSRIs are used with migraine therapy (e.g., **dihydroergotamine, sumatriptan**), certain opioids (e.g., **dextromethorphan, fentanyl, meperidine, pentazocine**), **lithium,** or tryptophan. Serotonin syndrome has also been reported with the concomitant use of two serotonin reuptake inhibitors. The syndrome requires immediate medical attention and may include the following symptoms: excitement, hypomania, restlessness, loss of consciousness, confusion, disorientation, anxiety, agitation, motor weakness, myoclonus, tremor, hemiballismus, hyperreflexia, ataxia, dysarthria, incoordination, hyperthermia, shivering, pupillary dilation, diaphoresis, emesis, and tachycardia.
CYP3A4 metabolism of **sibutramine** is inhibited by **ketoconazole** (AUC and C_{max} of 58% and 36% for M_1 and of 20% and 19% for M_2, respectively) and to a lesser extent by **erythromycin** (small increases in the AUC [<14%] for M_1 and M_2, a small reduction in C_{max} for M_1 [11%], a slight increase in C_{max} for M_2 [10%]).

References

De Santis M, Straface G, Cavaliere AF, et al. Drug Saf 2006; 29:255-9.
Garcia-Bournissen F, Shrim A, Koren G. Can Fam Physician 2007; 53:229-30.
Kadioglu M, Ulku C, Yaris F, et al. Brth Defects Res A Clin Mol Teratol 2004; 70:545-6.

Summary

Pregnancy Category: C
Lactation Category: U

- There are no indications for **sibutramine** during pregnancy and lactation.

Sildenafil—(Viagra)

International Brand Name—Aphrodil (Israel); Edegra (India); Ejertol (Colombia); Erectol (Argentina); Erilin (Colombia); Eroxim (Colombia); Penegra (India, South Africa); Rigix (Paraguay); Ripol (Chile); Sildefil (Argentina); Viagra (Canada, Colombia, Hong Kong, Indonesia, Japan, Korea, Mexico, Peru, Philippines, Singapore, Taiwan, Thailand); Vigain (Israel); Zwagra (Israel)

Drug Class	PDE inhibitors
Indications	Erectile dysfunction
Mechanism	PDE5 inhibitor
Dosage with Qualifiers	No FDA—approved indications for women • **Contraindications—**hypersensitivity to drug or class, nitrate use • **Caution—**CAD, hepatic dysfunction, severe renal disease, hypotension
Maternal Considerations	**Sildenafil** is suggested as a treatment for sexual arousal disorder in premenopausal women. It is effective in postmenopausal women for the treatment of female sexual arousal disorder. Though there are no adequate reports or well-controlled studies of **sildenafil** in pregnant women, it is a potentially attractive agent as it increases the t/2 of NO, and there are several reports of its use to treat pulmonary artery hypertension during pregnancy. **Sildenafil** has also been tested as an agent to increase uterine blood flow and endometrial development in women undergoing IVF. ***Side effects*** include severe hypotension, MI, ventricular arrhythmia, sudden death, stroke, TIA, increased intraocular pressure, headache, flushing, dyspepsia, nasal congestion, UTI, blurred or blue-tinted vision, diarrhea, dizziness, rash, and photophobia.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **sildenafil** crosses the human placenta. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically. There is some interesting study using **sildenafil** as an agent to minimize the impact of acute perinatal asphyxia.
Breastfeeding Safety	There is no published experience in pregnancy. It is unknown whether **sildenafil** enters human breast milk.
Drug Interactions	Metabolism is mediated principally by CYP3A4 and CYP2C9. Thus, inhibitors of these enzymes may reduce and inducers increase **sildenafil** clearance. Population pharmacokinetic analyses indicate a reduction in **sildenafil** clearance and/or an increase of oral bioavailability when used with CYP3A4 substrates and the combination of CYP3A4 substrates and β-blockers. **Cimetidine,** a nonspecific CYP inhibitor, caused a 56% increase in **sildenafil.** **Erythromycin,** a CYP3A4 inhibitor, increased **sildenafil** AUC by 182%. **Saquinavir,** a CYP3A4 inhibitor, increased the **sildenafil** C_{max} 140% and the AUC 210%. **Ritonavir,** a potent CYP3A4 inhibitor, increased the **sildenafil** C_{max} 300% and the AUC 1000%. At 24h, the plasma levels were still 200ng/ml, compared to 5ng/ml with **sildenafil.** The endothelin receptor antagonist **bosentan** (a moderate inducer of CYP3A4, CYP2C9, and possibly CYP2C19) decreased the **sildenafil** AUC 63% and C_{max} 63%.

May enhance the hypotensive effect of the α-blocker **doxazosin.** There have been infrequent reports of symptomatic postural hypotension. These reports included dizziness and light-headedness, but not syncope.
May enhance the hypotensive effect of **amlodipine.**

References

Berman JR, Berman LA, Toler SM, et al. J Urol 2003; 170:2333-8.
Frattarelli JL, Miller BT, Scott RT Jr. Reprod Biomed Online 2006; 12:722-9.
Huang S, DeSantis ER. Am J Health Syst Pharm 2007; 64:1922-6.
Sánchez-Aparicio P, Mota-Rojas D, Nava-Ocampo AA, et al. Am J Obstet Gynecol 2008; 198:127.e1-6.
Sher G, Fisch JD. Hum Reprod 2000; 15:806-9.

Summary

Pregnancy Category: B
Lactation Category: U

- There are currently no indications for **sildenafil** during pregnancy or lactation.
- Sildenafil is effective for the treatment of female sexual arousal disorder in postmenopausal women.

Silver nitrate

International Brand Name—None identified.

Drug Class — Antibacterials; Ophthalmics

Indications — Prevention of gonorrheal ophthalmia neonatorum

Mechanism — Precipitates bacterial proteins

Dosage with Qualifiers

Prevention of gonorrheal ophthalmia neonatorum—apply 2gtt 1% solution each eye shortly after birth

- **Contraindications—**hypersensitivity to drug or class
- **Caution—**unknown

Maternal Considerations

Silver nitrate has been used for decades to prevent neonatal gonorrheal conjunctivitis. Unfortunately, it does not prevent chlamydial conjunctivitis and has been largely replaced with **erythromycin** ointment.
Side effects include chemical conjunctivitis.

Fetal Considerations — Not relevant

Breastfeeding Safety — Not relevant

Drug Interactions — No clinically relevant interactions identified.

References

de Toledo AR, Chandler JW. Infect Dis Clin North Am 1992; 6:807-13.
Schaller UC, Klauss V. Bull World Health Organ 2001; 79:262-3.

Summary

Pregnancy Category: B
Lactation Category: S

- **Silver nitrate** provides effective prophylaxis for gonorrheal conjunctivitis, but does not treat the more prevalent chlamydia well.

Silver sulfadiazine topical—(Canflame; Dermazin; Flamazine; Flammazine; Geben; Sildimac; Silvadene; Silvazine; Silverderma; Silverol; Silvirin; Sofargen; SSD; Thermazene)

International Brand Name—Aldo-Silvederma (Hong Kong); Brandiazin (Germany); Burnazin (Indonesia); Dermazin (Hong Kong, Indonesia); Flamazine (Canada, Denmark, England, Finland, Hong Kong, Ireland, Israel, Malaysia, Norway, South Africa, Taiwan, Thailand); Flammazine (Austria, Belgium, Bulgaria, France, Germany, Netherlands, Philippines, Spain, Switzerland); Flugen (Taiwan); Geben (Japan); Silbecor (South Africa); Silvadyn (Ecuador); Silverdiazina (Peru); Silverol (Israel, Thailand); Silvirin (India); Sofargen (Italy); Sterizol (Philippines); Sulfaplata (Colombia, Dominican Republic, El Salvador, Guatemala, Honduras, Panama); Uburn (Taiwan); Ustionil (Italy)

Drug Class

Antibacterials; Dermatologics

Indications

2nd or 3rd degree burns

Mechanism

Bacteriostatic; inhibits dihydropteroate

Dosage with Qualifiers

2nd or 3rd degree burns—apply to débrided wound qd to bid

NOTE: 1% cream.

- **Contraindications**—hypersensitivity to drug or class
- **Caution**—unknown

Maternal Considerations

While burn injuries to pregnant women are not rare, the literature is indeed sparse. There are no adequate reports or well-controlled studies of **silver sulfadiazine** in pregnant women. Absorption of **silver sulfadiazine** varies depending upon the percentage of body surface area and the extent of the tissue damage.

Side effects include neutropenia, leukopenia, erythema multiforme, burning, pain, pruritus, skin necrosis, and rash.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **silver sulfadiazine** crosses the human placenta. Considering the route and concentration, it is unlikely the maternal systemic concentration will reach a clinically relevant level. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically.

Breastfeeding Safety

There are no adequate reports or well-controlled studies in nursing women. It is unknown whether **silver sulfadiazine** enters human breast milk. Considering the route and concentration, it is unlikely the breastfed neonate will ingest a clinically relevant amount.

Drug Interactions

No clinically relevant interactions identified.

References

Gang RK, Bajec J, Tahboub M. Burns 1992; 18:317-20.
Prasanna M, Singh K. Burns 1996; 22:234-7.

Summary

Pregnancy Category: B
Lactation Category: S (likely)

- **Silver sulfadiazine** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Simethicone—(Mylicon)

International Brand Name—None identified.

Drug Class	Gastrointestinals
Indications	Flatulence
Mechanism	Alters gas surface tension
Dosage with Qualifiers	Flatulence—80-120mg PO qid (pc and hs) prn; max 480mg/d • **Contraindications**—hypersensitivity to drug or class, intestinal perforation, GI obstruction • **Caution**—unknown
Maternal Considerations	**Simethicone** significantly reduces vomiting, stomach discomfort, and abdominal pain post-cesarean section. Bowel function appears to return more rapidly. ***Side effects*** include nausea and diarrhea.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. While it is unknown whether **simethicone** crosses the human placenta, it is unlikely the maternal systemic concentration reaches a clinically relevant level. Rodent teratogenicity studies have not been conducted.
Breastfeeding Safety	There are no adequate reports or well-controlled studies in nursing women. While it is unknown whether **simethicone** enters human breast milk, it is unlikely the maternal systemic concentration reaches a clinically relevant level. It is generally considered compatible with breastfeeding.
Drug Interactions	No clinically relevant interactions identified.
References	Avramovic D, Sulovic V, Lazarevic B, et al. Jugosl Ginekol Obstet 1979; 19:307-11.
Summary	**Pregnancy Category: C** **Lactation Category: S** • **Simethicone** is effective for the relief of flatulence and post–cesarean section abdominal discomfort.

Simvastatin—(Zocor)

International Brand Name—None identified.

Drug Class	Antihyperlipidemics; HMG-CoA reductase inhibitors
Indications	Hypercholesterolemia, hypertriglyceridemia, dysbetalipoproteinemia, familial hypercholesterolemia, secondary prevention of CV events
Mechanism	HMG-CoA reductase inhibitor
Dosage with Qualifiers	Hypercholesterolemia—begin 20mg PO qd; max 80mg/d Hypertriglyceridemia—begin 20mg PO qd; max 80mg/d

Dysbetalipoproteinemia—begin 20mg PO qd; max 80mg/d
Familial hypercholesterolemia—40mg PO qpm; max 80mg/d
Secondary prevention of CV events—begin 20mg PO qd (40mg PO qd if goal >45% reduction LDL); max 80mg/d

NOTE: multiple drug interactions alter dosing (e.g., ***amiodarone, cyclosporine,*** *other fibrates,* ***verapamil****).*

- **Contraindications**—hypersensitivity to drug or class, active hepatic disease, unexplained elevated LFTs
- **Caution**—hepatic dysfunction, alcohol abuse, severe renal disease

Maternal Considerations

Simvastatin is a synthetic statin that reduces the overall lipid level and the associated risk of adverse CV events. It may modestly increase the risk of cholelithiasis. **Simvastatin** does not affect gonadotropin function in premenopausal women. There are no adequate reports or well-controlled studies of **simvastatin** in pregnant women. Post-marketing studies do not suggest an increase in adverse outcomes. However, atherosclerosis is a chronic process. Discontinuation during pregnancy should have little impact on the long-term therapeutic outcome of primary hypercholesterolemia.
Side effects include rhabdomyolysis, hepatotoxicity, constipation, diarrhea, flatus, dyspepsia, nausea, gallstones, asthenia, myalgias, elevated CPK and LFTs, and rash.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **simvastatin** crosses the human placenta. Post-marketing studies are reassuring, as are rodent studies, which reveal no evidence of teratogenicity despite doses that were multiples of the MRHD. Inadvertent exposure would not be a medical indication for pregnancy termination. However, cholesterol and other products of the cholesterol biosynthesis pathway are essential components for fetal development. *In vitro,* **simvastatin** sharply inhibited migration of extravillous trophoblast from villi into matrigel. Further, it inhibited half of the proliferative events in the villi and increased apoptosis of cytotrophoblast cells compared to control. Finally, **simvastatin** significantly decreased secretion of progesterone from the placental explants. Thus, exposed pregnancies may be at increased risk for IUGR. It is generally considered the potential fetal risk of **simvastatin** use outweighs the benefit to the mother.

Breastfeeding Safety

There are no adequate reports or well-controlled studies in nursing women. It is unknown whether **simvastatin** enters human breast milk.

Drug Interactions

Metabolized by CYP3A4, and potent inhibitors increase the risk of myopathy by reducing the elimination of **simvastatin**. These agents include **clarithromycin, cyclosporine, erythromycin,** HIV protease inhibitors, **itraconazole, ketoconazole, nefazodone,** and large quantities of grapefruit juice (>1quart daily).
Amiodarone and **verapamil** each increase risk of myopathy/rhabdomyolysis.
Increases (>0.3ng/ml) **digoxin** levels. Patients taking digoxin should be monitored appropriately.
Increases the effect of coumarin anticoagulants: INR increased from a baseline of 1.7 to 1.8 and from 2.6 to 3.4 in the volunteer and patient studies, respectively. The INR should be determined before starting **simvastatin** and frequently enough during early therapy to ensure that no significant alteration occurs. If the dose of **simvastatin** is changed or discontinued, the same procedure should be repeated.

■ **References** ····· Caroli-Bosc FX, Le Gall P, Pugliese P, et al. Dig Dis Sci 2001; 46:540-4.
Manson JM, Freyssinges C, Ducrocq MB, Stephenson WP. Reprod Toxicol 1996; 10:439-446.
Plotkin D, Miller S, Nakajima S, et al. J Clin Endocrinol Metab 2002; 87:3155-61.
Pollack PS, Shields KE, Burnett DM, et al. Birth Defects Res A Clin Mol Teratol 2005; 73:888-96.

■ **Summary** ·····

Pregnancy Category: X
Lactation Category: NS

- **Simvastatin** should be avoided during pregnancy and lactation.
- Inadvertent exposure is not an indication for pregnancy termination.

Sirolimus

International Brand Name—Rapamune (Colombia, Israel, Mexico, New Zealand)

■ **Drug Class** ····· Immunosuppressants

■ **Indications** ····· Adjunct, renal transplant

■ **Mechanism** ····· Inhibits T cell activation/proliferation in response to antigenic and IL-2, IL-4, and IL-15 stimulation

■ **Dosage with Qualifiers** ····· Adjunct, renal transplant—2mg PO qd combined with **cyclosporine** and corticosteroids; alternative 15mg PO initially, then 5mg PO qd

NOTE: hepatic dosing; monitor renal function; antimicrobial and CMV prophylaxis suggested; complete drug history essential because of interactions with commonly used agents.

- **Contraindications**—hypersensitivity to drug or class, acute infection
- **Caution**—sun exposure

■ **Maternal Considerations** ····· A growing number of obstetric patients have benefited from organ transplant. Pregnancy is considered reasonable if the patient is 2y post-transplantation, has good renal function without proteinuria, no uncontrolled arterial hypertension, and no evidence of ongoing rejection. Adverse outcomes are otherwise common and these pregnancies should be managed in a tertiary care center. The clearance of **sirolimus** is modestly increased in women. There are no adequate reports or well-controlled studies of **sirolimus** in pregnant women. The published experience is limited to case reports and moderate-sized series. It is generally avoided in favor of **tacrolimus** or **azathioprine** with or without steroids.

Side effects include hyperlipidemia, hypercholesterolemia, increased BUN/Cr, opportunistic infection, epistaxis, lymphocele, insomnia, hemolytic-uremic syndrome, herpes zoster, malaise, skin ulcer, increased LDH, hypotension, diabetes mellitus, tinnitus, deafness, facial edema, atrial fibrillation, CHF, hemorrhage, hypervolemia, palpitation, peripheral vascular disorder, syncope, tachycardia, thrombophlebitis, thrombosis, vasodilation, anorexia, dysphagia, eructation, esophagitis, flatulence, gastritis,

gastroenteritis, gingivitis, ileus, abnormal LFTs, mouth ulceration, oral moniliasis, stomatitis, skin cancer, and lymphoma.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **sirolimus** crosses the human placenta. Early pregnancy exposure has not been associated with an increased risk of structural malformations. **Sirolimus** is embryotoxic in rodents. *In vitro,* it inhibits the growth of fetal myocardial cells.

Breastfeeding Safety

There are no adequate reports or well-controlled studies in nursing women. It is unknown whether **sirolimus** enters human breast milk. Trace amounts are found in rat milk, and *in vitro,* **sirolimus** inhibited milk production.

Drug Interactions

A substrate for both CYP3A4 and P-glycoprotein (Pgp).
Should be taken 4h after **cyclosporine.** After simultaneous use, the mean C_{max} and AUC of **sirolimus** were increased by 116% and 230%, respectively, compared to **sirolimus** alone. After multiple-dose administration over 6mo of **sirolimus** given 4h after **cyclosporine** to post renal transplantation patients, **cyclosporine** clearance was reduced, and lower doses of **cyclosporine** were needed to maintain the targeted **cyclosporine** levels.
Diltiazem is a substrate and inhibitor of CYP3A4 and Pgp; **sirolimus** levels should be monitored and the dose adjusted as necessary.
Erythromycin (also **clarithromycin, telithromycin**) is a substrate and inhibitor of CYP3A4 and Pgp; use with **sirolimus** is not recommended. Use with **erythromycin** increased the **sirolimus** C_{max} and AUC 4.4- and 4.2-fold, respectively, and the T_{max} was increased by 0.4h. The **erythromycin** C_{max} and AUC were increased 1.6- and 1.7-fold, respectively, and T_{max} was increased by 0.3h.
Ketoconazole (also **itraconazole, voriconazole**) is a strong inhibitor of CYP3A4 and Pgp; use with **sirolimus** is not recommended. Multiple-dose **ketoconazole** increased the **sirolimus** C_{max}, T_{max}, and AUC by 4.3-fold, 38%, and 10.9-fold, respectively.
Rifampin (also **rifabutin**) is a strong inducer of CYP3A4 and Pgp. Use with **sirolimus** is not recommended. **Rifampin** increased **sirolimus** clearance by 5.5-fold (range = 2.8-10), which represents mean decreases in AUC and C_{max} of about 82% and 71%, respectively. Aternative therapeutic agents with less enzyme induction potential should be considered.
Verapamil is a substrate and inhibitor of CYP3A4 and Pgp; **sirolimus** concentrations should be monitored and the dose adjusted as necessary. Simultaneous use increased the **sirolimus** C_{max} and AUC 2.3- and 2.2-fold, respectively.
Other drugs that *increase* **sirolimus** levels include (but are not limited to) **bromocriptine, cimetidine, cisapride, clotrimazole, danazol, fluconazole,** HIV-protease inhibitors (e.g., **indinavir, ritonavir**), **metoclopramide,** and **troleandomycin.**
Other drugs that *decrease* **sirolimus** levels include (but are not limited to) **carbamazepine, phenobarbital, phenytoin,** and **rifapentine.**
St. John's wort *(Hypericum perforatum)* induces CYP3A4 and Pgp, and there is a potential that its use may reduce **sirolimus** levels.
Immunosuppressants may affect response to vaccination. Therefore, the use of live vaccines should be avoided.

References

Burton PB, Yacoub MH, Barton PJ. Pediatr Cardiol 1998; 19:468-70.

Hang J, Rillema JA. Biochim Biophys Acta 1997; 1358:209-14.
[No authors]. Nephrol Dial Transplant 2002; 17(Suppl 4):50-5.
Sifontis NM, Coscia LA, Constantinescu S, et al. Transplantation 2006; 82:1698-702.

Summary

Pregnancy Category: C
Lactation Category: U

- **Sirolimus** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.
- There are alternative agents for which there is more experience regarding use during pregnancy and lactation.

Sodium bicarbonate—(Baros granules; Neut)

International Brand Name—None identified.

Drug Class

Alkalinizing agents; Electrolyte replacements

Indications

Metabolic acidemia

Mechanism

Increases serum bicarbonate

Dosage with Qualifiers

Metabolic acidemia—1mEq/kg IV; adjust dose based on ABG and clinical scenario

- **Contraindications**—hypersensitivity to drug or class, hypochloridemia, hypocalcemia
- **Caution**—CHF

Maternal Considerations

There are no adequate reports or well-controlled studies of **sodium bicarbonate** in pregnant women. There is no reason to expect pregnancy alters the risk of its use. It is most often used during pregnancy in association with the treatment of DKA. There are also rare reports of its use for pica resulting in severe hypokalemic metabolic alkalosis and rhabdomyolysis.
Side effects include metabolic alkalosis, extravasation cellulitis, edema, and hyponatremia.

Fetal Considerations

There are no adequate reports or well-controlled studies of **sodium bicarbonate** in human fetuses. Bicarbonate ions do equilibrate across the human placenta. There is no physiologic reason to expect a gradual correction of a metabolic acidosis would threaten the fetus. It is used during RBC transfusion of the profoundly anemic fetus to prevent severe acidemia and to resuscitate during fetal surgery. Rodent teratogenicity studies have not been conducted.

Breastfeeding Safety

There are no adequate reports or well-controlled studies in nursing women. It is unknown whether infused **sodium bicarbonate** enters human breast milk and increases milk concentration.

Drug Interactions

NE and **dobutamine** are incompatible with **sodium bicarbonate** solution.
Avoid adding to parenteral solutions containing calcium as precipitation or haze may result.

References

Grotegut CA, Dandolu V, Katari S, et al. Obstet Gynecol 2006; 107:484-6.

	Jennings RW, Adzick NS, Longaker MT, et al. J Pediatr Surg 1992; 27:1329-33. Weiner CP, Williamson RA, Wenstrom KD, et al. Am J Obstet Gynecol 1991; 165:1302-7.
Summary	**Pregnancy Category: C** **Lactation Category: S** • **Sodium bicarbonate** should be used during pregnancy and lactation when medically indicated.

Sodium ferric gluconate—(Ferrlecit)

International Brand Name—None identified.

Drug Class	Replacement; Vitamins/minerals
Indications	Iron deficiency in hemodialysed patients
Mechanism	Essential component for erythropoiesis
Dosage with Qualifiers	Iron deficiency in hemodialysed patients—25mg IV test dose over 60min followed by 100mg IV over 1h • **Contraindications—**hypersensitivity to drug or class, non–iron deficiency anemia, iron overload • **Caution—**unknown
Maternal Considerations	**Sodium ferric gluconate** is a stable macromolecular complex in sucrose injection. There is no adequate published experience with **sodium ferric gluconate** complex during pregnancy. Anaphylaxis has been reported during pregnancy. ***Side effects*** include anaphylaxis, iron toxicity, hypotension, flushing, headache, N/V, diarrhea, weakness, fatigue, injection site reactions, pain, fever, dyspnea, itching, and rash.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **sodium ferric gluconate** complex crosses the human placenta. Iron is transported across. There is no physiologic reason to expect an adverse effect if maternal iron content is in the normal range.
Breastfeeding Safety	There is no published experience in nursing women. It is unknown whether **sodium ferric gluconate** complex enters human breast milk. However, iron is a normal component of breast milk, and other iron supplements increase the milk concentration.
Drug Interactions	No clinically relevant interactions identified.
References	Cuciti C, Mayer DC, Arnette R, Spielman FJ. Int J Obstet Anesth 2005; 14:362-4. Kami K. Int J Anesth 2006; 15:264.
Summary	**Pregnancy Category: B** **Lactation Category: S** • **Sodium ferric gluconate** complex should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Sodium polystyrene—(Kayexalate; Resonium; Sps)

International Brand Name—Resinsodio (Spain); Resonium A (Austria, England, Germany, Hong Kong, Hungary, Ireland, Netherlands, Switzerland, Taiwan)

Drug Class	Resins
Indications	Hyperkalemia
Mechanism	Exchanges sodium for potassium in the large bowel
Dosage with Qualifiers	Hyperkalemia—15mg mixed in water or sorbitol PO qd to qid • **Contraindications**—hypersensitivity to drug or class, hypokalemia • **Caution**—severe CHF, severe hypertension, marked hypernatremia
Maternal Considerations	There is no published experience with **sodium polystyrene** during pregnancy. ***Side effects*** include hypokalemia, alkalosis, gastric irritation, anorexia, N/V, diarrhea, constipation, intestinal obstruction, fecal impaction, and hypocalcemia.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. **Sodium polystyrene** is not absorbed systemically and should pose no direct risk to the fetus. Rodent teratogenicity studies have not been performed.
Breastfeeding Safety	There is no published experience with **sodium polystyrene** in nursing women. However, the low maternal systemic concentration precludes a direct effect.
Drug Interactions	Use with nonabsorbable cation-donating antacids and laxatives may reduce the resin's potassium exchange capability. Magnesium hydroxide should not be used as one case of grand mal seizure has been reported. Intestinal obstruction due to concretions of aluminum hydroxide when used in combination with polystyrene has been reported. The toxic effects of **digitalis** on the heart, especially various ventricular arrhythmias and AV nodal dissociation, are likely to be exaggerated by hypokalemia, even with **digoxin** levels in the "normal range."
References	There is no published experience in pregnancy or during lactation.
Summary	**Pregnancy Category: C** **Lactation Category: S** • **Sodium polystyrene** should be used during pregnancy and lactation when medically indicated.

Sotalol—(Betapace; Sorine)

International Brand Name—Alosot (Uruguay); Beta-Cardone (England, Ireland); Betacor (Israel); Betades (Italy); Cardol (Australia); Darob (Austria); Favorex (Germany); Hipecor (Chile); Imigran (Austria, Brazil, Bulgaria, Chile, China, Colombia, Costa Rica, Czech Republic, Denmark, Dominican Republic, Ecuador, El Salvador, England, Finland, Germany, Greece, Guatemala, Honduras, Hong Kong, Hungary, Ireland, Italy, Japan, Korea, Malaysia, Mexico, Netherlands, Nicaragua, Norway, Panama, Paraguay, Peru, Philippines, Poland, South Africa, Spain, Sweden, Switzerland, Thailand, Uruguay, Venezuela); Jutalex (Germany); Rentibloc (Korea); Solavert (Australia); Sotab (Australia); Sotacor (Argentina, Austria, Brazil, Canada, China, Colombia, Denmark, England, Finland, Hong Kong, Indonesia, Ireland, Israel, Malaysia, Netherlands, Norway, Sweden, Thailand); Sotahexal (Australia, Germany, South Africa); Sotalex (Belgium, Bulgaria, Czech Republic, France, Germany, Greece, Hungary, Italy, Philippines, Poland, Portugal, Singapore, Switzerland); Sotaper (Ecuador); Sotapor (Spain)

Drug Class ..... Antiadrenergics; Antiarrhythmics, class III

Indications ..... Ventricular arrhythmia

Mechanism ..... Nonspecific β-blocker

Dosage with Qualifiers .....

Ventricular arrhythmia—begin 80mg PO q12h, titrate dose in hospital with continuous monitoring for at least 3d; max 640mg for refractory cases

NOTE: renal dosing; monitor ECG, QT interval, and CrCl; avoid abrupt withdrawal.

- **Contraindications**—hypersensitivity to drug or class, sinus bradycardia, 2nd and 3rd degree AV block, prolonged QT interval syndrome, cardiogenic shock, uncontrolled CHF, asthma, hypokalemia, hypomagnesemia
- **Caution**—renal dysfunction, sick sinus syndrome, compensated CHF, diabetes mellitus, diuretics, electrolyte abnormalities

Maternal Considerations .....

There are no adequate reports or well-controlled studies of **sotalol** in pregnant women. The published literature is limited to case reports. **Sotalol** reduces BP in hypertensive women, but its reported use during pregnancy is restricted to its properties as an antiarrhythmic agent.
Side effects include torsades de pointes, ventricular arrhythmia, CHF, prolonged QT interval, bradycardia (may be severe), dyspnea, fatigue, dizziness, chest pain, palpitations, asthenia, hypotension, headache, N/V, diarrhea, edema, sweating, and dyspepsia.

Fetal Considerations .....

There are no adequate reports or well-controlled studies in human fetuses. **Sotalol** crosses the human placenta, reaching an F:M ratio approximating unity, and is found in AF. It has been used to treat fetal tachyarrhythmia where the mean F:M **sotalol** plasma concentration is 1.1 (range, 0.67-2.87; SD, 0.63), and the mean AF:fetal blood ratio is 3.2 (range, 1.28-5.8; SD, 1.4). The response rate exceeded 75% in the largest report. The effectiveness of **sotalol,** however, cannot be extrapolated from maternal blood levels. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically. In rabbits, high doses are associated with embryonic death most likely secondary to embryonic arrhythmia.

Breastfeeding Safety .....

There are no adequate reports or well-controlled studies in nursing women. **Sotalol** enters human breast milk. Mean M:P ratios of 2.4-5.4 are reported, with milk levels ranging from 5 to 20.2mg/L. There was no consistent difference in **sotalol** concentration between pre- and postfeed milk samples. Using an

average milk intake of 0.15L/kg/d, it was calculated that an infant would have received a dose some 20-23% of the maternal dose. This dose was not associated with any bradycardia. However, because of the relatively large infant exposure to the drug, breastfeeding should be undertaken only when the infant is closely monitored and side effects such as bradycardia, hypotension, respiratory distress, or hypoglycemia are not demonstrable.

Drug Interactions

Class Ia antiarrhythmic drugs (e.g., **disopyramide, procainamide, quinidine**) and other class III drugs (e.g., **amiodarone**) are not recommended because of their potential to prolong refractoriness.
Use with caution in conjunction with calcium channel blocking drugs because of possible additive effects on AV conduction or ventricular function. Use of these drugs may have additive effects on BP, leading to hypotension.
Use with catecholamine-depleting drugs (e.g., **guanethidine, reserpine**) may produce an excessive reduction of resting sympathetic nervous tone. Patients should be monitored closely for hypotension and or marked bradycardia.
β-Agonists (e.g., **isoprenaline, salbutamol, terbutaline**) may require increased doses.
May potentiate the rebound hypertension sometimes observed after discontinuing **clonidine.**
Avoid use within 2h of antacids containing aluminum oxide and magnesium hydroxide as they may reduce the C_{max} and AUC by 26% and 20%, respectively. Use of an antacid 2h after **sotalol** has no effect on the pharmacokinetics or pharmacodynamics.
Use cautiously with other drugs known to prolong the QT interval, such as class I and III antiarrhythmic agents, phenothiazines, TCAs, **astemizole, bepridil,** certain oral macrolides, and certain quinolone antibiotics.
Proarrhythmic events are more common in **sotalol**-treated patients also receiving **digoxin.**

References

Abe K, Hamada H, Chen YJ, et al. Fetal Diagn Ther 2005; 20:459-62.
Hackett LP, Wojnar-Horton RE, Dusci LJ, et al. Br J Clin Pharmacol 1990; 29:277-8.
Lin CH, Lee CN. Taiwan J Obstet Gynecol 2008; 47:327-9.
O'Hare MF, Murnaghan GA, Russell CJ, et al. Br J Obstet Gynaecol 1980; 87:814-20.
Oudijk MA, Ruskamp JM, Ambachtsheer BE, et al. Paediatr Drugs 2002; 4:49-63.
Oudijk MA, Ruskamp JM, Ververs FF, et al. J Am Coll Cardiol 2003; 42:765-70.
Shannon ME, Malecha SE, Cha AJ. J Hum Lact 2000; 16:240-5.
Skold AC, Danielsson BR. Pharmacol Toxicol 2001; 88:34-9.
Wu TH, Huang LC, Ho M, et al. Taiwan J Obstet Gynecol 2006; 45:79-82.

Summary

Pregnancy Category: B
Lactation Category: S (possibly)

- **Sotalol** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.
- Efficient placental transport makes **sotalol** one of the agents of choice for the treatment of a fetal SVT.

Spectinomycin—(Trobicin)

International Brand Name—None identified.

Drug Class	Aminoglycosides; Antibiotics
Indications	Gonorrhea
Mechanism	Bactericidal—inhibits protein synthesis by binding the bacterial 30S ribosomal subunit
Dosage with Qualifiers	Gonorrhea, uncomplicated—2g IM (gluteus) ×1; increase to 4g if resistance (2g/injection) Gonorrhea, disseminated—2g IM (gluteus) ×3-7d • **Contraindications**—hypersensitivity to drug or class • **Caution**—unknown
Maternal Considerations	**Spectinomycin** is not effective for the treatment of syphilis, and may in fact mask or delay the symptoms of incubating syphilis. All patients with gonorrhea should be serologically tested for syphilis at diagnosis, and again 3mo later. There are no adequate reports or well-controlled studies of **spectinomycin** in pregnant women. Failure to achieve "microbiologic cure" is similar for common antibiotic regimens: **amoxicillin** plus **probenecid** compared with **spectinomycin** (OR 2.40, 95% CI 0.71-8.12), **amoxicillin** plus **probenecid** compared with **ceftriaxone** (OR 2.40, 95% CI 0.71-8.12), and **ceftriaxone** compared with **cefixime** (OR 1.22, 95% CI 0.16-9.04). Thus, the selection is based on sensitivities in the geographic locale, price, and the prevalence of syphilis. Sex partners should be tested and treated when possible. ***Side effects*** include urticaria, dizziness, nausea, chills, fever, injection site pain, insomnia, anemia, and elevated BUN and LFTs.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **spectinomycin** crosses the human placenta. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically.
Breastfeeding Safety	There is no published experience in nursing women. It is unknown whether **spectinomycin** enters human breast milk. Considering the likely dosage and that other aminoglycosides are generally considered safe for breastfeeding, the same should be true for **spectinomycin.**
Drug Interactions	No clinically relevant interactions identified.
References	Brocklehurst P. Cochrane Database Syst Rev 2002; (2):CD000098.
Summary	**Pregnancy Category: B** **Lactation Category: S** (likely) • **Spectinomycin** is one of several available effective agents for the treatment of gonorrhea during pregnancy and lactation.

Spironolactone—(Aldactone; Diatensec; Flumach; Osiren)

International Brand Name—Adultmin (Japan); Aldospirone (Israel); Almatol (Taiwan); Berlactone (Thailand); Diram (Japan); Flumach (France); Hypazon (Japan); Idrolattone (Italy); Merabis (Japan); Novospiroton (Canada); Osyrol (Germany, Japan); Pirolacton (Japan); Pondactone (Thailand); Resacton (Japan); Spiractin (Australia, South Africa); Spirix (Denmark, Finland, Norway, Sweden); Spiroctan (England, France, Netherlands, Switzerland); Spirolacton (Indonesia); Spirolang (Italy); Spiron (Denmark); Spirone (Peru); Spironex (Thailand); Spirono-Isis (Germany); Spironol (Israel); Spirotone (New Zealand); Tensin (South Africa); Xenalon Lactabs (Dominican Republic); Youlactone (Japan)

Drug Class ..... Diuretics, potassium sparing

Indications ..... Edema, CHF, diuretic-induced hypokalemia, hyperaldosteronism test, hypertension

Mechanism ..... Aldosterone receptor antagonist active in the distal convoluted tubule

Dosage with Qualifiers .....

Edema—25-50mg PO qd or bid
CHF—25mg PO qd
Diuretic-induced hypokalemia—25-100mg PO qd (only if oral potassium not appropriate)
Hyperaldosteronism test—400mg PO qd ×4-28d (until hypokalemia corrects)
Hypertension—25-50mg PO qd or bid

NOTE: renal dosing.

- **Contraindications**—hypersensitivity to drug or class, anuria, renal insufficiency, hyperkalemia
- **Caution**—hepatic or renal dysfunction, hyponatremia, diabetes mellitus

Maternal Considerations .....

Spironolactone increases sodium and water excretion while retaining potassium. There are no adequate reports or well-controlled studies of **spironolactone** in pregnant women. Diuretics should not be used to treat the physiologic edema of pregnancy and do not prevent preeclampsia. There are superior agents for such off-label indications as hirsutism. It has been used for the treatment of maternal Bartter's syndrome during pregnancy with success.
Side effects include renal failure, hepatotoxicity, menstrual irregularities, agranulocytosis, anaphylaxis, N/V, diarrhea, abdominal pain, headache, confusion, hirsutism, fever, rash, hyperkalemia, and metabolic acidosis.

Fetal Considerations ..... There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **spironolactone** crosses the human placenta. **Spironolactone** is an antiandrogen and can feminize male rats. However, there is at least one case report of an appropriately developed male newborn after high-dose treatment for maternal Bartter's syndrome.

Breastfeeding Safety ..... While **spironolactone** and its major active metabolite enter human breast milk, it is estimated that the breastfeeding neonate would ingest <0.5% of the daily maternal dose.

Drug Interactions .....

Use with ACEIs has been associated with severe hyperkalemia.
Use with alcohol, barbiturates, or narcotics may potentiate orthostatic hypotension.
Use with corticosteroids or ACTH may intensify electrolyte depletion, particularly hypokalemia.

Reduces the vascular responsiveness to NE. Exercise caution with patients undergoing regional or general anesthesia.
Possible increased responsiveness to nondepolarizing muscle relaxants may result.
Diuretic agents reduce the renal clearance of **lithium** and increase the risk of **lithium** toxicity.
In some patients, use with an NSAID can reduce the diuretic, natriuretic, and antihypertensive effect of loop, potassium-sparing, and thiazide diuretics and has been associated with severe hyperkalemia. The patient should be observed closely.
Increases the t/2 of **digoxin,** resulting in increased serum **digoxin** levels and subsequent digitalis toxicity.

References

Groves TD, Corenblum B. Am J Obstet Gynecol 1995; 172:1655-6.
Phelps DL, Karim Z. J Pharm Sci 1977; 66:1203.
Rigo J Jr, Glaz E, Papp Z. Am J Obstet Gynecol 1996; 174:297.

Summary

Pregnancy Category: D
Lactation Category: S

- **Spironolactone** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Stavudine—(d4T; Zerit)

International Brand Name—Stavir (India); Tonavir (Paraguay, Uruguay); Virostav (Malaysia); Zerit (Argentina, Canada, Chile, Ecuador, Hong Kong, Indonesia, Israel, Korea, Malaysia, Mexico, Peru, Singapore, South Africa, Thailand, Venezuela); Zeritavir (Brazil)

Drug Class

Antivirals; NRTIs

Indications

HIV infection

Mechanism

Reverse transcriptase inhibitor

Dosage with Qualifiers

HIV infection—40mg PO q12h; withhold if peripheral neuropathy develops

NOTE: renal dosing.

- **Contraindications**—hypersensitivity to drug or class, lactic acidosis, lactation
- **Caution**—hepatic or renal dysfunction, peripheral neuropathy, neurotoxic agents, AIDS, history of pancreatitis, bone marrow depression

Maternal Considerations

Stavudine is a synthetic thymidine nucleoside analog. There are no adequate reports or well-controlled studies of **stavudine** in pregnant women. Mean maternal pharmacokinetics are unaffected by labor. Pregnancy increases the risk of potentially fatal lactic acidosis/hepatic steatosis when combined with **didanosine** and other antiretroviral agents.
Side effects include hepatotoxicity, pancreatitis, lactic acidosis, peripheral neuropathy, severe motor weakness, leukopenia, thrombocytopenia, headache, N/V, diarrhea, abdominal pain, rash, fever, chills, anorexia, myalgia, insomnia, anemia, and elevated LFTs and amylase/lipase.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. **Stavudine** is concentrated in the human fetus, achieving an F:M concentration ratio of 1.32. Rodent studies revealed a possible

reduction in implantation numbers and only minor skeletal abnormalities even when the dose approximated 400× the MRHD. **Stavudine** readily crosses the rhesus macaque placenta.

Breastfeeding Safety

There is no published experience in nursing women. It is unknown whether **stavudine** enters human breast milk. It is excreted into rodent milk. Breastfeeding is contraindicated in HIV-infected nursing women when formula is available to reduce the risk of neonatal transmission.

Drug Interactions

Zidovudine competitively inhibits the intracellular phosphorylation of **stavudine.** Their combined use should be avoided. *In vitro* data suggest that **stavudine** phosphorylation is also inhibited by **doxorubicin** and **ribavirin.** Use with either of these drugs should be undertaken with caution.

References

Chappuy H, Treluyer JM, Jullien V, et al. Antimicrob Agents Chemother 2004; 48:4332-6.
Barreto RL, de Jesus Simões M, Amed AM, et al. J Obstet Gynaecol Res 2004; 30:242-5.
[No authors]. AIDS Treat News 2001; 358:8.
Patterson TA, Binienda ZK, Newport GD, et al. Teratology 2000; 62:93-9.
Sarner L, Fakoya A. Sex Transm Infect 2002; 78:58-9.
Wade NA, Unadkat JD, Huang S, et al. J Infect Dis 2004; 190:2167-74.

Summary

Pregnancy Category: C
Lactation Category: U

- **Stavudine** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.
- It may provide little HIV protection to the perinate despite placental transfer of the parent drug.
- Physicians are encouraged to register pregnant women under the Antiretroviral Pregnancy Registry (1-800-258-4263) for a better follow-up of the outcome while under treatment with **stavudine.**

St. John's Wort *(Hypericum perforatum)*

International Brand Name—None identified.

Drug Class

Herb

Indications

Depression

Mechanism

Unknown

Dosage with Qualifiers

Depression—300mg PO tid; max 1500mg

- **Contraindications—**hypersensitivity to drug or class, HIV
- **Caution—**cataract

Maternal Considerations

St. John's wort is an herb used medicinally for centuries. The composition of **St. John's wort** and how it might work are not well understood. It contains multiple bioactive substances. The naphthodianthrones hypericin and pseudohypericin and multiple flavonoids have generated interest as potential

antidepressant and antiviral agents. *In vitro* studies reveal MAO inhibitory activity. Studies suggest that **St. John's wort** is of no benefit in treating major depression of moderate severity.
A National Institutes of Health study revealed that concomitant administration of **St. John's wort** and **indinavir** substantially decreased **indinavir** plasma concentrations, potentially due to induction of CYP3A4 by **St. John's wort.** There are no adequate reports or well-controlled studies of **St. John's wort** during pregnancy. Relevant questions remain regarding the use of **St. John's wort** in HIV-positive pregnant women treated concomitantly with protease inhibitors and NNTRIs. **St. John's wort** is best avoided during pregnancy.
Side effects include early-onset cataract, dry mouth, dizziness, sexual dysfunction, GI symptoms, increased sensitivity to sunlight, fatigue, and reduction of the effectiveness of several drugs.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **St. John's wort** crosses the human placenta. One rodent study suggests maternal administration before and throughout gestation does not affect long-term growth and physical maturation of the exposed offspring.

Breastfeeding Safety

There are no adequate reports or well-controlled studies of **St. John's wort** in breastfeeding women. One observational study suggests an increased prevalence of neonatal drowsiness/lethargy compared to control. Another study noted that hyperforin was excreted into breast milk at low levels, but was at or below the level of detection in the neonates (n = 2). M:P ratios ranged from 0.04 to 0.13. The relative infant dose of 0.9-2.5% indicates that infant exposure to hyperforin through milk is comparable to levels reported in most studies assessing antidepressants or neuroleptics. No side effects were seen in the mothers or infants.

Drug Interactions

St. John's wort is a weak inducer of CYP3A4 and, as such, may decrease the concentrations of drugs metabolized by this enzyme (e.g., **indinavir**).

References

Dugoua JJ, Mills E, Perri D, Koren G. Can J Clin Pharmacol 2006; 13:e268-76.
Goldman RD, Koren G; Motherisk Team. Can Fam Physician 2003; 49:29-30.
Hypericum Depression Trial Study Group. JAMA 2002; 287:1807-14.
Klier CM, Schmid-Siegel B, Schäfer MR, et al. J Clin Psychiatry 2006; 67:305-9.
Lee A, Minhas R, Matsuda N, et al. J Clin Psychiatry 2003; 64:966-8.
Piscitelli SC, Burstein AH, Chaitt D, et al. Lancet 2000; 355:547-8.
Rayburn WF, Gonzalez CL, Christensen HD, Stewart JD. Am J Obstet Gynecol 2001; 184:191-5.
Shelton RC, Keller MB, Gelenberg AJ, et al. JAMA 2001; 285:1978-86.

Summary

Pregnancy Category: C
Lactation Category: S

- **St. John's wort** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.
- There are superior agents for the treatment of depression for which there is more experience regarding use during pregnancy and lactation.
- The FDA recommended that health care providers alert their patients that **St. John's wort** use might reduce the effectiveness of their other medications.

Streptokinase—(Kabikinase; K-Nase; Streptase; Zykinase)

International Brand Name—K-Nase (Korea); Zykinase (India)

Drug Class	Thrombolytics
Indications	MI, PE/DVT, AV cannula occlusion
Mechanism	Converts plasminogen to plasmin
Dosage with Qualifiers	MI—1.5million U IV over 60min PE/DVT—begin 250,000U IV over 30min, then 100,000U/h for either 72h (DVT) or 24h (PE); begin within 7-10d of occlusion AV cannula occlusion—100,000-250,000U IV over 30min • **Contraindications**—hypersensitivity to drug or class, recent stroke, active internal bleeding, recent trauma, intracranial tumor, ulcerative colitis, severe hypertension, rheumatic valvular disease, <10d since a diagnostic arterial procedure • **Caution**—recent delivery, recent GI bleeding, left-sided heart thrombosis, hypertension, diabetic retinopathy, subacute bacterial endocarditis
Maternal Considerations	**Streptokinase** is a purified bacterial protein produced by group C β-hemolytic streptococci. There is no residual thrombotic material in 60-75% of patients treated with **streptokinase** vs. only 10% of those treated with **heparin.** Therapy preserves venous valve function in most cases, avoiding the pathologic changes that cause postphlebitic syndrome, which follows in 90% of the DVT patients treated with **heparin** alone. There are no adequate reports or well-controlled studies of **streptokinase** in pregnant women, though numerous case reports suggest relative safety compared to therapeutic alternatives. Of special note is its success with thrombotic mechanical mitral valves. Hemorrhage complicates <10% but may be severe. Because of the increased likelihood of resistance due to anti-streptokinase antibody, **streptokinase** may be ineffective within 1y of prior administration, or a streptococcal infection, such as streptococcal pharyngitis, acute rheumatic fever, or acute glomerulonephritis secondary to a streptococcal infection. ***Side effects*** include anaphylaxis, cholesterol embolism, arrhythmia, severe bleeding, stroke, hypotension, fever, and bronchospasm.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **streptokinase** crosses the human placenta. The published case reports provide some reassurance. Rodent teratogenicity studies have not been conducted.
Breastfeeding Safety	There is no published experience in nursing women. It is unknown whether **streptokinase** enters human breast milk.
Drug Interactions	The addition of **aspirin** increases minimally the risk of minor bleeding (3.9% vs 3.1%).
References	Anbarasan C, Kumar VS, Latchumanadhas K, Mullasari AS. J Heart Valve Dis 2001; 10:393-5. Arneson H, Heilo A, Jakobsen E, et al. Acta Med Scand 1978; 203:457-463.

Henrich W, Schmider A, Henrich M, Dudenhausen JW. J Perinat Med 2001; 29:155-7.
Turrentine MA, Braems G, Ramirez MM. Obstet Gynecol Surv 1995; 50:534-41.

Summary

Pregnancy Category: C
Lactation Category: U

- **Streptokinase** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Succinylcholine—(Anectine; Celocurin; Quelicin; Sucostrin; Suxamethonium; Sux-Cert)

International Brand Name—Anectine (England, Ireland, Mexico, Spain); Celocurin (Sweden); Celocurine (France); Curalest (Netherlands); Ethicholine (Malaysia, New Zealand); Fosfitone (Argentina, Uruguay); Lysthenon (Austria, Bulgaria, Germany, Switzerland, Taiwan); Midarine (India); Myoplegine (Belgium); Myotenlis (Italy); Pantolax (Germany); Quelicin Chloride (Brazil, Canada, Ecuador); Relaxin (Taiwan); Succi (Argentina); Succicholine (Korea); Succinyl-Asta (Indonesia); Succinyl Forte (Israel); Sukolin (Finland, Hungary); Suxamethonium (New Zealand); Suxameton (Denmark); Suxametonio Cloruro (Chile, Paraguay)

Drug Class

Musculoskeletal agents; Neuromuscular blockers, depolarizing

Indications

Paralysis; anesthesia

Mechanism

Stimulates ACh motor end plates

Dosage with Qualifiers

Paralysis, anesthesia, short term—0.6-1.5mg/kg IV over 10-30sec; max 150mg
Paralysis, long term—0.5-10mg/min continuous IV

NOTE: onset 30-60sec, duration 6-10min.

- **Contraindications**—hypersensitivity to drug or class, pseudocholinesterase deficiency, narrow-angle glaucoma, penetrating eye injury, history of malignant hyperthermia, bradycardia, severe burns, hyperkalemia, neuromuscular disorders, history of rhabdomyolysis
- **Caution**—stroke, severe hepatic disease, myasthenia gravis

Maternal Considerations

There are no adequate reports or well-controlled studies of **succinylcholine** in pregnant women. It is the drug routinely used in rapid-sequence induction of general anesthesia to facilitate tracheal intubation for cesarean delivery. The large clinical experience is reassuring. Plasma cholinesterase levels decrease by ¼ during pregnancy and for several days postpartum. Thus, a higher proportion of patients may experience prolonged apnea in response to **succinylcholine** when pregnant compared to nonpregnant.
Side effects include arrhythmias, bradycardia, tachycardia, respiratory depression, CV collapse, malignant hyperthermia, apnea, hyperkalemia, rhabdomyolysis, myoglobinemia, muscle twitching, postoperative myalgia and stiffness, excess salivation, and increased intraocular pressure.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. Small amounts of **succinylcholine** are known to cross the placenta, but under normal conditions the amount of drug does not endanger the fetus. But because the amount that crosses depends on the M:F concentration gradient, apnea and

flaccidity can occur in the neonate after repeated high doses, or in the presence of atypical maternal plasma cholinesterase. Rodent teratogenicity studies have not been conducted.

Breastfeeding Safety

There are no adequate reports or well-controlled studies in nursing women. It is unknown whether **succinylcholine** enters human breast milk. However, considering the indication and dosing, one-time **succinylcholine** use is unlikely to pose a clinically significant risk to the breastfeeding neonate.

Drug Interactions

Neuromuscular blockade may be increased by **aprotinin,** β-adrenergic blockers, **chloroquine, desflurane, diethylether, isoflurane, lidocaine, lithium,** magnesium salts, **metoclopramide,** certain nonpenicillin antibiotics, **oxytocin, procainamide, promazine, quinidine, quinine, terbutaline,** and **trimethaphan.** Blockade may also be enhanced by drugs that reduce plasma cholinesterase activity (e.g., chronically administered oral contraceptives, glucocorticoids, or certain MAOIs) or by drugs that irreversibly inhibit plasma cholinesterase.

References

Guay J, Grenier Y, Varin F. Clin Pharmacokinet 1998; 34:483.
van der Kleijn E, Drabkova J, Crul JF. Br J Anaesth 1973; 45:1169-77.

Summary

Pregnancy Category: C
Lactation Category: S

- There is extensive clinical experience with **succinylcholine** during pregnancy that is reassuring.
- **Succinylcholine** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Sucralfate—(Calmidan; Carafate; Scrat; Sucafate; Sucrace; Ulcona; Ulcumaag; Ulsidex; Yuwan-S)

International Brand Name—Adopilon (Japan); Alsucral (Czech Republic, Finland, Malaysia, Portugal, Singapore); Alusac (Uruguay); Andapsin (Sweden); Antepsin (Argentina, Denmark, Ecuador, England, Finland, Ireland, Italy, Norway); Bisma (Japan); Dip (Colombia, Ecuador); Dolisec (Greece); Exinol (Venezuela); Hexagastron (Denmark); Inpepsa (Indonesia); Iselpin (Philippines); Keal (France, Taiwan); Melicide (Greece); Musin (Indonesia); Neciblok (Indonesia); Peptonorm (Greece); Succosa (Finland, Sweden); Sucrabest (Germany); Sucralbene (Hungary); Sucralfin (Italy); Sucramal (Italy); Sulcran (Chile, Peru); Sulcrate (Canada); Treceptan (Chile, Ecuador); Ufarene (Greece); Ulcar (France, South Africa); Ulcekon (India); Ulcerlmin (Japan, Korea); Ulcertec (Malaysia, Singapore); Ulcogant (Austria, Belgium, Costa Rica, Czech Republic, Dominican Republic, El Salvador, Germany, Guatemala, Honduras, Hungary, Netherlands, Nicaragua, Panama, Peru, Switzerland); Ulcyte (Australia); Ulsaheal (Bahrain, Iraq, Jordan, United Arab Emirates); Ulsanic (Hong Kong, Israel, South Africa, Thailand); Ulsicral (Indonesia); Ulsidex Forte (Indonesia); Unival (Mexico); Urbal (Spain); Venter (Bulgaria, Poland); Yuwan S (Japan)

Drug Class

Antiulcer agents; Cytoprotectives; Gastrointestinals

Indications

Duodenal ulcer

Mechanism

Coats the ulcer with proteinaceous exudate

Dosage with Qualifiers

Duodenal ulcer—1g PO qid (treatment) or bid (maintenance)

- **Contraindications**—hypersensitivity to drug or class, dysphagia, GI obstruction
- **Caution**—renal dysfunction

Maternal Considerations

GERD poses a special challenge in pregnancy. Lifestyle and dietary modifications, change in sleeping posture, and antacid

	medications are the first lines of therapy. When these interventions are unsuccessful, **sucralfate** should be next. Therapy with H_2 receptor antagonists or proton pump inhibitors are generally reserved for women with refractory symptoms. There are no adequate reports or well-controlled studies of **sucralfate** in pregnant women. ***Side effects*** include diarrhea, N/V, flatulence, constipation, rash, dizziness, insomnia, and bezoar formation.
Fetal Considerations	There are no adequate reports or well-controlled studies of **sucralfate** in human fetuses. It is only minimally absorbed across the GI tract, and thus should pose no risk to the fetus. Rodent studies are reassuring.
Breastfeeding Safety	There are no adequate reports or well-controlled studies in nursing women. While it is unknown whether **sucralfate** enters human breast milk, it is only minimally absorbed across the GI tract and should pose no risk to the breastfeeding neonate.
Drug Interactions	May reduce absorption of **cimetidine, digoxin,** fluoroquinolone antibiotics, **ketoconazole, phenytoin, quinidine, ranitidine, tetracycline, theophylline,** and **thyroxine.** Dosing 2h before or after **sucralfate** eliminates the interaction.
References	Broussard CN, Richter JE. Drug Saf 1998; 19:325-37. Charan M, Katz PO. Curr Treat Options Gastroenterol 2001; 4:73-81.
Summary	**Pregnancy Category: B** **Lactation Category: S** • **Sucralfate** is a first-line agent for the treatment of GERD during pregnancy and lactation.

Sufentanil—(Sufenta)

International Brand Name—Fentafienil (Italy); Sufenta (Argentina, Austria, Belgium, Brazil, Canada, Chile, Czech Republic, Denmark, France, Indonesia, Malaysia, Netherlands, Norway, Poland, Portugal, South Africa, Sweden, Taiwan, Uruguay); Sufenta Forte (South Africa)

Drug Class	Analgesics, narcotic; Anesthesia, general
Indications	General anesthesia, neuraxial anesthesia
Mechanism	Binds to multiple opiate receptors
Dosage with Qualifiers	General anesthesia—begin 2-8mcg/kg IV when used with inhalational anesthetics, up to 30mcg/kg when used with amnestic and oxygen alone; titrate additional smaller doses to desired effect Epidural during labor—several regimens, including 10-15mcg **sufentanil** plus 10ml 0.125% **bupivacaine** Intrathecal during labor—several regimens, including 5-7.5mcg with or without **bupivacaine** • **Contraindications**—hypersensitivity to drug or class • **Caution**—respiratory depression, hepatic or renal dysfunction
Maternal Considerations	**Sufentanil** is a potent opioid. When used in balanced general anesthesia, **sufentanil** has perhaps 10× the potency of **fentanyl.**

It is popular combined with a local anesthetic for a variety of neuraxial anesthetic techniques during labor. However, when choosing between **fentanyl** and **sufentanil, sufentanil** costs more and has a greater risk of dosing error because of its higher potency. The duration of analgesia is reduced in **cocaine**-abusing women.

Side effects include laryngospasm, respiratory depression, chest stiffness, ventricular arrhythmia, bronchospasm, hypotension, bradycardia, pruritus, N/V, chills, postoperative confusion, biliary spasm, constipation, ureteral colic, and blurred vision.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. **Sufentanil** crosses the human placenta, achieving an F:M ratio of unity. Because of its low initial umbilical vein concentration, **sufentanil** may be the opioid of choice when delivery is imminent (<45min). Fetal acidosis increases placental transfer. It is used for fetal analgesia during a variety of procedures. Rodent studies are generally reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically. Embryotoxicity does occur at doses twice the MRHD.

Breastfeeding Safety

There are no adequate reports or well-controlled studies in nursing women. However, considering the indication and dosing, one-time **sufentanil** use is unlikely to pose a clinically significant risk to the breastfeeding neonate.

Drug Interactions

Chronic use of calcium channel and β-blockers may increase the incidence and degree of bradycardia and hypotension during induction.

Use with benzodiazepines may decrease BP and SVR.

References

Clement HJ, Caruso L, Lopez F, et al. Br J Anaesth 2002; 88:809-13.

De Eccher L, Martino C, Bacchilega I, et al. Minerva Anestesiol 2002; 68:83-7.

Krishna BR, Zakowski MI, Grant GJ. Can J Anaesth 1997; 44:996-1001.

Nelson KE, Rauch T, Terebuh V, D'Angelo R. Anesthesiology 2002; 96:1070-3.

Ross VH, Moore CH, Pan PH, et al. Anesth Analg 2003; 97:1504-8.

Senat MV, Fischer C, Ville Y. Prenat Diagn 2002; 22:354-6.

Wang LZ, Zhang YF, Tang BL, Yao KZ. Br J Anaesth 2007; 98:792-6.

Summary

Pregnancy Category: C

Lactation Category: S

- **Sufentanil** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.
- It is a useful adjunct for labor epidural analgesia, allowing for a decreased quantity of local anesthetic, which helps preserve motor function.

Sulconazole nitrate topical—(Exelderm; Sulcosyn)

International Brand Name—Excerderm (Japan); Exelderm (Ecuador, England, Ireland, Korea, Portugal, Taiwan); Minot (Argentina); Myk (France); Myk 1 (Belgium, Netherlands); Suldisyn (Greece)

Drug Class	Antifungals; Dermatologics
Indications	Tinea pedis, tinea cruris, tinea corporis, tinea versicolor
Mechanism	Imidazole that inhibits cell membrane ergosterol synthesis
Dosage with Qualifiers	Tinea pedis—apply bid ×4w Tinea cruris—apply qd or bid ×3w Tinea corporis—apply qd or bid ×3w Tinea versicolor—apply qd or bid ×3w *NOTE: available in 1% cream or solution.* • **Contraindications**—hypersensitivity to drug or class • **Caution**—unknown
Maternal Considerations	There is no published experience with **sulconazole** during pregnancy. ***Side effects*** include pruritus, burning, and erythema.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **sulconazole** crosses the human placenta. Considering the dose and route, it is unlikely the maternal systemic concentration will reach a clinically relevant level. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically. Embryotoxicity was noted at doses 100× the MRHD.
Breastfeeding Safety	There is no published experience with **sulconazole** in nursing women. However, considering the dose and route, it is unlikely the breastfed neonate would ingest clinically relevant amounts.
Drug Interactions	No clinically relevant interactions identified.
References	There are no current relevant references.
Summary	**Pregnancy Category: C** **Lactation Category: S** (likely) • **Sulconazole** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Sulfadiazine—(Microsulfon)

International Brand Name—None identified.

Drug Class	Antibiotics; Sulfonamides
Indications	Toxoplasmosis
Mechanism	Bacteriostatic—inhibits dihydropteroate synthesis
Dosage with Qualifiers	Toxoplasmosis—2-8g PO qd in 3-4 divided doses ×4w plus **pyrimethamine** 25mg/d *NOTE: if AIDS, give 6mo or longer.* • **Contraindications**—hypersensitivity to drug or class, porphyria • **Caution**—hepatic or renal dysfunction, G6PD deficiency, hypovolemia
Maternal Considerations	Toxoplasmosis is one of the most common parasitic infections in humans. There are no adequate reports or well-controlled studies of **sulfadiazine** in pregnant women for maternal disease. **Sulfadiazine** is also marketed as a silver-based cream used as an adjunct for the prevention and treatment of wound sepsis in patients with 2nd and 3rd degree burns. ***Side effects*** include hemolytic anemia, Stevens-Johnson syndrome, thrombocytopenia, leukopenia, hepatitis, acute renal failure, kernicterus in the newborn, fever, dizziness, headache, N/V, diarrhea, photosensitivity, rash, and hematuria.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. **Sulfadiazine** crosses the human placenta and is used as a treatment for fetal toxoplasmosis in combination with **pyrimethamine.** Controversy continues as to how effective it is in preventing disease transmission. Since it is effective in the rhesus monkey model, treatment delay may explain the controversy. Rodent teratogenicity studies have not been performed. Other sulfonamides given at multiples of the MRHD are associated with cleft palate and bony abnormalities. It is also standard postnatally for the treatment of congenital toxoplasmosis. The extensive human experience associated with congenital toxoplasmosis is reassuring. There is no published experience to suggest any increase in the risk of kernicterus.
Breastfeeding Safety	There is no published experience in nursing women. While it is unknown whether **sulfadiazine** enters human breast milk, it is excreted into cows' milk. There are no adverse effects published in breastfed children.
Drug Interactions	No clinically relevant interactions identified.
References	Couvreur J, Thulliez P, Daffos F, et al. Fetal Diagn Ther 1993; 8:45-50. Gilbert RE, Gras L, Wallon M, et al. Int J Epidemiol 2001; 30:1303-8. Schmidt DR, Hogh B, Andersen O, et al. Arch Dis Child 2006; 91:661-5. Schoondermark-van de Ven EM, Melchers WJ, Galama JM, et al. Eur J Obstet Gynecol Reprod Biol 1997; 74:183-8.

Summary

Pregnancy Category: C
Lactation Category: S (likely)

- **Sulfadiazine** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Sulfamethoxazole—(Gamazole; Gantanol; Sinomin; Urobak)

International Brand Name—Abacin (Italy); Abactrim (Spain); Alcorim-F (India); Anitrim (Mexico); Antrimox (Ireland); Apo-Sulfatrim (Canada); Bacidal (Philippines); Bacin (Hong Kong, Malaysia, Thailand); Bacterol (Chile); Bacterol Forte (Chile); Bacticel (Argentina); Bactifor (Spain); Bactoprim (Indonesia); Bactramin (Japan); Bactrim (Argentina, Australia, Costa Rica, Dominican Republic, Ecuador, El Salvador, Guatemala, Honduras, India, Indonesia, Malaysia, Mexico, Nicaragua, Panama, South Africa, Thailand); Bactrim DS (Australia, India); Bactrimel (Greece, Netherlands); Bactrim F (Colombia); Bactrim Forte (Austria, Bulgaria, Costa Rica, Czech Republic, Dominican Republic, El Salvador, Finland, France, Guatemala, Honduras, Nicaragua, Panama, Portugal, Sweden); Baktar (Japan); Bencole (South Africa); Briscotrim (South Africa); Chemitrim (Hong Kong); Chemoprim (Thailand); Cipaprim (Peru); Cipaprim Forte (Peru); Colizole (India); Colizole DS (India); Comox (England); Conprim (Thailand); Cosig Forte (Australia); Costazole (Philippines); Cotribase (Philippines); Cotrim (Hong Kong, Taiwan); Cotrim-Diolan (Israel); Cotrim DS (Malaysia); Cotrimel (Hong Kong); Cotrimel Forte (Hungary); Cotrix (Israel); Cozole (Philippines); Diseptyl (Israel); Duocide (Taiwan); Duratrimet (Germany); Ectaprim (Mexico); Epitrim (Israel); Esbesul (Slovenia); Espectrin (Brazil); Eusaprim (Austria, Belgium, Finland, France, Germany, Italy, Netherlands, Norway, Sweden, Switzerland); Eutrim (Mexico); Fectrim (England); Fedimed (Philippines); Fermagex (Philippines); Gantaprim (Italy); Gantrim (Italy); Hulin (Spain); Ikaprim (Indonesia); Infectrim (Peru); Introcin (Chile); Isobac (Mexico); Isotrim (Italy); Kemocid (Indonesia); Kemotrim (Indonesia); Kepinol (Germany); Ladar Child (Thailand); Lagatrim (Israel, Puerto Rico, South Africa); Lagatrim Forte (Puerto Rico, South Africa); Lastrim (Thailand); Leprim (Philippines); Lescot (Argentina); Medixin (Italy); Metrim (Thailand); Mezenol (South Africa); Microtrim (Germany); Missile (Argentina); Moxalas (Indonesia); M-Trim (Thailand); Nopil (Ecuador, Israel); Nopil Forte (Ecuador); Novotrimel (Canada); Nufaprim Forte (Indonesia); Omsat (Germany, South Africa); Oriprim DS (Kenya, Tanzania, Uganda, Zimbabwe); Oxaprim (Italy, Japan); Piltrim (Philippines); Plurisul Forte (Peru); Purbal (South Africa); Resprim (Australia, Israel, Malaysia); Resprim Forte (Australia); Salvatrim (Dominican Republic, El Salvador, Honduras, Panama); Septra (Canada); Septran (Costa Rica, Dominican Republic, El Salvador, Honduras, India, Panama, South Africa, Uruguay); Septrin (Argentina, Colombia, England, Hong Kong, Indonesia, Israel, Korea, Malaysia, Mexico, New Zealand, Peru, Philippines, South Africa, Spain, Taiwan); Septrin DS (Hong Kong, Thailand); Septrin Familia (Mexico); Septrin Forte (Australia); Septrin S (Thailand); Servitrim (Mexico); Sigaprim (Germany); Sinotrim (Korea); Stopan (Japan); Sugaprim (India); Sulfacet (Germany); Sulfaprim (Malaysia); Sulfinam (Colombia); Sulfotrimin (Germany); Sulthrim (Colombia); Sumetropin (Peru); Suntrim (Thailand); Suntrim Forte (Thailand); Suprim (Peru); Suprin (Italy); TMS (Germany); Trim (Italy, South Africa); Trimaxazole (Singapore); Trimel (New Zealand); Trimephar (Philippines); Trimesulf F (Colombia); Trimetox (Mexico); Trimezol (Ecuador); Trimezole (Indonesia); Trimoxis (Philippines); Trisul (New Zealand); Trisulcom (Philippines); Trizakim (Mexico); Trizole (Indonesia, Philippines); Ulfaprim (Indonesia); Unitrizole (Philippines); Xeroprim (South Africa); Zamboprim (Philippines); Zultrop (Indonesia); Zultrop Forte (Indonesia)

Drug Class

Antibiotics; Sulfonamides

Indications

Bacterial infection (e.g., pyelonephritis, cystitis, meningitis, otitis media)

Mechanism

Bacteriostatic—inhibits dihydropteroate synthesis

Dosage with Qualifiers

Bacterial infection—begin 2g PO ×1, then 1g PO bid

NOTE: may be combined with ***trimethoprim*** *(Septra).*

- **Contraindications**—hypersensitivity to drug or class
- **Caution**—G6PD deficiency

Maternal Considerations

There are no adequate reports or well-controlled studies of **sulfamethoxazole** in pregnant women. When combined with **trimethoprim,** it is effective for the treatment of Q fever and for the treatment/prophylaxis of PCP. **Trimethoprim-sulfamethoxazole** is an alternative to high-dose penicillin for the treatment of listeriosis. It is also used to treat cystitis, but there are growing rates of bacterial resistance.

Side effects include agranulocytosis, aplastic anemia, hemolytic anemia, seizures, erythema multiforme, hypoglycemia, exfoliative dermatitis, rash, hepatocellular necrosis, and various allergic reactions.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. **Sulfamethoxazole** readily crosses the human placenta. One study noted a small increase in the rate of CV malformations after treatment with **trimethoprim-sulfamethoxazole** in the 2nd and 3rd trimesters. The causative agent was unclear. There is no published evidence to suggest it is associated with bilirubin toxicity, as is **sulfisoxazole.** Rodent studies performed at high multiples of the MRHD revealed an increased prevalence of cleft palate. It is probably best to avoid during the 1st trimester as it is an inhibitor of folate synthesis.

Breastfeeding Safety

There are no adequate reports or well-controlled studies in nursing women. It is unknown whether **sulfamethoxazole** enters human breast milk.

Drug Interactions

Use with thiazides is associated with an increased incidence of thrombocytopenia with purpura.
May prolong the INR in patients receiving **warfarin.** The adequacy of anticoagulation should be closely monitored.
May inhibit the hepatic metabolism of **phenytoin,** potentially increasing the risk of **phenytoin** toxicity.
May displace **methotrexate** from plasma protein-binding sites, increasing free **methotrexate.**
May interfere with the Jaffé alkaline picrate reaction assay for Cr, resulting in overestimations of about 10% in the range of normal values.

References

Ahmad H, Mehta NJ, Manikal VM, et al. Chest 2001; 120:666-71.
Bawdon RE, Maberry MC, Fortunato SJ, et al. Gynecol Obstet Invest 1991; 31:240-2.
Czeizel AE, Rockenbauer M, Sorensen HT, Olsen J. Reprod Toxicol 2001; 15:637-46.
Hernandez-Diaz S, Werler MM, Walker AM, Mitchell AA. N Engl J Med 2000; 343:1608-14.
Raoult D, Fenollar F, Stein A. Arch Intern Med 2002; 162:701-4.
Silver HM. Obstet Gynecol Surv 1998; 53:737-40.

Summary

Pregnancy Category: C
Lactation Category: U

- **Sulfamethoxazole** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Sulfasalazine—(Azaline; Azaline EC; Azulfidine)

International Brand Name—Azulfidina (Mexico); Azulfidine (Chile, Germany, Greece, Venezuela); Azulfidine EN-tabs (Argentina, Chile); Azulfin (Brazil); Colo-Pleon (Germany); Disalazin (Peru); Gastropyrin (Finland); Pleon RA (Germany); Pyralin EN (Australia); Rosulfant (Colombia); Salazine (Taiwan); Salazodin (Uruguay); Salazopirina (Portugal); Salazopyrin (Australia, Austria, Canada, China, Denmark, England, Finland, Hungary, India, Italy, Japan, New Zealand, Norway, South Africa, Sweden, Switzerland); Salazopyrina (Spain); Salazopyrine (Belgium, France, Netherlands); Salazopyrine EC (Belgium); Salazopyrin-EN (Bulgaria, Canada, Colombia, Czech Republic, England, Finland, Hong Kong, India, Israel, Italy, Korea, Malaysia, Norway, South Africa, Sweden, Taiwan, Thailand); Salazopyrin Entabs (Denmark, Israel); Salopyr (Finland); Saridine (Thailand); Sulcolon (Indonesia); Sulfazine (Ireland); Zopyrin (Korea)

Drug Class

Inflammatory bowel disease agents; Salicylates

Indications

Ulcerative colitis, rheumatoid arthritis, Crohn's disease

Mechanism

Unknown

Dosage with Qualifiers

Ulcerative colitis—begin 500mg PO qd pc for several days of improvement, then 500mg PO qid pc
Rheumatoid arthritis—begin 500mg PO qd pc for several days, then 500mg PO qid pc
Crohn's disease—begin 500mg PO qd pc for several days, then 500mg PO qid pc

NOTE: obtain a CBC biweekly for the first 3mo of treatment; monitor renal function periodically.

- **Contraindications**—hypersensitivity to drug or class, hypersensitivity to salicylates, hepatic or renal dysfunction, porphyria, intestinal or urinary obstruction
- **Caution**—G6PD deficiency

Maternal Considerations

Bacteria in the gut metabolize **sulfasalazine** to 5-aminosalicylic acid and sulfapyridine in a fashion unaffected by gender.
There are no adequate reports or well-controlled studies of **sulfasalazine** in pregnant women.
Side effects include Stevens-Johnson syndrome, epidermal necrolysis, exfoliative dermatitis, agranulocytosis, hepatitis, peripheral neuropathy, hemolytic anemia, headache, depression, urticaria, rash, pruritus, N/V, diarrhea, abdominal pain, anorexia, hematuria, leukopenia, jaundice, and fever.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. **Sulfasalazine** and sulfapyridine cross the placenta with the M:F concentration ratios reaching unity. Large epidemiologic studies identify no evidence for human teratogenicity or an increased prevalence of adverse outcomes. Rodent studies are also reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically.

Breastfeeding Safety

There are no adequate reports or well-controlled studies in nursing women. Insignificant amounts of uncleaved **sulfasalazine** and 5-aminosalicylic acid are found in human milk; sulfapyridine levels are 30-60% of maternal serum. Sulfapyridine has poor bilirubin-displacing capacity.

Drug Interactions

May reduce the absorption of **folate** and **digoxin.**

References

Ambrosius Christensen L, Rasmussen SN, Hansen SH, et al. Acta Obstet Gynecol Scand 1987; 66:433-5.
Connell W, Miller A. Drug Saf 1999; 21:311-23.
Esbjorner E, Jarnerot G, Wranne L. Acta Paediatr Scand 1987; 76:137-42.
Norgard B, Czeizel AE, Rockenbauer M, et al. Aliment Pharmacol Ther 2001; 15:483-6.
Rahimi R, Nikfar S, Rezaie A, Abdollahi M. Reprod Toxicol 2008; 25:271-5.

Summary

Pregnancy Category: B
Lactation Category: S

- **Sulfasalazine** is first-line therapy for the treatment of inflammatory bowel disease during pregnancy and lactation.

Sulfisoxazole—(Gantrisin; Gulfasin; Isoxazine; Lipo Gantrisin; Novosoxazole; Oxazole; Sosol; Soxa; Sulfalar; Sulfazin; Sulfazole; Sulphafurazole; Sulsoxin; Thiasin; Truxazole; Urazole)

International Brand Name—None identified.

Drug Class	Antibiotics; Sulfonamides
Indications	Bacterial infection (e.g., acute, recurrent, or chronic UTIs; meningococcal meningitis; otitis media)
Mechanism	Bacteriostatic—inhibits dihydropteroate synthesis
Dosage with Qualifiers	Bacterial infection—500-1000mg PO q6h ×10-21d *NOTE: renal dosing.* • **Contraindications—**hypersensitivity to drug or class, porphyria • **Caution—**hepatic or renal dysfunction
Maternal Considerations	There are no adequate reports or well-controlled studies of **sulfisoxazole** in pregnant women. **Sulfisoxazole** is an alternative to **ampicillin,** which some feel should no longer be used in the treatment of asymptomatic bacteriuria because of high rates of resistance. It has been used as an alternative for the treatment of chlamydia in **erythromycin**-allergic women. ***Side effects*** include Stevens-Johnson syndrome, jaundice, aplastic anemia, agranulocytosis, leukopenia, thrombocytopenia, pseudomembranous colitis, stomatitis, hepatitis, vasculitis, photosensitivity, anorexia, N/V, rash, headache, and dizziness.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **sulfisoxazole** crosses the human placenta. A large human experience is reassuring as there are no reports suggesting teratogenicity. Rodent studies performed at multiples of the MRHD were associated with cleft palate and bony abnormalities.
Breastfeeding Safety	There are no adequate reports or well-controlled studies in nursing women. Only small amounts of **sulfisoxazole** enter human breast milk, and it is generally considered compatible with breastfeeding.
Drug Interactions	May increase the INR in patients taking **warfarin.** Appropriate monitoring is indicated. Competes with **thiopental** for plasma protein binding. In one study, **sulfisoxazole** reduced the **thiopental** required for anesthesia and shortened the awakening time. May displace **methotrexate** from plasma protein-binding sites, increasing free **methotrexate** concentrations. Potentiates the hypoglycemic activity of sulfonylureas, as well as cause hypoglycemia by itself.
References	Kauffman RE, O'Brien C, Gilford P. J Pediatr 1980; 97:839-41. McNeeley SG Jr, Ryan GM Jr, Baselski V. Sex Transm Dis 1989; 16:60-2.

Summary

Pregnancy Category: C
Lactation Category: S

- **Sulfisoxazole** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.
- A long clinical experience is reassuring.

Sulindac—(Antribid; Arthridex; Biflace; Clinoril; Clisundac; Daclin; Imbaral; Lindak; Lyndak; Reumofil; Sudac)

International Brand Name—Aclin (Australia, Hong Kong, Malaysia); Aflodac (Italy); Algocetil (Italy); Apo-Sulin (Canada); Arthrocine (France); Cenlidac (Taiwan); Citireuma (Italy); Clidol (Korea); Copal (Mexico); Daclin (New Zealand); Dometon (Taiwan); Imbaron (China); Kenalin (Mexico); Klimacobal (Greece); Norilafin (Greece); Novo-Sundac (Canada); Sulen (Italy); Sulic (Italy); Sulindaco Lisan (Costa Rica); Sulindal (Spain); Sulindec (Taiwan); Sulinol (Italy); Suloril (Taiwan); Sulreuma (Italy); Zirofalen (Greece)

Drug Class

Analgesics, non-narcotic; NSAID

Indications

Osteoarthritis or rheumatoid arthritis, anti-inflammatory, ankylosing spondylitis, acute gout

Mechanism

Unknown; inhibits prostaglandin synthesis

Dosage with Qualifiers

Osteoarthritis or rheumatoid arthritis—150-200mg PO bid; max 400mg/d
Anti-inflammatory—200mg PO bid ×7-14d; max 400mg/d
Ankylosing spondylitis—150-200mg PO bid; max 400mg/d
Acute gout—150-200mg PO bid; max 400mg/d

- **Contraindications**—hypersensitivity to drug or class, NSAID- or aspirin-induced asthma
- **Caution**—CHF, GI bleeding, hypertension

Maternal Considerations

Sulindac is an NSAID, also possessing analgesic and antipyretic activities. It also inhibits certain transcription factors such as NF-κB and AP-1, as does **ibuprofen** but not **indomethacin.** There are no adequate reports or well-controlled studies of **sulindac** in pregnant women. Very limited study suggests it is equally effective as **indomethacin** for the prolongation of pregnancy in women with preterm labor. The use of **sulindac** until 34w after successful tocolysis fails to reduce the incidence of readmission for preterm labor or prolong the gestational age at delivery. It has also been used prophylactically in monochorionic twin pregnancies to reduce the volume of AF and stabilize the fetal lie. ***Side effects*** include GI bleeding, acute renal failure, bronchospasm, thrombocytopenia, Stevens-Johnson syndrome, interstitial nephritis, hepatotoxicity, agranulocytosis, N/V, abdominal pain, dyspepsia, constipation, headache, dizziness, rash, drowsiness, urticaria, elevated LFTs, and tinnitus.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. **Sulindac** crosses the human placenta, producing F:M ratios approximating 0.4. Fetal levels are dependent on the maternal, as NSAID agents are not metabolized by the fetal kidney. Like other NSAIDs, **sulindac** causes dose-dependent and reversible ductal constriction and oligohydramnios. Rodent studies reveal an increased incidence of cleft palate (not seen with **indomethacin**), and there is an increased risk of IUGR and fetal death.

Breastfeeding Safety

There are no adequate reports or well-controlled studies in nursing women. It is unknown whether **sulindac** enters human breast milk; it does enter rat milk.

Drug Interactions

Dimethyl sulfoxide may reduce the plasma levels of the active sulfide metabolite of **sulindac** and potentially its efficacy. This combination has also been reported to cause peripheral neuropathy.

Aspirin significantly depressed the plasma levels of the active sulfide metabolite of **sulindac.** Since the combination did not have a favorable effect on the therapeutic response, it is not recommended.

Use with other NSAIDs is not recommended due to the increased possibility of GI toxicity, with little or no increase in efficacy.

NSAIDs decrease the tubular secretion of **methotrexate** and thus may potentiate its toxicity.

NSAIDs may increase **cyclosporine** toxicity, possibly due to decreased synthesis of renal prostacyclin.

References

Carlan SJ, O'Brien WF, O'Leary TD, Mastrogiannis D. Obstet Gynecol 1992; 79:223-8.

Humphrey RG, Bartfield MC, Carlan SJ, et al. Obstet Gynecol 2001; 98:555-62.

Kramer WB, Saade GR, Belfort M, et al. Am J Obstet Gynecol 1999; 180:396-401.

Lampela ES, Nuutinen LH, Ala-Kokko TI, et al. Am J Obstet Gynecol 1999; 180:174-80.

Montenegro MA, Palomino H. J Craniofac Genet Dev Biol 1990; 10:83-94.

Pasquini L, Wimalasundera RC, Fichera A, et al. Ultrasound Obstet Gynecol 2006; 28:681-7.

Tegeder I, Pfeilschifter J, Geisslinger G. FASEB J 2001; 15:2057-72.

Summary

Pregnancy Category: C
Lactation Category: U

- Though NSAIDs share certain characteristic effects on pregnant women and their fetuses, they are not interchangeable.
- **Sulindac** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Sumatriptan—(Imigran; Imitrex)

International Brand Name—Cetatrex (Indonesia); Imigran (Austria, Brazil, Bulgaria, Chile, China, Colombia, Costa Rica, Czech Republic, Denmark, Dominican Republic, Ecuador, El Salvador, England, Finland, Germany, Greece, Guatemala, Honduras, Hong Kong, Hungary, Ireland, Italy, Japan, Korea, Malaysia, Mexico, Netherlands, Nicaragua, Norway, Panama, Paraguay, Peru, Philippines, Poland, South Africa, Spain, Sweden, Switzerland, Thailand, Uruguay, Venezuela); Imigrane (France); Imigran Radis (England, Ireland); Imiject (France); Imitrex (Argentina, Belgium, Canada, Indonesia, Israel); Migragesin (Colombia); Migranol (Israel); Sumitrex (India); Suvalan (Australia)

Drug Class

Migraines; Serotonin receptor agonists

Indications

Migraine headache

Mechanism

5-HT_1 agonist

Dosage with Qualifiers

Migraine headache—6mg SC ×1, may repeat in 1h, max 12mg/d; or 25-100mg PO ×1, may repeat after 2h, max 200mg/d; or 1spray per nostril (20mg/spray)

NOTE: available in oral, parenteral, and nasal spray forms.
*NOTE: May be combined with **naproxen**.*

- **Contraindications**—hypersensitivity to drug or class, uncontrolled hypertension, CAD, basilar or hemiplegic migraine, MAOI <14d
- **Caution**—peripheral or cerebrovascular disease, hepatic dysfunction, 5-HT_1 or ergot derivative agonist <24h, cardiac risk factors

Maternal Considerations

There are no adequate reports or well-controlled studies of **sumatriptan** in pregnant women.
Side effects include coronary vasospasm, acute MI, ventricular tachycardia, ventricular arrhythmia, death, hypertensive crisis, stroke, bowel or peripheral vascular ischemia, asthenia, chest pain, neck tightness, dizziness, flushing, paresthesias, rhinitis (spray), rash, taste changes (spray), pruritus, urticaria, tinnitus (spray), myalgias, palpitations, somnolence, and sweating.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. Only a small amount of **sumatriptan** (<5%) crosses the human placenta by passive transport, and should pose minimal risk to the fetus. Metabolites do not cross. Epidemiologic studies are reassuring. Rodent studies conducted at doses at least 6× the MRHD revealed embryotoxicity and vascular and skeletal abnormalities. No adverse effects were noted at lower doses.

Breastfeeding Safety

There are no adequate reports or well-controlled studies in nursing women. A small amount of **sumatriptan** enters human breast milk, but the quantity absorbed by the neonate will be negligible.

Drug Interactions

Ergot-containing drugs may cause prolonged vasospastic reactions. Because there is a theoretical basis that these effects may be additive, use of **ergotamine**-containing or ergot-type medications (e.g., **dihydroergotamine, methysergide**) and **sumatriptan** within 24h of each other should be avoided.
Use with MAO-A inhibitors is contraindicated as they can reduce **sumatriptan** clearance.
SSRIs (e.g., **fluoxetine, fluvoxamine, paroxetine, sertraline**) have been reported, rarely, to cause weakness, hyperreflexia, and incoordination when used with **sumatriptan.** Appropriate observation of the patient is advised.

References

Fox AW, Chambers CD, Anderson PO, et al. Headache 2002; 42:8-15.
Hilaire ML, Cross LB, Eichner SF. Ann Pharmacother 2004; 38:1726-30.
Kallen B, Lygner PE. Headache 2001; 41:351-6.
Loder E. CNS Drugs 2003; 17:1-7.
Schenker S, Yang Y, Perez A, et al. Proc Soc Exp Biol Med 1995; 210:213-20.
Shuhaiber S, Pastuszak A, Schick B, et al. Neurology 1998; 51:581-3.
Wojnar-Horton RE, Hackett LP, Yapp P, et al. Br J Clin Pharmacol 1996; 41:217-21.

Summary

Pregnancy Category: C
Lactation Category: S (likely)

- **Sumatriptan** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.
- A fairly large body of clinical experience is reassuring.

Tacrine—(Cognex; THA)

International Brand Name—Cognex (Austria, Belgium, Chile, China, France, Germany, Peru); Cognitiv (Argentina); Tacrinal (Brazil); Talem (Argentina)

Drug Class	Alzheimer's disease agents; Cholinesterase inhibitors
Indications	Alzheimer's dementia
Mechanism	Reversible cholinesterase inhibitor
Dosage with Qualifiers	Alzheimer's dementia—begin 10mg PO qid ×4w; increase by 10mg qid q4w based on response • **Contraindications**—hypersensitivity to drug or class, **tacrine** hepatotoxicity, hepatic dysfunction, cardiac conduction defects • **Caution**—unknown
Maternal Considerations	**Tacrine** presumably elevates ACh in the cerebral cortex by slowing the degradation of ACh released by still-intact cholinergic neurons. It also appears to reduce excitatory amino acid toxicity. There is no evidence it alters the underlying dementia process. Plasma concentrations are 50% higher in women than men. There are no adequate reports or well-controlled studies of **tacrine** in pregnant women. The published literature is limited to two case reports 3 decades ago when it was used as a general anesthetic adjunct during cesarean delivery. ***Side effects*** include hepatotoxicity, bradycardia, seizures, N/V, diarrhea, constipation, flatulence, abdominal pain, dyspnea, anorexia, weight loss, rash, agitation, insomnia, ataxia, and confusion.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **tacrine** crosses the human placenta. Rodent teratogenicity studies have not been conducted.
Breastfeeding Safety	There is no published experience in nursing women. It is unknown whether **tacrine** enters human breast milk.
Drug Interactions	Increases the **theophylline** t/2 and plasma level by about 2-fold. Monitoring of the plasma concentrations and appropriate dose reduction of **theophylline** are recommended. **Cimetidine** increases the C_{max} and AUC by approximately 54% and 64%, respectively. May interfere with the activity of anticholinergic medications. A synergistic effect is to be expected if used with **succinylcholine,** cholinesterase inhibitors, or cholinergic agonists such as **bethanechol.** **Fluvoxamine** increased the **tacrine** C_{max} and AUC 5- and 8-fold, respectively, increasing the likelihood of N/V, sweating, and diarrhea.
References	Takada-Takatori Y, Kume T, Sugimoto M, et al. Eur J Pharmacol 2006; 549:19-26.
Summary	**Pregnancy Category: C** **Lactation Category: U** • **Tacrine** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Tacrolimus—(FK 506; Prograf, Protopic)

International Brand Name—Mustopic Oint (India); Prograf (Argentina, Brazil, Canada, Chile, Colombia, Denmark, England, France, Germany, Hong Kong, Ireland, Japan, Korea, Malaysia, Mexico, Paraguay, Philippines, Singapore, South Africa, Taiwan, Thailand, Uruguay); Protopic (England, France, Hong Kong, Ireland)

Drug Class	Immunosuppressants; Transplantation agents; Eczema agents
Indications	Prophylaxis against liver or kidney transplant rejection
Mechanism	Inhibits T-cell activation
Dosage with Qualifiers	Transplant rejection prophylaxis—0.1-0.2mg/kg/d PO in 2 divided doses; alternatively, 0.03-0.05mg/kg/d as continuous IV infusion • **Contraindications**—hypersensitivity to drug or class • **Caution**—hepatic or renal dysfunction
Maternal Considerations	A growing number of obstetric patients have benefited from organ transplantation. Pregnancy is considered reasonable if the patient is 2y post transplantation, has good renal function without proteinuria, no uncontrolled arterial hypertension, and no evidence of ongoing rejection. However, these women are at high risk for an adverse outcome and should be followed at a tertiary care hospital. There are no adequate reports or well-controlled studies of **tacrolimus** in pregnant women. Though it has been used widely during pregnancy without obvious adverse effect, the published experience is limited to case series. Clearance is not significantly altered. ***Side effects*** include thrombocytopenia, nephrotoxicity, hypertension, hyperkalemia, seizures, diabetes mellitus, immunosuppression, malignancy, nausea, diarrhea, headache, insomnia, abdominal pain, tremor, weakness, fever, hyperglycemia, anemia, itching, elevated LFTs, anorexia, and renal dysfunction.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses, and little animal experience. It is unknown whether **tacrolimus** crosses the placenta. Human studies do not reveal obvious evidence of teratogenicity. Immunosuppression is a theoretic concern.
Breastfeeding Safety	There are no adequate reports or well-controlled studies in nursing women. **Tacrolimus** does enter human breast milk but at a very low concentration (<2ng/ml) with an M:P ratio <0.55. Using this information, the estimated dose ingested by a neonate would be <1mg/kg/d. Considering the low bioavailability of **tacrolimus** (<32%), the amount absorbed would be even lower (0.02-0.5% of the mother's weight-adjusted dose).
Drug Interactions	Care should be taken with drugs associated with renal dysfunction due to the potential for additive or synergistic impairment. These drugs include, but are not limited to, aminoglycosides, **amphotericin B, cisplatin,** and possibly **cyclosporine.** Patients switched from **cyclosporine** to **tacrolimus** should receive the first **tacrolimus** dose no sooner than 24h after the last **cyclosporine** dose. Metabolized mainly by CYP3A, and substances that inhibit these isozymes may decrease the metabolism or increase the bioavailability of **tacrolimus.** In contrast, drugs known to induce

CYP3A may result in an increased metabolism of **tacrolimus** or decreased bioavailability, resulting in decreased plasma levels. Monitoring with appropriate dose adjustments is essential. Drugs that may increase **tacrolimus** blood levels include calcium channel blockers (e.g., **diltiazem, nicardipine, nifedipine, verapamil**), antifungal agents (e.g., **clotrimazole, fluconazole, itraconazole, ketoconazole, voriconazole**), macrolide antibiotics (e.g., **clarithromycin, erythromycin, troleandomycin**), gastrointestinal prokinetic drugs (e.g., **cisapride, metoclopramide**), and other drugs (e.g., **bromocriptine, chloramphenicol, cimetidine, danazol, ethinyl estradiol, lansoprazole,** magnesium-aluminum hydroxide, **methylprednisolone, nefazodone, omeprazole,** and protease inhibitors).

Drugs that may decrease **tacrolimus** blood levels include anticonvulsants (e.g., **carbamazepine, phenobarbital, phenytoin**), antimicrobials (e.g., caspofungin, **rifabutin, rifampin**), **St. John's wort,** and **sirolimus**. Frequent monitoring of **tacrolimus** blood levels and appropriate dose adjustments are essential.

May affect the pharmacokinetics of other drugs (e.g., **phenytoin**) and increase their concentration.

Grapefruit juice affects CYP3A-mediated metabolism and should be avoided.

The use of live vaccines should be avoided; live vaccines include, but are not limited to, measles, mumps, rubella, oral polio, BCG, yellow fever, and TY 21a typhoid.

Interaction studies with **tacrolimus** ointment have not been conducted. Based on its minimal absorption, interactions of **tacrolimus** ointment with systemically administered drugs are unlikely. Use of known CYP3A4 inhibitors in patients with widespread and/or erythrodermic disease should be undertaken with caution. Examples of such drugs are calcium channel blockers, **cimetidine, erythromycin, fluconazole, itraconazole,** and **ketoconazole.**

References

Armenti VT, Moritz MJ, Davison JM. Drug Saf 1998; 19:219-32.

Farley DE, Shelby J, Alexander D, Scott JR. Transplantation 1991; 52:106-10.

French AE, Soldin SJ, Soldin OP, Koren G. Ann Pharmacother 2003; 37:815-8.

Garcia-Donaire JA, Acevedo M, Gutiérrez MJ, et al. Transplant Proc 2005; 37:3754-5.

Gardiner SJ, Begg EJ. Obstet Gynecol 2006; 107:453-5.

Jain A, Venkataramanan R, Fung JJ, et al. Transplantation 1997; 64:559-65.

Kainz A, Harabacz I, Cowlrick IS, et al. Transplantation 2000; 70:1718-21.

Summary

Pregnancy Category: C
Lactation Category: U

- Although **tacrolimus** is widely used in transplantation patients, there is limited information on its reproductive effects.
- Current experience suggests the benefits of **tacrolimus** far exceed its theoretic risks to the pregnancy and newborn.

Tamoxifen—(Dignotamoxi; Nolvadex; Valodex)

International Brand Name—Exiphen (El Salvador, Guatemala, Honduras, Panama); Gynatam (Philippines); Istubol (Canada); Kessar (France, Germany, Greece, Italy, Philippines, South Africa, Switzerland); Mamofen (India); Moxafen (Korea); Noltam (England); Nolvadex-D (Hong Kong, Israel, Malaysia); Novofen (Taiwan, Thailand); Oncetam (France); Tadex (Finland, Taiwan); Tamaxin (Denmark, Sweden); Tamifen (Indonesia, Israel); Tamofen (China, Denmark, England, Finland, Germany, Indonesia, Israel, New Zealand, Norway, Singapore, Thailand); Tamofene (France); Tamoplex (Netherlands, Peru, Philippines, South Africa, Switzerland); Tamosin (Australia); Tamoxasta (Germany); Tamoxen (Israel); Tamoxi (Israel); Tamoxsta (Philippines); Taxus (Colombia, Peru); Tecnofen (Mexico); Zitazonium (China, Hong Kong, Hungary, Philippines, Thailand)

Drug Class ..... Antineoplastics; Antineoplastics, antiestrogen; SERMs

Indications ..... Breast cancer, mastalgia, ovulation induction

Mechanism ..... Partial estrogen receptor antagonist/agonist

Dosage with Qualifiers .....

Breast cancer, metastatic—10-20mg PO qd or bid
Breast cancer, adjuvant—10mg PO bid ×5y
Breast cancer, ductal *in situ*—10mg PO bid ×5y after surgery and radiation therapy
Breast cancer, prophylaxis—10mg PO bid ×5y for high-risk women begun during menses after a negative hCG test
Mastalgia—10mg PO qd ×4mo
Ovulation induction—5-40mg PO bid ×4d

- **Contraindications**—hypersensitivity to drug or class, undiagnosed genital bleeding, history of thromboembolism, coumarin anticoagulation
- **Caution**—bone metastases, thrombocytopenia, leukopenia

Maternal Considerations .....

Tamoxifen is one of four SERMs marketed in the US. The effect of SERMs on the estrogen receptor is tissue-dependent. It is an antagonist in the breast. The potential role of **tamoxifen** in the prevention of breast cancer is unclear and the subject of several large ongoing trials. It appears to reduce the incidence of ER^+ invasive and noninvasive cancer. Until the completion of these trials, prophylaxis should probably be confined to women at high risk. **Tamoxifen** is an agonist in the uterus, increasing the risk of endometrial cancer and sarcoma. It is associated with an increased risk of thromboembolic disease. **Tamoxifen** does not cause infertility. Rather, it appears equal to **clomiphene** for ovulation induction in anovulatory women. There are no adequate reports or well-controlled studies of **tamoxifen** in pregnant women. Breast cancers diagnosed during pregnancy and lactation typically are aggressive and present at an advanced stage. All women should be counseled on fertility preservation options. The timing of treatment modalities in pregnant women is complex and requires multidisciplinary input. Alternatives that are relatively safe for both mother and fetus are available, though unforeseen risks may exist. The published literature includes numerous cases of breast cancer diagnosed during pregnancy, with surgery followed by **tamoxifen** therapy usually after the 1st trimester. There were no obvious drug-related complications. The addition of **tamoxifen** to a regimen of **misoprostol** for medical abortion is unnecessary.

Side effects include thromboembolism, CVA, endometrial cancer, endometrial hyperplasia, hot flashes, vaginal discharge, irregular menses, increased bone or tumor pain, hypercalcemia, thrombocytopenia, leukopenia, pancytopenia, leiomyomas, ovarian cysts, retinopathy, cataracts, dizziness, peripheral edema,

fatigue, headache, visual changes, vulvar pruritus, hair loss, anorexia, and elevated LFTs.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **tamoxifen** crosses the human placenta. **Tamoxifen** has effects on genital tract development similar to estrogen. There are several reports suggesting an association between 1st trimester exposure and craniofacial abnormalities. In rodents, **tamoxifen** inhibits uteroplacental artery dilation, decreases placental and fetal weights, and as a consequence increases the risk of fetal death.

Breastfeeding Safety

There are no adequate reports or well-controlled studies in nursing women. It is unknown whether **tamoxifen** enters human breast milk. It is generally recommended women not breastfeed while taking **tamoxifen.**

Drug Interactions

May augment the anticoagulant effects of **warfarin.** Careful monitoring of INR is recommended.
There is an increased risk of thromboembolic events occurring when cytotoxic agents are used in combination.
Reduces **letrozole** plasma levels by ⅓.
Plasma levels are reduced when used with **rifampin** or **aminoglutethimide,** probably due to the induction of CYP3A4.
Phenobarbital may lower the steady-state **tamoxifen** levels.
Use with **bromocriptine** increases serum **tamoxifen** and *N*-desmethyltamoxifen levels.

References

Berger JC, Clericuzio CL. Am J Genet A 2008; 146A:2141-4.
Boostanfar R, Jain JK, Mishell DR Jr, Paulson RJ. Fertil Steril 2001; 75:1024-6.
Boostanfar R, Jain JK, Park M, Mishell DR Jr. Contraception 1999; 60:353-6.
Helewa M, Levesque P, Provencher D, et al. J Obstet Gynaecol Can 2002; 24:164-80.
Issacs RJ, Hunter W, Clark K. Gynecol Oncol 2001; 80:405-8.
Kelly HL, Collichio FA, Dees EC. Breast Dis 2005-2006; 23:95-101.
Nakai M, Uchida K, Teuscher C. J Androl 1999; 20:626-34.
[No authors]. Obstet Gynecol 2002; 100:835-43.
Sadek S, Bell SC. Br J Obstet Gynaecol 1996; 103:630-41.
Tewari K, Bonebrake RG, Asrat T, Shanberg AM. Lancet 1997; 350:183.
Woo JC, Yu T, Hurd TC. Arch Surg 2003; 138:91-8.

Summary

Pregnancy Category: D
Lactation Category: U

- **Tamoxifen** should be avoided during pregnancy and lactation unless maternal survival requires it.

Tazarotene topical—(Tazorac)

International Brand Name—Zorac (England, France, Germany, Ireland, Israel, South Africa)

Drug Class	Dermatologics; Retinoids
Indications	Psoriasis, acne vulgaris
Mechanism	Unknown; retinoid
Dosage with Qualifiers	Psoriasis—apply to affected area qhs Acne vulgaris—apply to affected area qhs *NOTE: obtain pregnancy test before initiating therapy; available in cream (0.05%) and gel (0.05%, 0.1%) formats.* • **Contraindications**—hypersensitivity to drug or class, pregnancy • **Caution**—avoid sun
Maternal Considerations	There is no published experience with **tazarotene** during pregnancy. The maternal systemic concentration is reportedly low. ***Side effects*** include birth defects, pruritus, burning, erythema, and irritation.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **tazarotene** crosses the human placenta. The maternal systemic concentration is reportedly low, and unpublished rodent teratogenicity studies reputedly are reassuring. Other drugs in this group are potent teratogens in mammals. Rodents treated topically with doses approximating 20% of the surface area have a greater risk of embryo loss and fetal malformation, including neural tube and cardiac anomalies.
Breastfeeding Safety	There is no published experience in nursing women. It is unknown whether **tazarotene** enters human breast milk. It is excreted into rodent milk. However, considering the dose and route, it is unlikely the breastfed neonate would ingest clinically relevant amounts.
Drug Interactions	Use with other dermatologic medications and cosmetics with a strong drying effect should be avoided. It is advisable to "rest" a patient's skin until the effects of such preparations subside before using **tazarotene** cream.
References	Duvic M. Cutis 1998; 61:22-6.
Summary	**Pregnancy Category: X** **Lactation Category: U** • **Tazarotene** is a known teratogen in rodents even at levels below the MRHD, and should probably be avoided during pregnancy and lactation pending the availability of additional study confirming safety.

Technetium-99m (^{99m}Tc)—(Cardiolite; Cardiotec; Cardiotech; Ceretec; Miraluma; Neurolite; NeoTect; RBC-Scan; Ultratag)

International Brand Name—None identified.

Drug Class	Diagnostics, radiopharmaceutical
Indications	Diagnostic imaging
Mechanism	Radioactive label attached to a variety of peptides with assorted binding profiles
Dosage with Qualifiers	Available in multiple formats bound to a variety of peptides for imaging of structures such as the heart, brain, and biliary system, and for localization of malignancy and bleeding • **Contraindications**—hypersensitivity to drug or class • **Caution**—unknown
Maternal Considerations	**Technetium-99m** decays by isomeric transition with a t/2 of 6h. Its clearance is reduced in women. There are no adequate reports or well-controlled studies of **technetium-99m** in pregnant women. There is a long clinical experience that supports its use during pregnancy when medically indicated. A diagnostically indicated test should not be withheld because of pregnancy. ***Side effects*** include metallic taste, burning at the injection site, facial swelling, numbness of hand/arm, hypotension, and nausea.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. **Technetium-99m** crosses the human placenta, but delivers a maximal total fetal dose of <5mGy, far below the 50mGy considered the threshold for concern. Rodent teratogenicity studies have not been performed.
Breastfeeding Safety	There are no adequate reports or well-controlled studies in nursing women. **Technetium-99m** is excreted in human milk during lactation for about 24h after administration. While formula feedings for at least 24h after testing may seem prudent, a single case report suggests this may not be necessary. In this instance, sample radioactivity concentration peaked at 15h and decayed monoexponentially (half-clearance time was 4.8h). The estimated effective dose to the infant from ingestion alone was approximately 0.02mSv, suggesting interruption of breastfeeding may not be necessary during early lactation.
Drug Interactions	No clinically relevant interactions identified.
References	Adelstein SJ. Teratology 1999; 59:236-9. McCauley E, Mackie A. Br J Radiol 2002; 75:464-6. Owunwanne A, Omu A, Patel M, et al. J Nucl Med 1998; 39:1810-3. Romney BM, Nickoloff EL, Esser PD, Alderson PO. Radiology 1986; 160:549-54.

Summary

Pregnancy Category: C
Lactation Category: S (likely)
- **Technetium-99m** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.
- Pregnancy is not a valid reason to withhold a diagnostically indicated test.

Tegaserod—(Zelnorm)

International Brand Name—Colonaid (Chile); Tegibs (India); Zelmac (Colombia, Hong Kong, Indonesia, Israel, Korea, Malaysia, Singapore, Taiwan, Thailand); Zelnorm (Canada, Philippines)

Drug Class

Gastrointestinals; Serotonin receptor agonists

Indications

Irritable bowel syndrome in women characterized by constipation

Mechanism

5-HT_4 agonist stimulating peristalsis while decreasing visceral sensitivity

Dosage with Qualifiers

Irritable bowel syndrome—6mg PO 30-60min ac bid ×4-6w; may repeat ×1

- **Contraindications**—hypersensitivity to drug or class, severe renal dysfunction, moderate to severe hepatic disease, history of bowel obstruction, abdominal adhesions, sphincter of Oddi dysfunction, symptomatic gallbladder disease, diarrhea
- **Caution**—mild hepatic dysfunction

Maternal Considerations

There are no published reports of **tegaserod** use during pregnancy.
Side effects include cholecystitis, headache, nausea, abdominal pain, flatulence, diarrhea, and dizziness.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **tegaserod** crosses the human placenta. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically.

Breastfeeding Safety

There is no published experience in nursing women. **Tegaserod** enters human breast milk with a high M:P ratio. Its impact on the neonate is unknown.

Drug Interactions

No clinically relevant interactions identified.

References

There is no published experience in pregnancy or during lactation.

Summary

Pregnancy Category: B
Lactation Category: U
- **Tegaserod** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.
- There are alternative agents for which there is more experience regarding use during pregnancy and lactation that may suffice in the short term.

Telmisartan—(Micardis)

International Brand Name—Micardis (Argentina, Australia, Brazil, Canada, Chile, Colombia, Costa Rica, Dominican Republic, El Salvador, Guatemala, Honduras, Hong Kong, Indonesia, Malaysia, Mexico, Nicaragua, Panama, Paraguay, Peru, Philippines, Singapore, Thailand, Uruguay); Predxal (Mexico); Pritor (Argentina, Australia, Korea, Mexico, Peru, Philippines, Venezuela); Pritoral (Chile); Telma-20 (India)

Drug Class	ACEI/A2R-antagonists
Indications	Hypertension
Mechanism	AT-1 antagonist
Dosage with Qualifiers	Hypertension—begin 40mg PO qd if monotherapy; max 80mg/d • **Contraindications**—hypersensitivity to drug or class, pregnancy • **Caution**—history of ACEI-related angioedema, renal artery stenosis, hepatic or renal dysfunction, CHF, hyponatremia
Maternal Considerations	The plasma concentration of **telmisartan** is 2-3× higher in females than in males. There is no published experience with **telmisartan** during pregnancy. Inhibitors of the renin-angiotensin system should be avoided during pregnancy for fetal indications. The lowest effective dose should be used when **telmisartan** is required during pregnancy for BP control. ***Side effects*** include angioedema, hypotension, dizziness, URI symptoms, back pain, diarrhea, fatigue, dyspepsia, neutropenia, leukopenia, and hyperkalemia.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **telmisartan** crosses the human placenta. Inhibitors of the renin-angiotensin system are considered contraindicated throughout pregnancy as their use has been associated with cranial hypoplasia, anuria, reversible or irreversible renal failure, death, oligohydramnios, prematurity, IUGR, and PDA. If oligohydramnios is observed, **telmisartan** should be discontinued unless considered lifesaving for the mother. Antenatal surveillance (e.g., BPP) may be appropriate, depending upon gestational age. Oligohydramnios may not appear until after irreversible injury. There is a single report of neonatal renal failure after antenatal exposure. Neonates exposed should be closely observed for hypotension, oliguria, and hyperkalemia. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically.
Breastfeeding Safety	There is no published experience in nursing women. It is unknown whether **telmisartan** enters human breast milk. It is excreted into rodent milk.
Drug Interactions	Increases in **digoxin** peak (49%) and trough levels (20%). Thus, **digoxin** levels should be monitored when initiating, adjusting, and discontinuing **telmisartan.**
References	Pietrement C, Malot L, Santerne B, et al. J Perinatol 2003; 23:254-5.
Summary	**Pregnancy Category: C** (1st trimester), **D** (2nd and 3rd trimesters) **Lactation Category: U** • **Telmisartan** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

- There are fetal risks throughout pregnancy. The lowest effective dose should be used when **telmisartan** is required during pregnancy for BP control.
- There are numerous alternative agents with a superior safety profile for which there is more experience regarding use during pregnancy and lactation.

Temazepam—(Euhypnos; Levanxol; Normison; Planum; Restoril)

International Brand Name—Cerepax (Argentina); Lenal (Argentina); Levanxene (Argentina)

Drug Class	Benzodiazepines; Hypnotics; Sedatives
Indications	Insomnia
Mechanism	Benzodiazepine and possibly GABA receptor agonist
Dosage with Qualifiers	Insomnia, short-term—7.5-30mg PO qhs • **Contraindications**—hypersensitivity to drug or class • **Caution**—azole antifungal
Maternal Considerations	Residual medication effects (“hangover”) are essentially absent with **temazepam,** and early morning awakening, a particular problem for the geriatric patient, is significantly reduced compared to similar agents. REM sleep is unchanged. There are no adequate reports or well-controlled studies of **temazepam** in pregnant women. One case report suggested an association with a fetal demise. ***Side effects*** include respiratory depression, seizures, coma, drowsiness, headache, fatigue, nervousness, lethargy, dizziness, N/V, anxiety, depression, dry mouth, diarrhea, abdominal pain, euphoria, weakness, blurred vision, nightmares, and vertigo.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. **Temazepam** crosses the 2nd trimester human placenta, achieving an F:M ratio approximating 0.38 1h after 10mg IV. The ratio was stable between 60 and 120min, but rose with advancing gestation age. Third trimester studies are unavailable. Several studies suggest an increased prevalence of fetal malformation after **diazepam** use during the 1st trimester. Decreased fetal movement frequently follows IV **diazepam** administration, and prolonged CNS depression may occur in neonates due to their inability to metabolize. It is unknown whether the effect of **temazepam** is similar. The shortest course and the lowest dose should be used if indicated during pregnancy. Rodent teratogenicity studies reveal an increased prevalence of skeletal abnormalities and embryo loss.
Breastfeeding Safety	**Tenazepam** is excreted into breast milk. In the one report, at concentrations of 26-28mcg/L for the pre- and postfeed samples, the M:P ratio for **temazepam** ranged from <0.09 to <0.63 (mean <0.18). Benzodiazepines in general enter human breast milk and may cause lethargy, sedation, and weight loss in infants. Some newborns exposed antenatally to **diazepam** exhibit either the floppy infant syndrome, or marked neonatal withdrawal symptoms.

Drug Interactions	No clinically relevant interactions identified.
References	Cooper J, Jauniaux E, Gulbis B, Bromley L. Reprod Biomed Online 2001; 2:165-71. Lebedevs TH, Wojnar-Horton RE, Yapp P, et al. Br J Clin Pharmacol 1992; 33:204-6.
Summary	**Pregnancy Category: X** **Lactation Category: S** (possibly) • **Temazepam** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk. • There are alternative agents for which there is more experience regarding use during pregnancy and lactation. • While it is unlikely a one-time use would cause harm, continuous use should be avoided during pregnancy and lactation.

Temozolomide—(Temodar; Temoxol)

International Brand Name—Temodal (Australia, Canada, Hong Kong, Indonesia, Israel, Korea, Mexico, Philippines, Singapore, Thailand); Temoxol (South Africa)

Drug Class	Antineoplastics, alkylating agent
Indications	Astrocytoma, refractory
Mechanism	Alkylates guanine
Dosage with Qualifiers	Astrocytoma, refractory—multiple dosing regimens based on response and side effects • **Contraindications**—hypersensitivity to drug or class, hypersensitivity to DTIC • **Caution**—hepatic or renal dysfunction
Maternal Considerations	There is no published experience with **temozolomide** during pregnancy. ***Side effects*** include myelosuppression, N/V, abdominal pain, constipation, diarrhea, headache, fever, convulsions, hemiparesis, amnesia, insomnia, and viral infection.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **temozolomide** crosses the human placenta. Rodent teratogenicity studies reveal an increased prevalence of multiple malformations.
Breastfeeding Safety	There is no published experience in nursing women. It is unknown whether **temozolomide** enters human breast milk.
Drug Interactions	**Valproic acid** decreases oral clearance by about 5%.
References	There is no published experience in pregnancy or during lactation.
Summary	**Pregnancy Category: D** **Lactation Category: U** • **Temozolomide** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk; it is reserved for life-threatening circumstances.

Tenecteplase—(TNKase)

International Brand Name—Metalyse (Israel, Taiwan); TNKase (Canada)

Drug Class	Anticoagulants; Thrombolytics
Indications	MI
Mechanism	Tissue plasminogen activator
Dosage with Qualifiers	MI, acute—30-50mg IV ×1, weight dependent; max 50mg • **Contraindications**—hypersensitivity to drug or class, active internal bleeding, stroke, aneurysm, intracranial/spinal surgery or trauma, bleeding diathesis, uncontrolled hypertension • **Caution**—severe hepatic disease, hypertension, recent surgery or trauma, CVD, GPIIb/IIIa use, endocarditis, acute pericarditis, LV thrombus
Maternal Considerations	The published experience with **tenecteplase** during pregnancy is limited to case reports including one in the first trimester. ***Side effects*** include intracranial hemorrhage, stroke, severe bleeding, arrhythmia, and angioedema.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **tenecteplase** crosses the human placenta. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically. Embryotoxicity occurs with high doses.
Breastfeeding Safety	There is no published experience in nursing women. It is unknown whether **tenecteplase** enters human breast milk.
Drug Interactions	Anticoagulants (e.g., **heparin,** vitamin K antagonists) and drugs that alter platelet function (e.g., **aspirin, dipyridamole,** GP IIb/IIIa inhibitors) may increase the risk of bleeding.
References	Bessereau J, Desvignes O, Huon B, et al. Arch Mal Coeur Vaiss 2007; 100:955-8. Camacho Pulido A, Jimenez Sanchez JM, Montijano Vizcaino A, et al. An Med Interna 2008; 25:31-2. Maegdefessel L, Issa H, Scheler C, et al. Internist 2008; 49:868-72.
Summary	**Pregnancy Category: C** **Lactation Category: U** • **Tenecteplase** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Tenofovir—(Viread)

International Brand Name—Viread (Argentina, Canada)

Drug Class	Antivirals; NRTIs
Indications	HIV infection
Mechanism	Reverse transcriptase inhibitor
Dosage with Qualifiers	HIV infection—300mg PO qd in combination with other retrovirals • **Contraindications**—hypersensitivity to drug or class, CrCl <60ml/min, lactic acidosis • **Caution—**alcoholism, hepatic dysfunction
Maternal Considerations	There are few well-controlled studies of **tenofovir** in pregnant women. Intrapartum and neonatal single-dose **nevirapine** are essential components in the prevention of perinatal HIV in resource-constrained settings, but can induce resistance to NNRTIs. Recently, it was found that a single dose of **tenofovir** and **emtricitabine** at delivery reduced resistance to NNRTIs at 6w after delivery by half. The clearance of some NRTIs is increased during pregnancy. There are no data describing the effect of pregnancy on the pharmacokinetics of **tenofovir.** ***Side effects*** include lactic acidosis, hepatomegaly with steatosis, N/V, diarrhea, anorexia, and flatulence.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **tenofovir** crosses the human placenta. Small case series are to date reassuring. **Tenofovir** crosses the rhesus monkey placenta sufficiently well to lower the fetal viral load. In doing so, there is a transient delay in bone growth that may be IGF-I mediated. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically.
Breastfeeding Safety	There is no published experience in nursing women. It is unknown whether **tenofovir** enters human breast milk. However, it is excreted into macaque and rodent milk. Breastfeeding is contraindicated in HIV-infected nursing women where formula is available to reduce the risk of neonatal transmission.
Drug Interactions	Increases the C_{max} and AUC of **didanosine** by an unknown mechanism. Higher **didanosine** levels increase the risk of **didanosine**-associated pancreatitis and neuropathy. In adults weighing >60kg, the **didanosine** dose should be reduced to 250 mg. Data are not available to recommend a dose adjustment of **didanosine** for patients weighing <60 kg. **Tenofovir** and **didanosine** should be used together only with caution; patients receiving this combination closely monitored for **didanosine**-associated adverse events. Drugs that reduce renal function or compete for active tubular secretion may increase serum concentrations of **tenofovir** and/or increase the concentrations of other renally eliminated drugs (e.g., **acyclovir, adefovir, cidofovir, dipivoxil, ganciclovir, valacyclovir, valganciclovir**). **Atazanavir** and **lopinavir/ritonavir** increase **tenofovir** levels by an unknown mechanism. Patients should be monitored for **tenofovir**-associated adverse events.

Decreases the AUC and C_{min} of **atazanavir.** It is recommended that **atazanavir** 300mg be given with **ritonavir** 100mg if used with **tenofovir.**

References

Chi BH, Sinkala M, Mbewe F, et al. Lancet 2007; 370:1698-705.
Nurutdinova D, Onen NF, Hayes E, et al. Ann Pharmacother 2008; 42:1581-5.
Tarantal AF, Castillo A, Ekert JE, et al. J Acquir Immune Defic Syndr 2002; 29:207-20.

Summary

Pregnancy Category: B
Lactation Category: NS

- **Tenofovir** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.
- There are alternative agents for which there is more experience regarding use during pregnancy and lactation.
- Breastfeeding is contraindicated in HIV-infected nursing women where formula is available to reduce the risk of neonatal transmission.
- Physicians are encouraged to register pregnant women under the Antiretroviral Pregnancy Registry (1-800-258-4263) for a better follow-up of the outcome while under treatment with **tenofovir.**

Terazosin—(Hytrin)

International Brand Name—Adecur (Mexico); Conmy (Taiwan); Deflox (Spain); Dysalfa (France); Flotrin (Germany); Heitrin (Germany); Hitrin (Costa Rica, El Salvador, Guatemala, Honduras, Nicaragua, Panama); Hydrin (Korea); Hytracin (Japan); Hytrine (France, Korea); Hytrinex (Denmark, Sweden); Itrin (Italy); Kinzosin (Taiwan); Magnurol (Spain); Olyster (India); Teradrin (Taiwan); Teralfa (India); Terapam (Korea); Terasin (Korea); Tructum (Colombia); Vasomet (Japan); Vicard (Austria, Switzerland)

Drug Class — Adrenergic antagonists; α-Blocker

Indications — Hypertension

Mechanism — Peripheral α_1-antagonist

Dosage with Qualifiers — Hypertension—begin 1mg PO qhs; max 20mg/d

- **Contraindications**—hypersensitivity to drug or class
- **Caution**—unknown

Maternal Considerations — There is no published experience with **terazosin** during pregnancy.
Side effects include hypotension after the first dose, dizziness, vertigo, headache, palpitations, atrial fibrillation, thrombocytopenia, asthenia, nasal congestion, peripheral edema, pain, paresthesias, polyuria, nervousness, and blurred vision.

Fetal Considerations — There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **terazosin** crosses the human placenta. While rodent studies are generally reassuring, revealing no evidence of teratogenicity, embryotoxicity and IUGR were noted after doses higher than those used clinically.

Breastfeeding Safety — There are no adequate reports or well-controlled studies in nursing women. It is unknown whether **terazosin** enters human breast milk.

Drug Interactions

Verapamil increased **terazosin's** mean $AUC_{(0-24)}$ 11% following the first **verapamil** dose. After 3w of **verapamil,** the AUC of **terazosin** rose by 24% with associated increases in C_{max} (25%) and C_{min} (32%) means. **Terazosin** mean T_{max} decreased from 1.3 to 0.8h after 3w of **verapamil** treatment.

References

There is no published experience in pregnancy or during lactation.

Summary

Pregnancy Category: C
Lactation Category: U

- **Terazosin** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.
- There are alternative agents for which there is more experience regarding use during pregnancy and lactation.

Terbinafine—(Lamisil)

International Brand Name—Binasil (Korea); Curasil (Korea); Dermafin (Malaysia); Exifine (Malaysia); Interbi (Indonesia); Labijin (Korea); Lamifen (Philippines); Lamisil (China, Hong Kong, India, Indonesia, Japan, Korea, Malaysia, Philippines, Taiwan, Thailand); Lamisil Dermgel (France, New Zealand); Lapiderm (Korea); Lespo (Korea); Micoset (Chile); Micosil (Korea); Namuzol (Korea); Sulmedin (Taiwan); Terbifin (Hong Kong); Terbinex (Korea); Terbisil (Singapore); Terekol (Argentina); Terfine (Taiwan); Termisil (Indonesia)

Drug Class

Antifungals; Dermatologics

Indications

Onychomycosis, tinea

Mechanism

Inhibits squalene epoxidase, reducing cell membrane ergosterol synthesis

Dosage with Qualifiers

Onychomycosis—250mg PO qd ×6w (fingernails) or 12w (toenails)
Tinea—250mg PO qd ×2w

NOTE: check LFTs at baseline; CBC count if >6w.

- **Contraindications**—hypersensitivity to drug or class
- **Caution**—hepatic or renal dysfunction

Maternal Considerations

There is no published experience with **terbinafine** during pregnancy.
Side effects include hepatic failure, hepatotoxicity, Stevens-Johnson syndrome, erythema multiforme, toxic epidermal necrolysis, rash, pruritus, neutropenia, headache, diarrhea, dyspepsia, nausea, abdominal pain, constipation, flatulence, and urticaria.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **terbinafine** crosses the human placenta. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically.

Breastfeeding Safety

There is no published experience in nursing women. The manufacturer reports **terbinafine** achieves an M:P ratio of 7:1 after oral administration. Until data to the contrary becone available, breastfeeding should be avoided.

Drug Interactions

Inhibits CYP2D6-mediated metabolism. This may be of clinical relevance for compounds predominantly metabolized by this

enzyme, such as TCAs, β-blockers, SSRIs, and MAO-B inhibitors, if they have a narrow therapeutic range.
Increases the clearance of **cyclosporine** by 15%.
Rifampin, a CYP inducer, increases **terbinafine** clearance by 100%. **Cimetidine,** a CYP inhibitor, decreases **terbinafine** clearance by 33%.

References ..... There is no published experience in pregnancy or during lactation.

Summary .....

Pregnancy Category: B
Lactation Category: NS

- **Terbinafine** should be used during pregnancy only if the benefit justifies the potential perinatal risk.
- **Terbinafine** should probably be avoided during breastfeeding.
- There are alternative agents for which there is more experience regarding use during pregnancy and lactation.

Terbutaline—(Brethaire; Brethancer; Brethine; Bricanyl; Monovent; Syntovent)

International Brand Name—Asmabet (Indonesia); Asthmasian (Thailand); Ataline (Hong Kong, Malaysia, Thailand); Blucodil (Philippines); Brasmatic (Indonesia); Bricanyl retard (Denmark, Netherlands); Bricasma (Indonesia); Bronchodam (Philippines); Bronco Asmo (Thailand); Bucanil (Singapore); Bucaril (Thailand); Butylin (Hong Kong); Contimit (Germany); Draconyl (Greece); Glin (Taiwan); Lanterbine SR (Hong Kong); Nairet (Indonesia); Taziken (Mexico); Terasma (Indonesia); Terbasmin (Italy, Spain); Terbron (Hong Kong); Terbulin (Israel); Terburop (Colombia); Tismalin (Indonesia); Tolbin (Singapore); Vacanyl (Thailand)

Drug Class ..... Adrenergic agonists; β-Agonists; Bronchodilators

Indications ..... Asthma, tocolysis

Mechanism ..... β_2-Agonist

Dosage with Qualifiers .....

Asthma—5mg PO q6h prn; max 15mg/d; or 2 puffs INH q4-6h; or 0.25mg SC q15-30min ×2
Tocolysis—0.25mg SC q30min; max 1mg/4h; or 2.5-10mcg/min IV, max 30mcg/min

NOTE: available in oral, inhaler, or parenteral forms.

- **Contraindications**—hypersensitivity to drug or class
- **Caution**—diabetes mellitus, infection (with tocolysis), hypertension, hyperthyroidism, arrhythmia, seizures, hypokalemia

Maternal Considerations .....

Terbutaline is a popular and effective agent for the treatment of asthma during pregnancy. While generally considered a selective β_2-agonist based on *in vitro* study, its clinical profile is less specific. As with all other β-mimetics and most tocolytic agents, **terbutaline** is associated with an ~48h delay in delivery compared to placebo in women with preterm labor. Pregnancy outcome is altered only when coupled with antenatal steroid administration. As it is for all other currently available drugs, the use of either oral or continuous SC treatment is ineffective preterm labor prophylaxis. Maternal side effects are common and often lead to discontinuation of therapy. Serious adverse reactions, including pulmonary edema and maternal death, have been reported with **terbutaline.** In rodents, LPS enhances the tocolytic effect of **terbutaline**. Recently, it was concluded that

nifedipine and **indomethacin** are more cost-effective tocolytic agents than either **terbutaline** or **magnesium sulfate** because of the cost of monitoring and treating adverse events.
Not surprisingly, several large meta-analyses conclude that, of the currently available agents, **nifedipine** is the tocolytic of choice.
Terbutaline has also been used in the setting of fetal bradycardia while plans for delivery were underway. In one recent RCT, 110 women had nonreassuring FHR tracings in labor; 57 women received **terbutaline** and 53 women **nitroglycerin.** Successful resuscitation rates were similar (**terbutaline** 71.9% and **nitroglycerin** 64.2%; p = 0.38). **Terbutaline** resulted in lower contraction rates and a decreased prevalence of uterine tachysystole. Maternal MAP decreased with **nitroglycerin** but not **terbutaline. Terbutaline** also seems useful for the correction of **oxytocin**-induced tachysystole, but is probably medically indicated only when associated with an FHR abnormality.
Side effects include pulmonary edema, hypotension, tachycardia, palpitations, arrhythmia, nervousness, tremor, headache, N/V, drowsiness, sweating, muscle cramps, and hyperglycemia.

Fetal Considerations

Terbutaline crosses the human placenta, achieving an F:M ratio between 0.11 and 0.48 after a single IV dose immediately prior to elective cesarean delivery. Levels approach unity after several hours. Multiple case reports suggest it is chronotropic in fetuses with complete heart block. The effect, if any, is often transient perhaps because β-adrenergic innervation is still relatively immature even at birth. Allegations that **terbutaline** exposure during pregnancy causes autism cannot be sustained on any level because of the high doses studied coupled to a lack of evidence that **terbutaline** crosses the fetal blood-brain barrier.
Paradoxically, there is no receptor desensitization demonstrable in the fetal rat heart exposed chronically to **terbutaline.** Rodent studies are reassuring, showing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically.
Terbutaline increases the frequency of fetal breathing. Chronic **terbutaline** exposure increases cardiac size and HR in fetal guinea pigs. Overall, it appears long-term **terbutaline** use has measurable fetal affects at least in rodents.

Breastfeeding Safety

Terbutaline is excreted into human breast milk, reaching M:P ratios in excess of 2. Yet, the amount ingested is <1% of the maternal dose, and the neonatal level undetectable.

Drug Interactions

Other sympathomimetic agents should not be used with **terbutaline** since their combined effect on the CV system may be deleterious.
Use with caution in patients being treated with MAOIs or TCAs since the action of **terbutaline** on the vascular system may be potentiated.
β-Adrenergic blocking agents not only block the pulmonary effect of **terbutaline** but may trigger a severe attack in asthmatic patients.

References

Auman JT, Seidler FJ, Slotkin TA. Am J Physiol Regul Integr Comp Physiol 2001; 281:R1079-89.
Bergman B, Bokström H, Borgå O, et al. Eur J Respir Dis Suppl 1984; 134:81-6.
Goldenberg RL. Obstet Gynecol 2002; 100:1020-37.
Guinn DA, Goepfert AR, Owen J, et al. Am J Obstet Gynecol 1998; 179:874-8.
Hallak M, Moise K Jr, Lira N, et al. Am J Obstet Gynecol 1992; 167:1059-63.

Hayes E, Moroz L, Pizzi L, Baxter J. Am J Obstet Gynecol 2007; 197:383.e1-6.
Klukovits A, Marki A, Paldy E, et al. Nauyn Schmiedebergs Arch Pharmacol 2008; Dec 3 [Epub ahead of print].
Lindberg C, Boreus LO, de Chateau P, et al. Eur J Respir Dis Suppl 1984; 134:87-91.
[No authors]. Ann Allergy Asthma Immunol 2000; 84:475-80.
Pacheco LD, Rosen MP, Gei AF, et al. Am J Perinatol 2006; 23:377-80.
Petersen R, Carter LS, Chescheir NC, et al. Am J Obstet Gynecol 1989; 161:509-12.
Pullen KM, Riley ET, Waller SA, et al. Am J Obstet Gynecol 2007; 197:414.e1-6.
Robinson BV, Ettedgui JA, Sherman FS. Cardiol Young 2001; 11:683-6.
Tsatsaris V, Papatsonis D, Goffinet F, et al. Obstet Gynecol 2001; 97:840-7.
Wenstrom KD, Weiner CP, Merrill D, Niebyl J. Am J Perinatol 1997; 14:87-91.

Summary

Pregnancy Category: B
Lactation Category: S

- **Terbutaline** is a first-line treatment of asthma during pregnancy and lactation.
- There are alternative agents for tocolysis, such as **nifedipine,** that are more effective and have a superior safety profile.

Terconazole—(Terazol)

International Brand Name—Fungistat (Mexico); Fungistat 3 (Puerto Rico); Fungistat 5 (Colombia, Costa Rica, Dominican Republic, El Salvador, Guatemala, Honduras, Nicaragua, Panama); Gyno-Terazol (Belgium, Israel, Netherlands, Portugal); Gyno-Terazol 3 (Czech Republic); Terazol 3 (Canada); Terazol 7 (Canada); Tercospor (Germany)

Drug Class

Antifungals; Dermatologics

Indications

Vulvovaginal candidiasis

Mechanism

Unknown

Dosage with Qualifiers

Vulvovaginal candidiasis—1 applicator 4% qhs ×7d, or 8% ×3d, or 1 suppository PV qhs ×3d

NOTE: available in cream (0.4%, 0.8%) and suppository (80mg).

- **Contraindications**—hypersensitivity to drug or class
- **Caution**—unknown

Maternal Considerations

Terconazole is a member of a series of imidazoles whose effectiveness appears similar. There are no adequate reports or well-controlled studies of **terconazole** in pregnant women. Topical **imidazole** appears to be more effective than **nystatin** for treating symptomatic vaginal candidiasis in pregnancy. Treatment periods of 7d may be necessary during pregnancy rather than the shorter courses typically recommended.
Side effects include irritation, headache, and pruritus.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **terconazole** crosses the human placenta. Rodent studies are generally reassuring, revealing

no evidence of teratogenicity or IUGR until the dose exceeds 20× the MRHD, when skeletal abnormalities and embryotoxicity are noted. The no-effect oral dose (10mg/kg/d) produces a mean peak plasma level in pregnant rats 44× the mean peak plasma levels seen after intravaginal administration.

Breastfeeding Safety — There is no published experience in nursing women. It is unknown whether **terconazole** enters human breast milk.

Drug Interactions — No clinically relevant interactions identified.

References

Young GL, Jewell D. Cochrane Database Syst Rev 2001; (4):CD000225.

Summary

Pregnancy Category: C
Lactation Category: U

- **Terconazole** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.
- There are alternative agents for which there is more experience regarding use during pregnancy and lactation.

Tetanus immune globulin—(Hyper-Tet; Hypertet)

International Brand Name—BayTet (Canada, Israel, Philippines); IG tetano/tetanus immune globulin (Israel, Philippines); Tetabulin (Austria, Hong Kong, Italy, Korea, Switzerland); Tetabuline (Belgium); Tetagam (Germany, Indonesia, South Africa); Tetagamma (Italy); Tetagam-P (Greece); Tetaglobulin (Germany); Tetaglobuline (Israel, Malaysia, Philippines, South Africa, Thailand); Tetagloman (Austria); Tetamyn enzimatico liofilizado (Mexico); Tetanobulin (Taiwan); Tetanogamma (Dominican Republic); Tetanosson (Greece); Tetuman berna (Hong Kong, Malaysia, Peru, Philippines, South Africa)

Drug Class — Immune globulins

Indications — Tetanus prophylaxis following injury with unknown/uncertain vaccination history, active tetanus

Mechanism — Passive immunity

Dosage with Qualifiers

Tetanus prophylaxis following injury with unknown/uncertain vaccination history—250IU deep IM; administer in different extremities, and with separate syringes, tetanus and diphtheria toxoids
Active tetanus—dose depends on severity; see package insert

- **Contraindications**—hypersensitivity to drug or class
- **Caution**—thrombocytopenia, bleeding disorder

Maternal Considerations

Tetanus immune globulin creates passive immunity to the toxin of *C. tetani*. Naturally acquired immunity to tetanus toxin is rare in the US. Universal primary vaccination, with subsequent timed boosters to maintain adequate antitoxin levels, is required for all age groups. There are no adequate reports or well-controlled studies of **tetanus immune globulin** in pregnant women. Tetanus is a highly lethal disease and a significant cause of maternal death in some locales. It appears the antibodies produced in response to **tetanus toxoid** during pregnancy have low protective capacity, strengthening the importance of **tetanus immune globulin** prophylaxis during pregnancy. The long clinical experience suggests safety.

Side effects include injection site soreness, fever, angioneurotic edema, and nephrotic syndrome.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. **Tetanus immune globulin** crosses the human placenta and provides at least partial coverage for the neonate. Maternal immunization does not interfere with neonatal response to the DPT series. The degree of IgG transfer is lower in the preterm compared to the term neonate, and there appears to be a maximal transfer rate. Rodent teratogenicity studies have not been performed, but there is no reason to hypothesize the antibody may damage the fetus.

Breastfeeding Safety

There are no adequate reports or well-controlled studies in nursing women. It is unknown whether **tetanus immune globulin** enters human breast milk. However, the long clinical experience in humans is reassuring. It does enter the colostrum of horses and actually can reduce the foal's response to vaccination.

Drug Interactions

Antibodies in immunoglobulin preparations may interfere with the response to live viral vaccines such as measles, mumps, polio, and rubella. Use of such vaccines should be delayed approximately 3mo after **tetanus immune globulin.**

References

Kutukculer N, Kurugol Z, Egemen A, et al. J Trop Pediatr 1996; 42:308-9.

Morell A, Sidiropoulos D, Herrmann U, et al. Pediatr Res 1986; 20:933-6.

Okoko BJ, Wesuperuma LH, Ota MO, et al. J Health Popul Nutr 2001; 19:59-65.

Pasetti MF, Dokmetjian J, Brero ML, et al. Am J Reprod Immunol 1997; 37:250-6.

Wesumperuma HL, Perera AJ, Pharoah PO, Hart CA. Ann Trop Med Parasitol 1999; 93:169-77.

Wilson WD, Mihalyi JE, Hussey S, Lunn DP. Equine Vet J 2001; 33:644-50.

Summary

Pregnancy Category: C
Lactation Category: S

- **Tetanus immune globulin** is considered safe and effective during pregnancy and lactation.

Tetanus toxoid—(Tetanus toxoid adsorbed)

International Brand Name—Anatetall (Malaysia, Philippines, Thailand); Anatoxal Tetanica Berna (Peru); Clostet (England); TE Anatoxal (Austria); TE Anatoxal Berna (Switzerland); Tetanol (Ecuador, Germany, Greece, Honduras, Mexico, South Africa); Tetatox (Italy); Tetavax (England, Germany, Hong Kong, Malaysia, Philippines, South Africa, Thailand); Tet-Tox (New Zealand)

Drug Class — Vaccines

Indications — Tetanus susceptibility

Mechanism — Active immunization

Dosage with Qualifiers

Tetanus susceptibility—*primary immunization:* 0.5ml IM q4-8w ×2, then 0.5ml IM 6-12mo after the 2nd trimester; *booster:* 0.5ml IM q10y

- **Contraindications**—hypersensitivity to drug or class, acute respiratory infection or other active infection (unless emergency), immunosuppressive agents
- **Caution**—unknown

Maternal Considerations

Serologic tests demonstrate naturally acquired immunity to tetanus toxin is rare in the US. Universal primary vaccination, with subsequent timed boosters to maintain adequate antitoxin levels, is required for all age groups. Tetanus is a highly lethal disease and a significant cause of maternal death in some locales. **Tetanus toxoid** is a highly effective antigen; a completed primary series generally induces protection that persists ≥10 years. Increasing the interval between primary immunizing doses to 6mo or longer does not interfere with the final immunity. Any dose of **tetanus toxoid** received, even a decade earlier, is counted as the first immunizing injection. There are no adequate reports or well-controlled studies of **tetanus toxoid** in pregnant women. Pregnant women do respond. In many geographic locales, a cogent argument can be made for routine immunization with at least 1 dose during pregnancy to protect both mother and newborn.

Side effects include injection site soreness, fever, malaise, lymphadenopathy, generalized aches, hypotension, and pruritus.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. The antibodies generated in response to **tetanus toxoid** appear to cross the human placenta, and are capable of stimulating active immunity in the term fetus. The long clinical experience with immunization during pregnancy is reassuring. Maternal immunization protects against neonatal tetanus and should be public policy in many geographic locales.

Breastfeeding Safety

There are no adequate reports or well-controlled studies in nursing women. It is unknown whether **tetanus toxoid** enters human breast milk.

Drug Interactions

No clinically relevant interactions identified.

References

Czeizel AE, Rockenbauer M. In J Gynaecol Obstet 1999; 64:254-8.
Gupta SD, Keyl PM. Pediatr Infect Dis J 1998; 17:316-21.
Maral MI, Cirak M, Aksakal FN, et al. Eur J Epidemiol 2001; 17:661-5.
Rochat R, Akhter HH. Lancet 1999; 354:565.
Vanderbeeken Y, Sarfati M, Bose R, Delespesse G. Am J Reprod Immunol Microbiol 1985; 8:39-42.

Summary

Pregnancy Category: C
Lactation Category: S

- **Tetanus toxoid** is considered safe and effective during pregnancy and lactation.

Tetracaine—(Ak-T-Caine; Dermacaine; Pontocaine; Tetocain)

International Brand Name—Ametop (South Africa); Pantocain (Indonesia); Tetocaine (Taiwan)

Drug Class

Anesthetics, local

Indications

Spinal anesthetic

Mechanism

Blocks Na/K channels, inhibiting nerve impulse transmission

Dosage with Qualifiers

Spinal anesthesia—5-15mg intraspinal between L2 and L4

NOTE: volume load to minimize the risk of hypotension.

- **Contraindications**—hypersensitivity to drug or class; associated conditions that increase the risks of spinal anesthesia, including generalized septicemia (relative), injection site infection (absolute), increased ICP (absolute), uncontrolled hypotension (absolute)
- **Caution**—arrhythmia, hypotension, hypovolemia, shock

Maternal Considerations

Tetracaine produces 2-3h of surgical anesthesia depending on the site of surgery (i.e., intra-abdominal vs. lower limb/perineal). The extent and degree of anesthesia depend on dose, specific gravity of the anesthetic solution, volume used, and the position of the patient during and immediately after injection. There are no adequate reports or well-controlled studies of **tetracaine** in pregnant women. Although once routinely used (mixed with either 10% glucose or 10% **procaine**) for spinal anesthesia for cesarean delivery, **tetracaine** has been supplanted by **bupivacaine** as the spinal agent of choice for cesarean delivery.
Side effects of spinal anesthesia include those related to systemic hypotension–associated medullary/pontine hypoperfusion (e.g., unconsciousness, respiratory/cardiac arrest, N/V) as well as those related to post–dural puncture headache (e.g., tinnitus, blurry vision, occipitofrontal cephalgia).

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **tetracaine** crosses the human placenta. Considering the dose and route, it is unlikely the maternal systemic concentration will reach a clinically relevant level. Rodent teratogenicity studies have not been performed.

Breastfeeding Safety

There is no published experience in nursing women. It is unknown whether **tetracaine** enters human breast milk. Other local anesthetics are excreted. Considering the indication and dosing, one-time **tetracaine** use is unlikely to pose a clinically significant risk to the breastfeeding neonate.

Drug Interactions

Avoid use with a sulfonamide.

References

Pan PM, Lin ZF, Lim J, et al. Ma Zui Xue Za Zhi 1989; 27:349-52.

Summary

Pregnancy Category: C
Lactation Category: S

- Although supplanted by **bupivacaine** for cesarean delivery, **tetracaine** is still a popular agent for spinal anesthesia for longer surgical procedures.

Tetracycline—(Achromycin; Acrimicina; Actisite; Ala-Tet; Alphacycline; Ambramycin; Austramycin; Bekatetracyn; Biocycline; Bristacycline; Brodspec; Cofarcilina; Cyclopar; Emtet-500; Hydracycline; Maviciclina; Nelmicyn; Nor-Tet; Panmycin; Polfamycine; Robitet; Sarocycline; Sumycin; Supramycin; Tega-Cycline; Teline; Telmycin; Tetocyn; Tetracap; Tetrachel; Tetraciclina; Tetracitro-S; Tetracon; Tetracyn; Tetralan; Tetram; Tetramed; Topicycline; Upcyclin; Wesmycin; Wintellin; Wintrex; Xepacycline)

International Brand Name—Achromycin V (Canada, Israel, Japan, South Africa); Acromicina (Argentina, Italy, Mexico); Ambramicina (Italy, Spain); Apocyclin (Finland); Apo-Tetra (Canada); Beatacycline (Singapore); Bristaciclina (Spain); Cadicycline (South Africa); Calociclina (Italy); Ciclotetryl (Argentina); Combicyclin (Indonesia); Conmycin (Indonesia); Cyclabid (South Africa); Dhatracin (Malaysia); Dicyclin Forte (India); Dumocyclin (Denmark, Finland); Economycin (England); Enkacyclin (Indonesia); Florocycline (France); Hexacycline (France); Hostaciclina (Ecuador); Hostacyclin (Austria, Greece); Hostacycline (Belgium, India, Philippines, South Africa); Hostacycline-P (South Africa); Hydromycin (Thailand); Ibicyn (Taiwan); Ikacycline (Indonesia); Kemoclin (Indonesia); Latycin (Australia, Israel, Singapore); Lenocin (Thailand); Medocycline (Hong Kong); Mysteclin (Australia); Novotetra (Canada); Ofticlin (Mexico); Omnaze (Argentina); Orencyclin F-500 (Peru); Oricyclin (Finland); Pantocycline (Thailand); Parenciclina (Mexico); Pervasol (Argentina); Polarcyclin (Finland); Quimocyclar (Mexico); Recycline (Israel); Resteclin (India); Rimatet (Israel, Puerto Rico, South Africa); Servitet (Malaysia, Thailand); Steclin (Argentina, Germany); Steclin V (South Africa); Subamycin (India); Tefilin (Germany); Tetra-Atlantis (Mexico); Tetrabioptal (Italy); Tetrablet (Germany); Tetra Central (Thailand); Tetracitro S (Germany); Tetralen (Spain); Tetralim (Thailand); Tetralution (Germany); Tetramig (France); Tetrana (Thailand); Tetranase (Peru); Tetrano (Thailand); Tetrarco (Indonesia, Netherlands); Tetrarco L.A. (Austria); Tetraseptin (Switzerland); Tetrasuiss (Israel, Puerto Rico, South Africa, Taiwan); Tetrecu (Ecuador); Tetrex (Australia, Israel, Japan, Mexico, South Africa); Tevacycline (Israel); Triphacyclin (Switzerland)

Drug Class	Antibiotics; Dermatologics; Ophthalmics; Tetracyclines
Indications	Bacterial infection, *Chlamydia* infection, acne vulgaris
Mechanism	Bacteriostatic—inhibits protein synthesis
Dosage with Qualifiers	Bacterial infection—1-2g qd divided bid or qid at least 1h ac or 2h pc *Chlamydia* infection—500mg PO qid at least 1h ac or 2h pc ×7d Acne vulgaris—250-500mg PO qid at least 1h ac or 2h pc *NOTE: renal dosing; available in oral, ointment (3%), and parenteral formats.* • **Contraindications**—hypersensitivity to drug or class, pregnancy • **Caution**—hepatic or renal dysfunction
Maternal Considerations	**Tetracycline** is a broad-spectrum antibiotic prepared from certain *Streptomyces* species. When penicillin is contraindicated, tetracycline-class agents are alternatives for the treatment of gonorrhea (1.5g PO, then 0.5g qid for a total of 9.0g), syphilis and yaws, *Listeria monocytogenes, Clostridium* species, *B. anthracis, Fusobacterium fusiforme* (Vincent's infection), and *Actinomyces* species. **Tetracycline** may be more hepatotoxic than **doxycycline.** There are no adequate reports or well-controlled studies of **tetracycline** in pregnant women. It is generally avoided during pregnancy because of fetal considerations. ***Side effects*** include pseudotumor cerebri, hepatotoxicity, Jarisch-Herxheimer reaction, pseudomembranous colitis,

pericarditis, tooth discoloration in progeny, N/V, dyspepsia, anorexia, diarrhea, photosensitivity, stomatitis, oral and/or vulvovaginal candidiasis, urticaria, lightheadedness, dizziness, ataxia, tinnitus, headache, blurred vision, neutropenia, thrombocytopenia, and increased BUN.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. **Tetracycline** crosses the human placenta and may cause a yellow-gray-brown tooth discoloration in adults after fetal/childhood exposure. It is unlikely topically applied **tetracycline** achieves a clinically relevant systemic level. Another tetracycline**, oxytetracycline** (but not **doxycycline**) is associated with an increased risk of NTDs, cleft palate, and CV defects. There are no similar studies for **tetracycline.** Rodent studies are otherwise generally reassuring, revealing no evidence of teratogenicity, but some embryotoxicity at high doses.

Breastfeeding Safety

There are no adequate reports or well-controlled studies in nursing women. **Tetracycline** enters human breast milk, though the kinetics remain to be elucidated. Clinical experience suggests that maternal oral ingestion is compatible with breastfeeding.

Drug Interactions

Avoid using with a bactericidal antibiotic since bacteriostatic drugs may interfere with the bactericidal action.
Patients' anticoagulant therapy may require downward adjustment of the dose.
Use with **methoxyflurane** may cause fatal renal toxicity.
Absorption is impaired by antacids containing aluminum, calcium, or magnesium and preparations containing iron, zinc, or **sodium bicarbonate.**
May render low-**estradiol** oral contraceptives less effective.

References

Czeizel AE, Rockenbauer M. Eur J Obstet Gynecol Reprod Biol 2000; 88:27-33.
Heaton PC, Fenwick SR, Brewer DE. J Clin Pharm Ther 2007; 32:483-7.

Summary

Pregnancy Category: D
Lactation Category: S
- Parenteral and oral **tetracycline** should be avoided during pregnancy whenever possible.

Thalidomide—(Thalomid)

International Brand Name—Thado (Taiwan); Thalix (India)

Drug Class

Dermatologics; Immunomodulators

Indications

Erythema nodosum leprosum, HIV wasting, aphthous ulcer

Mechanism

Unknown

Dosage with Qualifiers

NOTE: Restricted access in US; call 1-888-423-5436 for information.
Erythema nodosum leprosum—begin 100-300mg PO ×2w or until symptoms improve, then decrease by 50mg/d q2-4w
HIV wasting—100-300mg PO qhs
Aphthous ulcer—200mg PO qd

NOTE: effective contraception obligatory 1mo before, during, and until 1mo after therapy; document negative hCG test 24h prior to initiating.

- **Contraindications**—hypersensitivity to drug or class, pregnancy, moderate/severe neuritis
- **Caution**—seizure disorder, reproductive age, CV disease

Maternal Considerations

Thalidomide is a known human teratogen and contraindicated during pregnancy. It is also excreted in semen, and treated males should wear a condom during coitus. Initially banned in the US, it has proven a superb drug for the treatment of several formerly resistant diseases. Its potential indications are growing, increasing the likelihood of an inadvertent pregnancy. Effective contraception is mandatory. While there are no reports of **thalidomide**-related birth defects in the US since its return to the market, there are scattered reports elsewhere, providing a constant reminder to providers. There are no adequate reports or well-controlled studies of **thalidomide** in pregnant women.
Side effects include severe birth defects, peripheral neuropathy, toxic epidermal necrolysis, seizures, bradycardia, hypertension, orthostatic hypotension, headache, Stevens-Johnson syndrome, drowsiness, dizziness, rash, diarrhea, fever, chills, increased appetite, weight gain, confusion, amnesia, mood changes, photosensitivity, neutropenia, and increased HIV viral load.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. **Thalidomide** crosses the human placenta and is a potent human (but not rodent) teratogen, causing limb abnormalities after 1st trimester exposure, perhaps by creating a pro-oxidant balance. Even a single 50mg dose can cause defects. If pregnancy occurs, the drug should be discontinued and the patient referred to a fetal medicine expert for evaluation and counseling. Any suspected fetal exposure to **thalidomide** must be reported to the FDA via the MedWatch program at 1-800-FDA-1088 and also to the Celgene Corporation. It is of note that recent cases of **thalidomide** embryopathy result from sharing medication and were not detected by normal surveillance procedures.

Breastfeeding Safety

There is no published experience in nursing women. It is unknown whether **thalidomide** enters human breast milk.

Drug Interactions

May enhance the sedative activity of barbiturates, **chlorpromazine,** ethanol, and **reserpine.**
Concomitant use of **carbamazepine, griseofulvin,** certain herbal supplements such as **St. John's wort,** HIV protease inhibitors, **modafinil,** penicillins, **phenytoin, rifabutin,** or **rifampin** with hormonal contraceptive agents may reduce the effectiveness of the contraception during and up to 1mo after discontinuation of these concomitant therapies. Therefore, women requiring treatment with one or more of these drugs must use two *other* effective or highly effective methods of contraception or abstain from heterosexual sexual contact while taking **thalidomide.**

References

Ances BM. Obstet Gynecol 2002; 99:125-8.
Dennery PA. Birth Defects Res C Embryo Today 2007; 81:155-62.
Fieldston E. Princet J Bioeth 1998; 1:83-93.
Kane S, Stone LJ, Ehrenpreis E. J Clin Gastroenterol 2002; 35:149-50.
Schuler-Faccini L, Soares RC, de Sousa AC, et al. Birth Defects Res A Clin Mol Teratol 2007; 79:671-2.
Teo SK, Harden JL, Burke AB, et al. Drug Metab Dispos 2001; 29:1355-7.

Summary

Pregnancy Category: X
Lactation Category: U

- **Thalidomide** is a known and potent human teratogen. It should be avoided during pregnancy, and pregnancy termination considered after inadvertent exposure.
- Any suspected fetal exposure to **thalidomide** must be reported to the FDA via the MedWatch program at 1-800-FDA-1088 and also to Celgene Corporation.

Theophylline—(Accurbron; Aerolate; Aloefilina; Aminomal; Aquaphyllin; Asmalix; Asperal; Bilordyl; Bronkodyl; Bykofilin; Constant-T; Elixicon; Elixomin; Elixophyllin; Hydro-Spec; Labid; Lanophyllin; Lixolin; Neulin-SA; Phyllocontin; Provent; Pulmo; Respbid; Slo-Bid; Slo-Phyllin; Solu-Phyllin; Somophyllin; Sustaire; Talofren; Teofilina; Teophyllin; Theo-24; Theobid; Theochron; Theoclear; Theocontin; Theocot; Theo-Dur; Theolair; Theomar; Theophyl; Theophylline Anhydrous; Theosol-80; Theospan Sr; Theostat 80; Theo-Time; Theovent; Theox; T-Phyl; Truxophyllin; Uni-Dur; Unifyl; Uniphyl)

International Brand Name—Aerobin (Germany); Aerodyne Retard (Austria); Afonilum Forte (Germany); Afonilum Mite (Germany); Afonilum Retard (Germany); Almarion (Thailand); Armophylline (France); Asmasalon (Philippines); Asperal-T (Belgium); Austyn (Korea); Bronchoretard (Germany); Bronsolvan (Indonesia); Cronasma (Germany); Deo-Q Syrup (Korea); Ditenaten (Germany); Elixofilina (Mexico, Peru); Euphylong (Hong Kong, Israel); Euphylong Retardkaps (Germany); Euphylong SR (Philippines); Godafilin (Spain); Lasma (England, Israel); Nefoben (Argentina); Neobiphyllin (China); Neulin SA (South Africa); Neulin-SR (Taiwan); Nuelin (Costa Rica, Denmark, Dominican Republic, El Salvador, Finland, Honduras, Malaysia, Norway, Panama, Philippines, Puerto Rico); Nuelin SA (Costa Rica, Dominican Republic, El Salvador, Guatemala, Honduras, Israel, Panama, South Africa); Nuelin SR (Australia, Hong Kong, Israel, Malaysia, Thailand); Pharphylline (Netherlands); Phylobid (India, South Africa); Protheo (China); Pulmidur (Austria, Germany); Quibron T SR (Canada, Indonesia); Slo-Theo (Hong Kong); Solosin (Germany); Somofillina (Italy); Teobid (Colombia); Teoclear (Korea); Teoclear LA (Argentina); Teofilina Retard (Colombia); Teolixir (Spain); Teolong (Mexico); Teosona (Argentina); Theo-2 (Belgium); Theo-Bros (Greece); Theolair S (Peru); Theolan (Korea, Taiwan); Theolin (Singapore); Theolin SR (Singapore); Theolong (Japan); Theomax (Spain); Theon (Switzerland); Theo PA (India); Theoplus (Bulgaria, Singapore, Spain); Theoplus Retard (Austria, Greece); Theospirex Retard (Austria, Switzerland); Theostat LP (France); Theotard (Israel); Theotrim (Israel); Theovent LA (Hong Kong); Theo von CT (Germany); Tiodilax (Argentina); Tyrex (Peru); Unicontin-400 Continus (India); Unifyl Retard (Switzerland); Uniphyl CR (Korea); Uniphyllin (Taiwan); Uniphyllin Continus (South Africa); Xanthium (Singapore); Xantivent (Switzerland)

Drug Class	Bronchodilators; Xanthine derivatives
Indications	Chronic asthma, COPD (maintenance)
Mechanism	PDE inhibitor increasing cAMP; adenosine receptor antagonist
Dosage with Qualifiers	Chronic asthma—begin 300mg PO qd in divided doses bid or tid ×3d, then 400mg/d ×3d, then 600mg/d if tolerated COPD (maintenance)—begin 300mg PO qd in divided doses bid or tid ×3d, then 400mg/d ×3d, then 600mg/d if tolerated

*NOTE: therapeutic level 10-20mcg/ml; exists in multiple formats with varying release rates. Dosing quoted for **theophylline** only.*

- **Contraindications**—hypersensitivity to drug or class, arrhythmia, seizures, peptic ulcer disease
- **Caution**—hepatic or renal dysfunction, hypothyroidism

Maternal Considerations

Theophylline has two distinct actions on the airways of women with reversible airway obstruction: bronchodilation and nonbronchodilator prophylactic effects. Although 1% of pregnant women have asthma, it is often underrecognized and suboptimally treated. Severe, uncontrolled asthma increases the likelihood of maternal and fetal morbidity and death. Pharmacologic therapy is often necessary during pregnancy. Women with well-controlled asthma during pregnancy have outcomes as good as those of their nonasthmatic peers. Its clearance of **theophylline** is altered little during either the 1st and 2nd trimesters, but significantly decreased in the 3rd trimester and puerperium. Benefit:risk considerations suggest inhaled asthma medications such as β-mimetics and corticosteroids are first-line agents, with **theophylline** a second-line agent for the treatment of asthma during pregnancy. The risk of exacerbation is high immediately postpartum, but overall severity usually reverts to preconception levels postpartum. Asthma tends to follow a similar course in subsequent pregnancies.
Side effects include arrhythmia, seizures, respiratory arrest, N/V, headache, insomnia, rash, alopecia, flushing, fever, nervousness, agitation, tremor, tachycardia, and palpitations.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. **Theophylline** crosses the human placenta, reaching an F:M ratio of unity in a brief time. It dilates *in vitro* constricted placental arteries. While the limited rat teratogen studies are reassuring, **theophylline** producing more than 5× the recommended human therapeutic concentration causes fetal toxicity, cleft palate, and skeletal malformations in rabbits. In the chick (a poor model for humans), **theophylline** is associated with an increased prevalence of CV malformations.

Breastfeeding Safety

Theophylline enters human breast milk, achieving an M:P ratio between 0.6 and 0.9. It can cause irritability in the nursing newborn, presumably because of the long neonatal t/2. Neonatal toxicity is unlikely. Women who choose to breastfeed should monitor their children's behavior closely.

Drug Interactions

The clinician should not assume that a drug does not interact with theophylline if it is not listed here. Individual patients may experience larger changes in serum theophylline concentrations than the value listed.
Blocks **adenosine** receptors, often necessitating a higher dose of **adenosine** to achieve the desired effect.
A single large dose of ethanol (3ml/kg of whiskey) decreases **theophylline** clearance by as much as ⅓ for up to 24h.
Allopurinol decrease **theophylline** clearance by up to 25%.
Aminoglutethimide, carbamazepine, and **phenobarbital** each may increase **theophyilline** clearance by microsomal enzyme induction and decrease levels by about 25%.
Cimetidine, ciprofloxacin, fluvoxamine, propranolol, and **tacrine** each decrease **theophylline** clearance by inhibiting CYP1A2, causing levels to rise by 40-100%. **Enoxacin** may increase the **theophylline** level by the same mechanism by more than 300%.

Clarithromycin and **erythromycin** decrease **theophylline** clearance by inhibiting CYP3A3, causing levels to rise 25-35%. **Erythromycin** steady-state serum levels decrease by a similar amount.
A larger dose of benzodiazepines (e.g., **diazepam, flurazepam, lorazepam**) may be required to produce the desired level of sedation as they increase CNS concentrations of **adenosine** and **theophylline** blocks **adenosine** receptors. Caution is indicated should the **theophylline** be discontinued.
Disulfiram, mexiletine, and **verapamil** decrease **theophylline** clearance by inhibiting hydroxylation and demethylation; levels may rise 50%.
Estrogen-containing oral contraceptives decrease **theophylline** clearance in a dose-dependent fashion, raising levels by as much as 30%. The effect of **progesterone** on **theophylline** clearance is unknown.
Use with **halothane** increases the risk of ventricular arrythmias.
Human recombinant interferon alfa-2a decreases clearance and almost doubles serum **theophylline** levels.
Isoproterenol (IV) increases clearance, lowering levels by some 20%.
Increases renal **lithium** clearance, necessitating a 40-60% increase in the dose of **lithium.**
Methotrexate decreases **theophylline** clearance and levels may rise more than 20%.
Moricizine increases clearance, decreasing levels by 25%.
May antagonize nondepolarizing neuromuscular blocking agents (e.g., **pancuronium**) possibly due to phosphodiesterase inhibition, requiring higher doses.
Pentoxifylline, propafenone, thiabendazole, and **ticlopidine** each decrease **theophylline** clearance, causing levels to rise 30-200%.
Phenytoin increases **theophylline** clearance by increasing microsomal enzyme activity. **Theophylline** decreases **phenytoin** absorption. As a result, serum **theophylline** *and* **phenytoin** levels decrease about 40%.
Rifampin increases clearance by increasing CYP1A2 and 3A3 activity, causing a 20-40% decrease in the **theophylline** level.
Sulfinpyrazone increases clearance by increasing demethylation and hydroxylation, causing a 20% decrease in the **theophylline** level.

References

Dombrowski MP. Obstet Gynecol Clin North Am 1997; 24:559-74.
Gardner MJ, Schatz M, Cousins L, et al. Eur J Clin Pharmacol 1987; 32:289-95.
Omarini D, Barzago MM, Bortolotti A, et al. Eur J Drug Metab Pharmacokinet 1993; 18:369-74.
Reinhardt D, Richter O, Brandenburg G. Monatsschr Kinderheilkd 1983; 131:66-70.
Schatz M. Semin Perinatol 2001; 25:145-52.
Shibata M, Wachi M, Kawaguchi M, et al. Methods Find Exp Clin Pharmacol 2000; 22:101-7.
Walters WA, Boura AL. Reprod Fertil Dev 1991; 3:475-81.

Summary

Pregnancy Category: C
Lactation Category: S (likely)

- **Theophylline** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.
- Though the long clinical experience is reassuring, **theophylline** cannot be excluded as a weak human teratogen at high doses.
- **Theophylline** is typically considered a second line agent during pregnancy.

Thiabendazole—(Mintezol; Tiabendazole; Triasox)

International Brand Name—None identified.

Drug Class ..... Antiparasitics

Indications ..... Helminthic infection, cutaneous larva migrans, visceral larva migrans, trichinosis, dracunculosis

Mechanism ..... Unknown

Dosage with Qualifiers .....

Helminthic (systemic pinworm, whipworm, roundworm, threadworm) infection—1.5g PO q12h ×2d; max 3g/d
Cutaneous larva migrans—25mg/kg PO q12h ×5-7d; max 3g/d
Visceral larva migrans—25mg/kg PO q12h ×5-7d; max 3g/d
Trichinosis—25mg/kg PO q12h ×5-7d; max 3g/d
Dracunculosis—25-37.5mg/kg PO q12h ×3d; max 3g/d

NOTE: take after meals with fruit juice; chew tablets before swallowing.

- **Contraindications**—hypersensitivity to drug or class, pinworm prophylaxis
- **Caution**—hepatic or renal dysfunction, anemia, volume depletion, malnutrition

Maternal Considerations ..... **Thiabendazole** is usually a second-line therapy for pinworm behind **piperazine.** However, when enterobiasis occurs, additional therapy is not required for most patients. **Thiabendazole** should be used for the following only when more specific therapy is unavailable or cannot be used or when further therapy with a second agent is desirable: uncinariasis (hookworm: *Necator americanus* and *Ancylostoma duodenale*); trichuriasis (whipworm); ascariasis (large roundworm). There are no adequate reports or well-controlled studies of **thiabendazole** in pregnant women. ***Side effects*** include hepatic dysfunction, jaundice, Stevens-Johnson syndrome, erythema multiforme, seizures, hallucinations, N/V, diarrhea, malodorous urine, nephrotoxicity, leukopenia, headache, numbness, tinnitus, yellow or blurred vision, dry mouth, rash, pruritus, dizziness, somnolence, and altered mental state.

Fetal Considerations ..... There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **thiabendazole** crosses the human placenta. It crosses the rodent placenta, though the kinetics remain to be elucidated. Rodent teratogen studies are inconsistent, revealing skeletal and cleft palate abnormalities at 10× the MRHD in only some investigations. These adverse effects are now thought likely the product of maternal toxicity.

Breastfeeding Safety ..... There are no adequate reports or well-controlled studies in nursing women. It is unknown whether **thiabendazole** enters human breast milk.

Drug Interactions ..... Use with xanthine derivatives (e.g., **theophylline**) should be undertaken cautiously as they may compete for sites of metabolism in the liver, thus elevating the serum levels of such compounds to potentially toxic levels.

References .....

Lankas GR, Nakatsuka T, Ban Y, et al. Food Chem Toxicol 2001; 39:367-74.

Yoneyama M, Ogata A, Fujii T, Hiraga K. Food Chem Toxicol 1984; 22:731-5.

Summary

Pregnancy Category: C
Lactation Category: U

- **Thiabendazole** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.
- Though probably not a significant human teratogen, it should be used only as a second-line agent.

Thiamine—(Actamin; Alivio; Anacrodyne; Benerva; Beneuril; Beneuron; Betabion; Betalin S; Betamin; Betatabs; Betaxin; Bevitine; Bewon; Biamine; Dumovit; Invite; Metabolin; Oryzanin; Ottovit; Tiamina; Vitamin B_1; Vitanon; Vitantial)

International Brand Name—None identified.

Drug Class

Vitamins/minerals

Indications

Dietary supplement, Wernicke's encephalopathy, beriberi, wet beriberi with CHF

Mechanism

Replacement

Dosage with Qualifiers

Dietary supplement—1.1mg PO qd
Wernicke's encephalopathy—100mg IV ×1, then 50-100mg IM/IV qd
Beriberi—10-20mg IM tid ×2w
Wet beriberi with CHF—10-30mg IV tid

- **Contraindications**—hypersensitivity to drug or class
- **Caution**—unknown

Maternal Considerations

Pure **thiamine** deficiency is rare. Multiple vitamin deficiencies should be suspected in any case of dietary inadequacy. There are no adequate reports or well-controlled studies of **thiamine** in pregnant women. Despite its inclusion in prenatal vitamins, **thiamine** deficiency is not uncommon during pregnancy. Wernicke's encephalopathy is reported during pregnancy, often in association with hyperemesis. When given as part of a multivitamin prenatal supplement, **thiamine** improves weight gain among HIV-infected women.
Side effects include cyanosis, angioedema, pruritus, urticaria, warmth, and injection site reaction.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. **Thiamine** is actively transported across the human placenta, reaching an F:M ratio of 10. Thus, maternal supplementation is unlikely to alter the fetal **thiamine** to any clinically relevant extent.

Breastfeeding Safety

There are no adequate reports or well-controlled studies in nursing women. **Thiamine** enters human breast milk, and maternal supplementation increases milk content. The **thiamine** content in milk from unsupplemented women is considered inadequate for requirements of the neonate.

Drug Interactions — No clinically relevant interactions identified.

References

Baker H, DeAngelis B, Holland B, et al. J Am Coll Nutr 2002; 21:33-7.
Link G, Zempleni J, Bitsch I. Int J Vitam Nutr Res 1998; 68:242-8.
Nail PA, Thomas MR, Eakin R. Am J Clin Nutr 1980; 33:198-204.
Villamor E, Msamanga G, Spiegelman D, et al. Am J Clin Nutr 2002; 76:1082-90.
Zempleni J, Link G, Kubler W. Int J Vitam Nutr Res 1992; 62:165-72.

Summary

Pregnancy Category: A
Lactation Category: S
- **Thiamine** is a standard component of prenatal vitamins, yet **thiamine** deficiency is not rare.
- Attention to **thiamine** replacement is important in women with presumed hyperemesis.

Thioguanine—(Tabloid)

International Brand Name—Lanvis (Belgium, Bulgaria, Canada, England, Finland, France, Greece, Hong Kong, Hungary, Israel, Malaysia, Netherlands, Sweden, Switzerland, Taiwan, Thailand)

Drug Class — Antineoplastics, antimetabolite

Indications — Acute nonlymphocytic leukemia

Mechanism — Purine analog that interfere with nucleic acid biosynthesis

Dosage with Qualifiers

Acute nonlymphocytic leukemia—multiple dosing regimens, typically as part of a multidrug protocol

- **Contraindications**—hypersensitivity to drug or class
- **Caution**—unknown

Maternal Considerations

There are no adequate reports or well-controlled studies of **thioguanine** in pregnant women. The published literature includes only case reports.
Side effects include bone marrow suppression, hyperuricemia, N/V, anorexia, stomatitis, intestinal necrosis and perforation, jaundice, and hepatomegaly.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. It is likely **thioguanine** crosses the human placenta, but in low concentration. In one case report, the 6-thioguanine nucleotide level was significantly lower in the erythrocytes of the infant compared to the mother (ratio 1:12). While most of the reported cases end with a normal outcome, few women receive monotherapy. It is possible **thioguanine** is at least a modest teratogen in humans. **Thioguanine** is teratogenic in rats at 5× the MRHD, causing embryotoxicity and an increased prevalence of cranial defects, general skeletal hypoplasia, hydrocephalus, ventral hernia, situs inversus, incomplete limb development, and IUGR.

Breastfeeding Safety

There is no published experience in nursing women. It is unknown whether **thioguanine** enters human breast milk. However, the **thioguanine** metabolite of **azathioprine** apparently does not enter breast milk to a detectable level.

Drug Interactions There is usually complete cross-resistance with **mercaptopurine.** Use caution when treating patients also taking an aminosalicylate derivative (e.g., **mesalazine, olsalazine, sulphasalazine**) as there is *in vitro* evidence they inhibit the TPMT enzyme.

References

de Boer NK, Van Elburg RM, Wilhelm AJ, et al. Scand J Gastroenterol 2005; 40:1374-7.
De Souza JJ, Bezwoda WR, Jetham D, Sonnendecker EW. S Afr Med J 1982; 62:295-6.
Requena A, Velasco JG, Pinilla J, Gonzalez-Gonzalez A.Eur J Obstet Gynecol Reprod Biol 1995; 63:139-41.
Sau A, Clarke S, Bass J, et al. BJOG 2007; 114:498-501.
Schafer AI. Arch Intern Med 1981; 141:514-5.

Summary

Pregnancy Category: D
Lactation Category: U

- **Thioguanine** may be used in life-threatening scenarios during pregnancy and lactation where maternal benefit takes precedence.
- The possibility **thioguanine** is a modest human teratogen has not been excluded.

Thiopental—(Pentothal)

International Brand Name—Anesthal (India); Hypnostan (Finland); Intraval (Israel, Puerto Rico); Nesdonal (France, Netherlands); Pentothal Sodico (Peru); Pentothal Sodium (Hong Kong, Indonesia); Sodipental (Colombia, Mexico); Thionyl (Korea); Thiopental (Israel); Tiopental Sodico (Colombia, Ecuador); Trapanal (Germany)

Drug Class Anesthesia, induction/maintenance; Barbiturates

Indications Induction and maintenance of anesthesia, increased ICP

Mechanism CNS depressant

Dosage with Qualifiers Induction and maintenance of anesthesia—*induction:* 4-6mg/kg IV; *maintenance:* 50-100mg IV, repeat as necessary for short surgical procedures
Increased ICP—1.5-3.5mg/kg IV in patients being mechanically hyperventilated; repeat as necessary before continuous IV infusion or substitution with **pentobarbital**

- **Contraindications**—hypersensitivity to drug or class, porphyria
- **Caution**—hepatic or renal dysfunction, severe CV disease, hypotension, increased ICP, myasthenia gravis, status asthmaticus

Maternal Considerations **Thiopental** is an ultra-short-acting CNS depressant in use for more than 60y. It induces hypnosis and anesthesia, but not analgesia. Recovery after a small dose is rapid, with some somnolence and retrograde amnesia. Repeated IV doses lead to prolonged anesthesia because the fatty tissues act as a reservoir. There are no adequate reports or well-controlled studies of **thiopental** in pregnant women. It remains a popular agent for rapid-sequence induction of general anesthesia for cesarean section. Hypotension and awareness are more common when it is used for induction than when **ketamine** is used.
Side effects include habituation, respiratory depression, CV collapse, arrhythmia, hypotension, tachycardia, thrombophlebitis, bradycardia, and dyspnea.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. **Thiopental** rapidly crosses the human placenta, achieving an F:M ratio approximating 0.8 within 5min of maternal IV administration. However, the long clinical history of use in pregnant women is reassuring. Peak levels occur in the fetal rat in 10min. In the fetal sheep, **thiopental** reduces cerebral blood flow and oxygen delivery, suggesting it should be avoided during a delivery for fetal distress. Rodent teratogen studies have not been performed. **Thiopental** is a teratogen in the chick embryo, increasing the prevalence of CNS malformations.

Breastfeeding Safety

There are no adequate reports or well-controlled studies in nursing women. **Thiopental** enters human breast milk, but the concentrations are negligible by 36h postoperatively.

Drug Interactions

Action may be prolonged by **probenecid.**
May be antagonized by **aminophylline** and **zimelidine.**

References

Andersen LW, Qvist T, Hertz J, Mogensen F. Acta Anaesthesiol Scand 1987; 31:30-2.
Esener Z, Sarihasasan B, Guven H, Ustun E. Br J Anaesth 1992; 69:586-8.
Krissel J, Dick WF, Leyser KH, et al. Eur J Anaesthesiol 1994; 11:115-22.
Morgan DJ, Blackman GL, Paull JD, Wolf LJ. Anesthesiology 1981; 54:474-80.
Novitt AD, Gilani SH. J Clin Pharmacol 1979; 19:697-700.
Pickering BG, Palahniuk RJ, Cote J, et al. Can Anaesth Soc J 1982; 29:463-7.

Summary

Pregnancy Category: C
Lactation Category: S

- **Thiopental** has been used as an adjunct for general anesthesia for decades without obvious pregnancy-specific risk.

Thioridazine—(Dazine; Meleretten; Mellaril; Mellaril-S; Novoridazine; Sonapex; Thinin; Winleril)

International Brand Name—Aldazine (Malaysia); Calmaril (Thailand); Mallorol (Sweden); Meleril (Argentina, Colombia, Peru, Spain); Melleretten (Austria, Germany, Italy, Netherlands, Switzerland); Melleril (Hong Kong, Indonesia, Japan, Mexico, Philippines, Poland, Sweden, Taiwan); Mellerzin (Taiwan); Mepiozin (Japan); Orsanil (Finland); Ridazin (Israel); Ridazine (Thailand); Thiomed (Thailand); Thioril (India); Thiosia (Thailand)

Drug Class

Antipsychotics; Phenothiazines

Indications

Refractory schizophrenia

Mechanism

Unknown; dopamine D_2 antagonist

Dosage with Qualifiers

Refractory schizophrenia—begin 50-100mg PO qd after baseline ECG and potassium; max 800mg/d

- **Contraindications**—hypersensitivity to drug or class, severe hypertension, hypotension, prolonged QT interval, arrhythmia, CNS depression, coma, narrow-angle glaucoma, electrolyte imbalance, paralytic ileus, GI obstruction, bone marrow depression, decreased CYP2D6 levels
- **Caution**—hepatic dysfunction, CV disease, CNS depressants, seizures, Parkinson's disease

Maternal Considerations	There are no adequate reports or well-controlled studies of **thioridazine** in pregnant women. The published literature is confined to case reports. ***Side effects*** include paralytic ileus, neuroleptic malignant syndrome, tardive dyskinesia, torsades de pointes, arrhythmia, menstrual irregularities, cholestatic jaundice, blood dyscrasias, seizures, QT interval prolongation, drowsiness, dry mouth, constipation, nausea, blurred vision, akathisia, tremor, weight gain, edema, galactorrhea, agranulocytosis, and skin or ocular pigmentation.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **thioridazine** crosses the human placenta.
Breastfeeding Safety	There is no published experience in nursing women. It is unknown whether **thioridazine** enters human breast milk.
Drug Interactions	Metabolism reduced by drugs that inhibit CYP2D6 (e.g., **fluoxetine, paroxetine**), and certain other drugs (e.g., **fluvoxamine, pindolol, propranolol**). The resulting increased **thioridazine** levels may increase the risk of serious, potentially fatal, cardiac arrhythmias, such as torsades de pointes–type arrhythmias. Therefore, **thioridazine** is contraindicated with these drugs and in patients who have a genetic defect leading to reduced levels of CYP2D6 (about 7% of the normal population).
References	Scanlan FJ. Med J Aust 1972; 1:1271-2.
Summary	**Pregnancy Category: C** **Lactation Category: U** • **Thioridazine** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Thiothixene—(Navane)

International Brand Name—Onaven (Korea); Orbinamon (Germany); Thixit (New Zealand)

Drug Class	Antipsychotics
Indications	Schizophrenia
Mechanism	Unknown; selective dopamine D_2 antagonist
Dosage with Qualifiers	Schizophrenia—begin 2-5mg PO tid; max 60mg/d • **Contraindications**—hypersensitivity to drug or class, coma, CNS depression, blood dyscrasias • **Caution**—seizures, glaucoma, alcohol withdrawal, CAD
Maternal Considerations	There are no adequate reports or well-controlled studies of **thiothixene** in pregnant women. The published literature consists of a single case report. ***Side effects*** include neuroleptic malignant syndrome, seizures, tardive dyskinesia, agranulocytosis, drowsiness, restlessness, agitation, insomnia, hypotension, blurred vision, dry mouth, acute withdrawal syndrome, tachycardia, photosensitivity, and elevated LFTs.

Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **thiothixene** crosses the human placenta. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically.
Breastfeeding Safety	There is no published experience in nursing women. It is unknown whether **thiothixene** enters human breast milk.
Drug Interactions	No clinically relevant interactions identified.
References	Milhovilovic M. Neuropsihijatrija 1970; 18:261-3.
Summary	**Pregnancy Category: C** **Lactation Category: U** • **Thiothixene** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Tiagabine—(Gabitril)

International Brand Name—Gabatril (Mexico); Gabitril (Australia, Austria, Denmark, England, France, Germany, Ireland, Italy, Poland)

Drug Class	Anticonvulsants
Indications	Complex partial seizures
Mechanism	Unknown
Dosage with Qualifiers	Complex partial seizures—begin 4mg PO qd, increase prn to 56mg/d in divided doses with food *NOTE: taper slowly to avoid withdrawal seizures.* • **Contraindications**—hypersensitivity to drug or class • **Caution**—hepatic dysfunction, EEG spike/wave
Maternal Considerations	**Tiagabine** is a 2nd-generation anticonvulsant frequently employed as adjunct therapy. It is not an enzyme inducer, and there is no interaction between **tiagabine** and oral contraceptive agents. There are no adequate reports or well-controlled studies of **tiagabine** in pregnant women. No systematic information is available on the pharmacokinetics during pregnancy. Caution dictates maternal levels be measured periodically. ***Side effects*** include CNS depression, withdrawal seizures, dizziness, asthenia, somnolence, N/V, impaired memory, and nervousness.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **tiagabine** crosses the human placenta. **Tiagabine** is a rodent teratogen, increasing the prevalence of craniofacial, appendicular, and visceral defects in addition to IUGR.
Breastfeeding Safety	There is no published experience in nursing women. It is unknown whether **tiagabine** enters human breast milk. It is excreted in rodent milk.
Drug Interactions	Population pK analyses suggest use with **carbamazepine** or **phenytoin** increases the **tiagabine** level by some 60%.

Population pK analyses also indicate that **tiagabine** clearance is 60% greater in patients taking **phenobarbital** or **primidone.** **Valproate** significantly decreased **tiagabine** binding *in vitro* from 96.3% to 94.8%, resulting in a 40% increase in the free **tiagabine** concentration. The clinical relevance of this *in vitro* finding is unknown.
As **tiagabine** is highly protein bound (96%), it has the potential to interact with other highly protein bound compounds. Such an interaction can potentially lead to higher free fractions of either **tiagabine** or the competing drug.

References ..... Crawford P. CNS Drugs 2002; 16:263-72.

Summary .....

Pregnancy Category: C
Lactation Category: U
- **Tiagabine** should probably be avoided during pregnancy and lactation unless there is no other option.

Ticarcillin—(Ticar; Timentin)

International Brand Name—Ticarcin (Korea); Ticarpen (Czech Republic, Netherlands, Spain); Triacilline (Belgium)

Drug Class ..... Antibiotics; Penicillins

Indications ..... Bacterial infection, including septicemia, skin and soft tissue infection, and acute and chronic respiratory infection

Mechanism ..... Bactericidal—inhibits cell wall mucopeptide synthesis

Dosage with Qualifiers ..... Bacterial infection—3-4g IV/IM q4-6h, or 200-300mg/kg IV divided q4-6h; max 24g/d

NOTE: renal dosing; may be combined with ***clavulanate*** *(Timentin) to extend bacterial coverage.*

- **Contraindications**—hypersensitivity to drug or class
- **Caution**—cephalosporin allergy, renal dysfunction, seizures, sodium restriction, bleeding disorder

Maternal Considerations .....

Ticarcillin is an extended-spectrum penicillin. It is primarily indicated for gram-negative infections and is often combined with an aminoglycoside. Clavulanic acid is a β-lactam that inactivates a wide range of β-lactamase enzymes commonly found in microorganisms resistant to penicillins and cephalosporins. The combination of **ticarcillin-clavulanate** has a microbiologic spectrum similar to **gentamicin** and **clindamycin.** There are no adequate reports or well-controlled studies of **ticarcillin** in pregnant women. Like other antibiotics, it reduces the risk of postpartum endomyometritis in women with PPROM, but may increase the proportion of neonates with sepsis secondary to **ampicillin**-resistant organisms.
Side effects include seizures, thrombocytopenia, Stevens-Johnson syndrome, neutropenia, rash, urticaria, prolonged bleeding time, bleeding, headache, dizziness, hypokalemia, hypernatremia, fatigue, fever, pseudomembranous colitis, flatulence, phlebitis, and elevated LFTs.

Fetal Considerations ..... There are no adequate reports or well-controlled studies in human fetuses. Transfer of **ticarcillin** across the human placenta is slow,

but it does accumulate in the fetal compartment over time. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically.

Breastfeeding Safety — There are no adequate reports or well-controlled studies in nursing women. **Ticarcillin** enters human breast milk. However, the quantity (2-2.5mg/L) is too low to have clinical relevance.

Drug Interactions — No clinically relevant interactions identified.

References

Edwards RK, Locksmith GJ, Duff P. Obstet Gynecol 2000; 96:60-4.
Fortunato SJ, Bawdon RE, Swan KF, et al. Am J Obstet Gynecol 1992; 167:1595-9.
Von Kobyletzki D, Dalhoff A, Lindemeyer H, Primavesi CA. Infection 1983; 11:144-9.

Summary

Pregnancy Category: B
Lactation Category: S

- **Ticarcillin** is generally considered safe during pregnancy and lactation for the indicated uses.

Ticlopidine—(Ticlid)

International Brand Name—Agulan (Indonesia); Anagregal (Italy); Antigreg (Malaysia, Singapore); Aplaket (Malaysia, Singapore, Thailand); Cartrilet (Indonesia); Cenpidine (Thailand); Clid (Korea); Clotidone (Philippines); Crodin (Korea); Declot (China, Taiwan); Desitic (Germany); Goclid (Indonesia); Licodin (China, Taiwan); Nufaclapide (Indonesia); Panaldine (Japan); Siclot (Thailand); Tacron (Korea, Singapore); Ticard (Thailand); Ticdine (Thailand); Ticlid (Australia, Belgium, Bulgaria, China, Czech Republic, France, Greece, Hong Kong, Hungary, Indonesia, Malaysia, Philippines, Poland, South Africa, Switzerland, Taiwan, Thailand); Ticlidil (Israel); Ticlodix (Portugal); Ticlodone (Greece, Italy, Korea, Spain); Ticlomed (France); Ticlon (Korea); Ticuring (Indonesia); Tikleen (India); Tiklid (Austria, Italy, Spain); Tiklyd (Germany); Tikol (Thailand); Tilodene (Australia, Singapore); Tiodin (Singapore); Tipidin (Hong Kong, Malaysia, Singapore); Tipidine (Thailand); Tyklid (India); Viladil (Thailand)

Drug Class — Platelet inhibitors

Indications — Thrombotic stroke prophylaxis

Mechanism — Inhibits ADP-induced platelet fibrinogen binding

Dosage with Qualifiers

Thrombotic stroke prophylaxis—250mg PO bid with meals

- **Contraindications**—hypersensitivity to drug or class, severe hepatic dysfunction, active bleeding, blood dyscrasias
- **Caution**—mild to moderate hepatic dysfunction

Maternal Considerations — **Ticlopidine** potentiates the effect of **aspirin** or other NSAIDs on platelet aggregation. There are no adequate reports or well-controlled studies of **ticlopidine** in pregnant women. The published experience is limited to case reports.
Side effects include pancytopenia, agranulocytosis, thrombocytopenia, intracranial hemorrhage, nephrotic syndrome, allergic pneumonitis, TTP, serum sickness, N/V, diarrhea, rash, hyponatremia, purpura, and neutropenia.

Fetal Considerations — There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **ticlopidine** crosses the human placenta. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically.

Breastfeeding Safety

There is no published experience in nursing women. It is unknown whether **ticlopidine** enters human breast milk. It is excreted into rodent milk.

Drug Interactions

Causes a 30% increase in the plasma t/2 of antipyrine and may have analogous effects on similarly metabolized drugs. Thus, the dose of drugs metabolized by hepatic microsomal enzymes with low therapeutic ratios or being given to patients with hepatic impairment may require adjustment.
Potentiates the effect of **aspirin** or other NSAIDs on platelet aggregation. The safety of the combination has not been established and it is not recommended.
Use after antacids may decrease plasma levels.
Cimetidine reduced the **ticlopidine** clearance by 50%.
May reduce the **theophylline** elimination t/2 from 8.6 to 12.2h with a comparable reduction in total plasma clearance of **theophylline.**

References

Rezig K, Diar N, Walcker JL. Ann Fr Anesth Reanim 2000; 19:544-8.
Ueno M, Masuda H, Nakamura K, Sakata R. Surg Today 2001; 31:1002-4.

Summary

Pregnancy Category: B
Lactation Category: U

- **Ticlopidine** is rarely indicated during pregnancy, but does not appear to require any unique considerations.
- There are alternative agents for which there is more experience regarding use during pregnancy and lactation.

Timolol—(Aquanil; Blocadren; Cusimolol; Dispatim; Equiton; Glauco-Opu; Glucolol; Glucomol; Nyolol; Ocupres; Optimol; Tiloptic; Timoptic; Timoptic-Xe; Timoptol; Timpotic)

International Brand Name—Apo-Timol (Canada); Apo-Timolol (New Zealand); Apo-Timop (Canada, New Zealand); Aquanil (Denmark, Finland, Norway, Sweden); Arutinol (Germany); Betim (Denmark, England, Greece, Ireland, Norway); Blocadren (Norway, Sweden); Blocanol (Finland); Cardina (Finland); Chibro-Timoptol (Germany); Cusimolol (Hungary, Spain); Digaol (France); Gen-Timolol (Canada); Glafemak (Greece); Glauco (Thailand); Glauco Oph (Thailand); Glaucopress (Indonesia); Glucomol (India); Hypermol (New Zealand); Imot Ofteno Al (Costa Rica, Dominican Republic, El Salvador, Guatemala, Honduras, Mexico, Nicaragua, Panama); Isotic Adretor (Indonesia); Molotic Eye Ocupres (India); Noval (Greece); Novo-Timol (Canada); Nylol (Israel); Nyogel (England, Ireland); Nyogel LP (France); Nyolol (Colombia, Mexico, Singapore, Taiwan); Nyolol Gel (Korea); Ocupres (India, South Africa); Ofal (Argentina); Ofan (Thailand); Oftan Timolol (China); Optimol (Australia, Denmark, Sweden); Proflax (Argentina); Temserin (Germany, Greece); Tenopt (Australia); Tilmat (New Zealand); Tiloptic (Israel); Timabak (Hong Kong, Singapore); Timacar (Denmark); Timacor (France); Timoftol (Spain); Timohexal (Germany, Hungary); Timol (Taiwan); Timolo (India); Timolol-POS (Israel); Tim Ophtal (Indonesia); Timoptic (Austria, Bulgaria, Canada, Czech Republic, Hungary, Japan, Korea, Switzerland); Timoptol (Belgium, China, Ecuador, England, France, Germany, Hong Kong, Ireland, Italy, Japan, Malaysia, Mexico, Netherlands, Philippines, Taiwan, Thailand); Timoptol-XE (China, Hong Kong, New Zealand, Peru, Philippines, Singapore); Timozzard (Mexico); Titol (Denmark); Unitimo (Korea); Ximex Opticom (Indonesia); Yesan (Greece)

Drug Class

Adrenergic antagonists; β-Blockers

Indications

Hypertension, angina, acute MI, migraine prophylaxis, glaucoma

Mechanism

Nonselective β-blocker

Dosage with Qualifiers

Hypertension—begin 10mg PO bid; max 60mg/d
Angina—5-15mg PO tid

Acute MI—10mg PO bid within 4w of MI
Migraine prophylaxis—10mg PO bid
Elevated intraocular pressure—1gtt qd or bid

- **Contraindications**—hypersensitivity to drug or class, CHF, bradycardia, 2nd or 3rd degree heart block, asthma, cardiogenic shock
- **Caution**—hepatic or renal dysfunction, diabetes mellitus

Maternal Considerations

There are no adequate reports or well-controlled studies of **timolol** in pregnant women. **Timolol** is superior to α-**methyldopa** for the treatment of puerperal hypertension. It is unclear whether **timolol** offers any therapeutic advantage over another β-blocker. There are only case reports of its use to treat glaucoma.
Side effects include CHF, bradycardia, hypotension, bronchospasm, fatigue, dizziness, headache, dyspnea, pruritus, nightmares, and Raynaud's syndrome.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. **Timolol** crosses the isolated perfused human placenta, though the *in vivo* kinetics remain to be elucidated. It decreases the FHR after administration to the ewe. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically.

Breastfeeding Safety

There are no adequate reports or well-controlled studies in nursing women. **Timolol** is excreted into human milk, achieving an M:P ratio of 0.8 in one study, but higher in another. In one woman using eye drops, the milk concentration ranged from 0-0.4 ng/ml. The theoretic relative infant dose would be 0.024%.

Drug Interactions

Use of the opthalmic preparation with **epinephrine** may cause mydriasis.
Use with calcium channel antagonists may cause AV conduction disturbances, LV failure, and hypotension. Avoid in patients with impaired cardiac function. Hypotension is more likely to occur if the calcium antagonist were a dihydropyridine derivative (e.g., **nifedipine**), while LV failure and AV conduction disturbances are more likely to occur with either **verapamil** or **diltiazem.**
Use with catecholamine-depleting drugs such as **reserpine** may cause hypotension and/or marked bradycardia, resulting in vertigo, syncope, or postural hypotension.
Use with **digitalis** and calcium antagonists may have additive effects in prolonging AV conduction time.
Use with **quinidine** may potentiate the level of systemic β-blockade (e.g., decreased HR) perhaps because **quinidine** inhibits CYP2D6.
Oral β-adrenergic blocking agents may exacerbate the rebound hypertension associated with **clonidine.**
Use with NSAIDs may blunt the hypotensive effect.
Patients with a history of atopy or a history of severe anaphylactic reaction to a variety of allergens may be more reactive to repeated accidental, diagnostic, or therapeutic challenge with such allergens while taking β-blockers. Such patients may be unresponsive to the usual doses of **epinephrine** used to treat anaphylactic reactions.

References

Fidler J, Smith V, De Swiet M. Br J Obstet Gynaecol 1983; 90:961-5.
Madadi P, Koren G, Freeman DJ, et al. J Glaucoma 2008; 17:329-31.
Schneider H, Proegler M. Am J Obstet Gynecol 1988; 159:42-7.

Summary

Pregnancy Category: C
Lactation Category: S (likely)
- **Timolol** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.
- There are alternative agents for which there is more experience regarding use during pregnancy and lactation.

Tinzaparin—(Innohep)

International Brand Name—Innohep (Argentina, Belgium, Canada, Colombia, Costa Rica, Denmark, Dominican Republic, El Salvador, England, France, Germany, Guatemala, Honduras, Hong Kong, Ireland, Israel, Italy, Malaysia, Netherlands, New Zealand, Panama, Philippines, Singapore, Thailand); Logiparin (Austria, Denmark, England, Finland, Greece, India, Netherlands, Sweden, Switzerland)

Drug Class

Anticoagulants; Antithrombotics; LMWHs

Indications

DVT

Mechanism

Binds ATIII, accelerating its anti-Xa activity

Dosage with Qualifiers

DVT—175 anti-Xa IU/kg SC qd at least 6d in hospitalized patients; overlap with **warfarin** until therapeutic INR

NOTE: renal dosing.

- **Contraindications**—hypersensitivity to drug or class, hypersensitivity to pork products, active or recent bleeding, conduction anesthesia, thrombocytopenia, history of heparin-induced thrombocytopenia
- **Caution**—bleeding tendency, recent major surgery, bacterial endocarditis, uncontrolled hypertension, diabetic retinopathy, platelet inhibitors, renal dysfunction

Maternal Considerations

Thromboembolic disease remains a major cause of pregnancy morbidity and death. **Tinzaparin** is an LMWH extracted from pig. It is at least as effective as unfractionated **heparin** for the treatment and prevention of thromboembolic disease. Post-cesarean section, it reduces thrombin-antithrombin complex concentration more effectively than **enoxaparin.** It is unknown whether that enhancement means improved prophylaxis. Most anesthesiologists prefer to wait 24h after the last dose of **tinzaparin** (even if given 175U/kg qd) before induction of neuraxial anesthesia. Because the clearance of other LMWHs are increased by pregnancy, it is probably best to monitor anti-Xa activity at least once per trimester and administer the drug in 2 divided doses beginning with 250IU/kg qd. In support of this conclusion, one study noted that women receiving **tinzaparin** (50IU/kg) frequently had peak (4h) anti-Xa levels <0.1IU/ml and that 46% of these patients required dose adjustment. Likewise, anti-Xa activity was found to be low over the 24h period. A starting dose of 75IU/kg, once daily, gave greater anti-Xa cover over the 24h period. The findings suggest the pharmacokinetics of **tinzaparin** are affected by pregnancy.
Side effects include hemorrhage, hematoma, skin necrosis, Stevens-Johnson syndrome, injection site reaction, and elevated LFTs.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. **Tinzaparin** does not cross the human placenta. Rodent studies are reassuring, revealing no evidence of

teratogenicity or IUGR despite the use of doses higher than those used clinically.

Breastfeeding Safety ..... There are no adequate reports or well-controlled studies in nursing women. It is unknown whether **tinzaparin** enters human breast milk.

Drug Interactions ..... Use with caution in patients receiving oral anticoagulants, platelet inhibitors (e.g., **dextran, dipyridamole,** NSAIDs [including **ketorolac**], **salicylates,** sulfinpyrazone), and thrombolytics because of an increased risk of bleeding.

References .....

Ellison J, Thomson AJ, Conkie JA, et al. Thromb Haemoat 2001; 86:1374-8.
Lykke JA, Gronlykke T, Langhoff-Roos J. Acta Obstet Gynecol Scand 2008; 87:1248-51.
Norris LA, Bonnar J, Smith MP, et al. Thromb Haemost 2004; 92:791-6.
Samama MM, Gerotziafas GT. Semin Thromb Hemost 2000; 26(Suppl 1):31-8.

Summary .....

Pregnancy Category: B
Lactation Category: U

- **Tinzaparin** is an alternative to **heparin** and other LMWHs during pregnancy, but has no clear advantage.

Tizanidine—(Zanaflex)

International Brand Name—Sirdalud (Bulgaria, Colombia, England, France, Greece, India, Indonesia, Ireland, Korea, Mexico, Norway, Peru, Philippines, Poland, Puerto Rico, Slovenia, South Africa, Sweden, Taiwan, Thailand); Sirdalud MR (Netherlands, Switzerland); Sirdalud Retard (Denmark, Finland); Ternelax (Philippines); Ternelin (Japan)

Drug Class ..... Adrenergic agonists; Musculoskeletal agents; Muscle relaxants

Indications ..... Spasticity

Mechanism ..... Mechanism unknown; centrally acting α_2-adrenergic agonist

Dosage with Qualifiers ..... Spasticity—4-8mg PO q8h prn; max 36mg/d

NOTE: renal dosing.
NOTE: taper slowly to minimize the risk of withdrawal and rebound hypertension, tachycardia, and hypertonia.

- **Contraindications—**hypersensitivity to drug or class
- **Caution—**renal dysfunction, oral contraceptives

Maternal Considerations ..... **Tizanidine** is effective for the treatment of tension headache and the spasticity associated with MS. Sedation is common. There are no adequate reports or well-controlled studies in pregnant women. Retrospective analysis of population pharmacokinetic data after single- and multiple-dose administration of 4mg showed women taking oral contraceptives had 50% lower clearance compared to women not on oral contraceptives. ***Side effects*** include hepatotoxicity, severe bradycardia, hypotension, dizziness, hallucinations, dry mouth, sedation, somnolence, asthenia, UTI, infection, constipation, pharyngitis, rhinitis, and increased spasm.

Fetal Considerations ..... There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **tizanidine** crosses the

human placenta. Rodent studies are predominantly reassuring, though the doses tested were only modest multiples of the MRHD. They reveal some evidence of prolonged pregnancy and embryotoxicity.

Breastfeeding Safety

There are no adequate reports or well-controlled studies in nursing women. It is unknown whether **tizanidine** enters human breast milk.

Drug Interactions

Ethanol increased the AUC of **tizanidine** by some 20% while also increasing its C_{max} by approximately 15%. This increase was associated with an increase in side effects. The CNS depressant effects of **tizanidine** and ethanol are additive.
Retrospective analysis of population pharmacokinetic data suggests that women also taking oral contraceptives have 50% lower clearance of **tizanidine.**
Rofecoxib may potentiate the adverse effects of **tizanidine.** Eight case reports of a potential **rofecoxib-tizanidine** drug interaction have been identified in post-marketing safety reports. Most of the adverse events involved the nervous system (e.g., hallucinations, psychosis, somnolence, hypotonia) and the CV system (e.g., hypotension, tachycardia, bradycardia). In all cases, the symptoms resolved following discontinuation of **tizanidine, rofecoxib,** or both. Rechallenges were not performed. The possible mechanism remains unclear.

References

There is no published experience in pregnancy or during lactation.

Summary

Pregnancy Category: C
Lactation Category: U
- **Tizanidine** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Tobramycin—(Aktob; Nebcin; Tobradistin; Tobrasix; Tobrex; Toround; Trazil)

International Brand Name—Artobin (Philippines); Bralifex (Indonesia); Cleo (Taiwan); Eyebrex (Philippines, Taiwan); Ikobel (Greece); Isotic Tobryne (Indonesia); Obry (Mexico); Ocumicin (Colombia); Ocuracin (Korea); Tirselon (Greece); Tobacin (India, Korea); Toberan (Korea); Tobramaxin (Germany); Tobrimin (Dominican Republic); Tobrin (Israel); Toravin (Korea); Trazil (El Salvador, Guatemala, Honduras, Nicaragua, Panama); Trazil ofteno (Mexico); Tronamycin (Korea)

Drug Class

Aminoglycosides; Antibiotics; Ophthalmics

Indications

Bacterial infection, endocarditis prophylaxis, cystic fibrosis, ocular infection

Mechanism

Bactericidal; binds 30S ribosomal subunit inhibiting protein synthesis

Dosage with Qualifiers

Bacterial infections—3-5mg/kg/d in divided doses
Endocarditis prophylaxis—1.5mg/kg IV 30-60min pre-procedure
Cystic fibrosis—300mg NEB q12h following 28d on/off cycles
Ocular infection—1-2gtt OS/OD q4-6h

NOTE: peak 4-12mcg/ml, trough 0.5-2mcg/ml after parenteral use.

- **Contraindications**—hypersensitivity to drug or class
- **Caution**—myasthenia gravis, vestibular/cochlear implant, nephrotoxic agents, renal dysfunction

Maternal Considerations

There are no adequate reports or well-controlled studies of **tobramycin** in pregnant women. The clearance of **tobramycin** during pregnancy and the puerperium is increased, requiring 3mg/kg or more to obtain adequate peak and trough levels. ***Side effects*** include nephrotoxicity, ototoxicity, neurotoxicity, pseudotumor cerebri, enterocolitis, diarrhea, N/V, pruritus, rash, weakness, tremor, muscle cramps, anorexia, headache, edema, increased salivation, tinnitus, vertigo, agranulocytosis, thrombocytopenia, elevated BUN/Cr, and muscle weakness.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **tobramycin** crosses the human placenta. Other aminoglycoside antibiotics do cross, and there are reports of total, irreversible, bilateral congenital deafness after **streptomycin.** Serious side effects to mother, fetus, or newborn are not reported after treatment with other aminoglycosides. **Tobramycin** likely poses no greater risk than **gentamicin** to the fetus. Systemic levels are much lower after nebulizer or ophthalmic administration compared to parenteral route. In the rat, **tobramycin** accumulates in the placenta. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically. The highest doses caused excess maternal toxicity with increased fetal wastage.

Breastfeeding Safety

There are no adequate reports or well-controlled studies in nursing women. Small amounts of **tobramycin** are excreted into human breast milk. Milk levels ranged from undetectable to 0.5mcg/ml in a study of 5 women treated with 80mg IM. As **tobramycin** is poorly absorbed orally, it is very unlikely the unsupplemented neonate would achieve a clinically relevant level.

Drug Interactions

Use with other drugs having neurotoxic or ototoxic potential should be avoided. Some diuretics enhance aminoglycoside toxicity by altering antibiotic concentrations in serum and tissue. Should not be used with **ethacrynic acid, furosemide, mannitol,** or **urea.**

References

Ferrini AM, Aureli P, Ricciardi C, et al. Pharmacol Res 1992; 26:277-84.
Festini F, Ciuti R, Taccetti G, et al. J Matern Fetal Neonatal Med 2006; 19:375-6.
Takase Z. Chemotherapy (Tokyo) 1975; 23:1402.

Summary

Pregnancy Category: D (**B** for ophthalmic applications)
Lactation Category: S

- **Tobramycin** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.
- There are alternative agents for which there is more experience regarding use during pregnancy and lactation.

Tocainide—(Tonocard)

International Brand Name—None identified.

Drug Class

Antiarrhythmics, class IB

Indications

Ventricular arrhythmia

Mechanism

Depresses phase 0 action, potential, stabilizing the membrane

Dosage with Qualifiers

Ventricular arrhythmia—begin 400mg PO q8h; max 2g/d; alternately, 7.5-11.3mg/kg IV over 15min

- **Contraindications**—hypersensitivity to drug or class, CHF, 2nd or 3rd degree heart block, hepatic or renal dysfunction
- **Caution**—unknown

Maternal Considerations

Tocainide is similar to **lidocaine.** There is no published experience with **tocainide** during pregnancy.
Side effects include blood dyscrasias, pulmonary fibrosis, CHF, ventricular arrhythmia, respiratory arrest, pulmonary edema, pneumonitis, dizziness, N/V, diarrhea, rash, nervousness, tremor, confusion, anorexia, mood changes, ataxia, blurred vision, paresthesias, arthritis, tachycardia, and hypotension.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **tocainide** crosses the human placenta. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically. Embryotoxicity occurs at high doses with maternal toxicity.

Breastfeeding Safety

There are no adequate reports or well-controlled studies in nursing women. **Tocainide** enters human breast milk, though the kinetics remain to be elucidated.

Drug Interactions

Pharmacodynamically similar to **lidocaine.** Their use together may cause an increased incidence of adverse reactions, including CNS adverse reactions such as seizure.

References

Wilson JH. J Cardiovasc Pharmacol 1988; 12:497.

Summary

Pregnancy Category: C
Lactation Category: U

- **Tocainide** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.
- There are alternative agents for which there is more experience regarding use during pregnancy and lactation.

Tolazamide—(Diabewas; Tolinase; Tolisan)

International Brand Name—Desumide (Taiwan); Norglycin (Germany); Tolanase (England, Ireland)

Drug Class

Hypoglycemics; Sulfonylureas

Indications

Diabetes mellitus type 2

Mechanism

Stimulates islet cell insulin release

Dosage with Qualifiers

Diabetes mellitus type 2—100-250mg PO qd; max 1g/d

- **Contraindications**—hypersensitivity to drug or class, hypersensitivity to sulfonamides
- **Caution**—unknown

Maternal Considerations

Diet remains the first-line treatment of diabetes mellitus type 2. Caloric restriction and weight loss are essential in the obese diabetic patient, and may alone be effective controlling blood glucose and symptoms. The importance of regular physical

activity should be stressed, and CV risk factors identified and corrected if possible. When this approach fails, oral hypoglycemic agents may be indicated. **Tolazamide** is a first-generation sulfonylurea. Sulfonylureas may be associated with an excess of CV death. There are no adequate reports or well-controlled studies of **tolazamide** in pregnant women. Additional study is necessary. Other oral hypoglycemic agents (e.g., **glyburide**) are poorly transported across the placenta.
Side effects include hypoglycemia, nausea, epigastric fullness, heartburn, leukopenia, agranulocytosis, thrombocytopenia, hemolytic anemia, aplastic anemia, pancytopenia, pruritus, erythema, urticaria, and morbilliform or maculopapular eruptions.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **tolazamide** crosses the human placenta. Prolonged, severe hypoglycemia (4-10d) has been reported in neonates delivered to women receiving a sulfonylurea at the time of delivery. This is most common with agents with a prolonged t/2. **Tolazamide** should be discontinued at least 2w before the EDC. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically. Only with the highest doses (>100× the MRHD) was embryotoxicity noted.

Breastfeeding Safety

There are no adequate reports or well-controlled studies in nursing women. It is unknown whether **tolazamide** enters human breast milk. Other sulfonylurea drugs are excreted into breast milk.

Drug Interactions

Hypoglycemic action may be potentiated by certain drugs, including β-adrenergic blocking agents, **chloramphenicol,** coumarins, MAOIs, NSAIDs and other drugs that are highly protein bound, **probenecid,** salicylates, and sulfonamides. When used with **tolazamide,** the patient should be closely observed for hypoglycemia.
Certain drugs (e.g., calcium channel–blocking drugs, corticosteroids, estrogens, **isoniazid, nicotinic acid,** oral contraceptives, phenothiazines, **phenytoin,** sympathomimetics, thiazides and other diuretics, thyroid products) tend to produce hyperglycemia and may lead to loss of control.
A potential interaction with **miconazole** leading to severe hypoglycemia has been reported.

References

There are no current relevant references.

Summary

Pregnancy Category: C
Lactation Category: U

- Though some oral hypoglycemic agents may have a role in the treatment of type 2 diabetes mellitus during pregnancy, there are alternative agents for which there is more experience regarding use during pregnancy and lactation.

Tolbutamide—(Aglicem; Aglycid; Ansulin; Diabecid-R; Dolipol; Fordex; Glucosulfa; Guabeta; Mobenol; Noglucor; Novobutamide; Orabet; Orinase; Orinase Diagnostic; Raston; Tolbusal; Tolbutamida Valdecases)

International Brand Name—Abemin (Japan); Arcosal (Denmark); Artosin (Netherlands); Diaben (Japan); Diatol (Hong Kong, New Zealand); Glyconon (England); Orsinon (Israel); Rastinon (Australia, Austria, Belgium, Denmark, England, Finland, Greece, Israel, Italy, Japan, Mexico, Portugal, Spain, Sweden, Switzerland); Tolsiran (Japan)

Drug Class	Hypoglycemics; Sulfonylureas
Indications	Diabetes mellitus type 2
Mechanism	Stimulates islet cell insulin release
Dosage with Qualifiers	Diabetes mellitus type 2—1-2g PO qd in divided doses; max 3g/d • **Contraindications**—hypersensitivity to drug or class, IDDM sole therapy, DKA • **Caution**—hypersensitivity to sulfonamides
Maternal Considerations	Diet remains the first-line treatment of diabetes mellitus type 2. Caloric restriction and weight loss are essential in the treatment of the obese diabetic patient, and may alone be effective in controlling blood glucose and symptoms. The importance of regular physical activity must also be stressed, and CV risk factors identified and corrected where possible. When this approach fails, oral hypoglycemic agents may be indicated. There are no adequate reports or well-controlled studies of **tolbutamide** in pregnant women. Efficient placental transport renders it a poor selection during pregnancy. ***Side effects*** include aplastic anemia, thrombocytopenia, bone marrow suppression, hypoglycemia, jaundice, leukopenia, SIADH, **disulfiram**-like reaction, headache, constipation, diarrhea, dyspepsia, anorexia, dizziness, rash, and photosensitivity.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. **Tolbutamide** crosses the human placenta relatively efficiently compared to **glyburide.** The fetal pancreas is responsive. Prolonged and severe hypoglycemia (4-10d) is reported in neonates born to mothers receiving a sulfonylurea at the time of delivery. This is more frequent with agents having a prolonged t/2. If **tolbutamide** is used during pregnancy, it should be discontinued at least 2w before the expected delivery date. **Tolbutamide** is teratogenic in rats, associated with an increased prevalence of ocular and bony abnormalities at doses 25-100× the MRHD. Similar studies in rabbits were negative.
Breastfeeding Safety	There are no adequate reports or well-controlled studies in nursing women. **Tolbutamide** enters human breast milk, but the kinetics remain to be elucidated.
Drug Interactions	Hypoglycemic action may be potentiated by certain drugs, including β-adrenergic blocking agents, **chloramphenicol,** coumarins, MAOIs, NSAIDs and other drugs that are highly protein bound, **probenecid,** salicylates, and sulfonamides. When used with **tolbutamide,** the patient should be closely observed for hypoglycemia.

Certain drugs (e.g., calcium channel–blocking drugs, corticosteroids, estrogens, **isoniazid, nicotinic acid,** oral contraceptives, phenothiazines, **phenytoin,** sympathomimetics, thiazides and other diuretics, thyroid products) tend to produce hyperglycemia and may lead to loss of control.
Concomitant ingestion of MAOIs, **oxyphenbutazone, phenylbutazone, probenecid,** salicylates, and sulfonamides, may interfere with results of a **tolbutamide** tolerance test.
A potential interaction with **miconazole** leading to severe hypoglycemia has been reported.

References

Christesen HB, Melander A. Eur J Endocrinol 1998; 138:698-701.
Elliott BD, Schenker S, Langer O, et al. Am J Obstet Gynecol 1994; 171:653-60.
Jensen DM, Sorensen B, Feilberg-Jorgensen N, et al. Diabet Med 2000; 17:281-6.
Moiel RH, Ryan JR. Clin Pediatr (Phila) 1967; 6:480.
Philipps AF, Dubin JW, Raye JR. Pediatr Res 1979;13:1375-8.

Summary

Pregnancy Category: C
Lactation Category: S

- Insulin remains the typical hypoglycemic agent of choice for the treatment of diabetes mellitus during pregnancy and lactation.
- However, in some patients, superior glycemic control may be achieved with an oral hypoglycemic agent (e.g., **glyburide**).

Tolmetin—(Donison; Midocil; Reutol; Safitex; Tolectin)

International Brand Name—None identified.

Drug Class

Analgesics, non-narcotic; NSAIDs

Indications

Osteoarthritis and rheumatoid arthritis

Mechanism

Unknown; inhibits cyclooxygenase and lipoxygenase, reducing prostaglandin synthesis

Dosage with Qualifiers

Osteoarthritis—200-600mg PO with food tid; max 1800mg/d
Rheumatoid arthritis—200-600mg PO with food tid; max 1800mg/d

- **Contraindications**—hypersensitivity to drug or class, ASA/NSAID-induced asthma
- **Caution**—nasal polyps, GI bleeding, hypertension, CHF

Maternal Considerations

There are no adequate reports or well-controlled studies of **tolmetin** in pregnant women.
Side effects include GI bleeding, acute renal failure, bronchospasm, Stevens-Johnson syndrome, interstitial nephritis, hepatotoxicity, dyspepsia, N/V, abdominal pain, headache, dizziness, rash, urticaria, drowsiness, tinnitus, agranulocytosis, thrombocytopenia, elevated LFTs, and fluid retention.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **tolmetin** crosses the human placenta. Rodent studies performed up to 1.5× the MRHD were reassuring, revealing no evidence of teratogenicity.

Some bone demineralization is seen at the highest doses. Other drugs in this class are known to cause constriction of the ductus arteriosus *in utero*. There is no reason to expect **tolmetin** is different.

Breastfeeding Safety

There are no adequate reports or well-controlled studies in nursing women. Small quantities of **tolmetin** are excreted into human breast milk. Though the kinetics remain to be elucidated, the milk level was only 0.18mg/ml 40min after 400mg PO.

Drug Interactions

Use with **warfarin** may be associated with an increased PT and bleeding.
As with other NSAIDs, use with **methotrexate** may reduce the tubular secretion of **methotrexate** and increase toxicity.
Ingestion with meals may reduce bioavailability.

References

Burdan F, Rozylo-Kalinowska I, Szumito J, et al. Cells Tissues Organs 2008; 187:221-32.
Sagraves R, Waller ES, Goehrs HR. Drug Intell Clin Pharm 1985; 19:55-6.

Summary

Pregnancy Category: C
Lactation Category: S (likely)
- **Tolmetin** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.
- There are many alternative agents for which there is more experience regarding use during pregnancy and lactation.

Tolterodine—(Detrol)

International Brand Name—Detrusitol (Colombia, England, France, Germany, Hong Kong, Indonesia, Ireland, Korea, Mexico, Peru, Philippines, Singapore, South Africa, Sweden, Taiwan, Thailand)

Drug Class

Antispasmodics; Urologics

Indications

Overactive bladder

Mechanism

Cholinergic receptor antagonist

Dosage with Qualifiers

Overactive bladder—2mg PO bid

NOTE: hepatic dosing.

- **Contraindications**—hypersensitivity to drug or class, narrow-angle glaucoma, gastric obstruction
- **Caution**—hepatic or renal dysfunction

Maternal Considerations

There is no published experience with **tolterodine** during pregnancy. There is also probably no indication for its use during pregnancy.
Side effects include anticholinergic psychosis, dry mouth, headache, dyspepsia, constipation, dry eyes, dizziness, blurred vision, somnolence, chest pain, cough, tachycardia, and peripheral edema.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **tolterodine** crosses the human placenta. It crosses the rodent placenta, concentrating in the placenta and the fetal liver, brain, and spinal cord. Rodent studies conducted at doses 20-25× the MRHD revealed

embryotoxicity, IUGR, and birth defects, including cleft palate and skeletal malformations. In guinea pigs, maternal treatment decreases ACh-mediated relaxation of isolated aorta.

Breastfeeding Safety

There is no published experience in nursing women. It is unknown whether **tolterodine** enters human breast milk. It is excreted at low levels into rodent milk, with neonates ingesting <0.5% of the dose.

Drug Interactions

Ketoconazole, a CYP3A4 inhibitor, significantly increased levels in patients who were poor metabolizers. For women receiving **ketoconazole** or other potent CYP3A4 inhibitors such as other azole anitfungals (e.g., **itraconazole, miconazole**), macrolide antibiotics (e.g., **clarithromycin, erythromycin**), **cyclosporine,** or **vinblastine,** the recommended dose should be halved.

References

Pahlman I, d'Argy R, Nilvebrant L. Arzneimittelforschung 2001; 51:125-33.

Summary

Pregnancy Category: C
Lactation Category: U

- **Tolterodine** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.
- Considering that the indication is not life-threatening, **tolterodine** should be avoided during pregnancy.

Topiramate—(Topamax)

International Brand Name—Epitomax (Finland); Topamax Sprinkle (Hong Kong, Israel, Korea, New Zealand)

Drug Class

Anticonvulsants

Indications

Tonic-clonic seizures, adjunct therapy

Mechanism

Unknown

Dosage with Qualifiers

Seizures, adjunct therapy—25-50mg PO qd, increase 25-50mg/w; usual dose 400mg/d in divided doses

NOTE: renal dosing.

- **Contraindications**—hypersensitivity to drug or class, hepatic dysfunction
- **Caution**—unknown

Maternal Considerations

Topiramate increases the metabolism of **ethinyl estradiol** and progestogens. If a women wishes to take OCPs, the preparation should contain at least 50mcg of **ethinyl estradiol.** **Levonorgestrel** implants are contraindicated because of the increased risk of contraceptive failure. Further, it is recommended that **medroxyprogesterone** injections be given q10w rather than q12w. There are no adequate reports or well-controlled studies of **topiramate** in pregnant women. **Folate** supplementation preconception is prudent. As for most psychotropic drugs, monotherapy and the lowest effective quantity given in divided doses to minimize the peaks may minimize the risks. Many recommend vitamin K (10mg PO qd) be given the last 4w of pregnancy for women taking hepatic enzyme–inducing

anticonvulsants such as **topiramate.** The scientific support for this practice is weak.
Side effects include nephrolithiasis, acute myopia, secondary angle-closure glaucoma, dizziness, somnolence, fatigue, language problems, memory difficulty, psychomotor slowing, nervousness, ataxia, nystagmus, depression, diplopia, mood disturbances, paresthesias, tremor, weight loss, confusion, abdominal pain, agitation, and URI.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. **Topiramate** readily crosses the human placenta, reaching F:M ratios approaching unity. There is too little human experience where **topiramate** is a teratogen in rodents. Preliminary after market data suggest an increase in major congenital malformations, especially oral clefts. There is a dose-dependent increase in the prevalence of craniofacial and limb malformations, and IUGR, even at doses a fraction of the MRHD.

Breastfeeding Safety

There are no adequate reports or well-controlled studies in nursing women. **Topiramate** enters human breast milk at low concentrations; breastfeeding neonates have levels around the lower limit of detection.

Drug Interactions

Reduced by 40-50% when used with either **carbamazepine** or **phenytoin.**
Use with **valproic acid** is associated with a 10% decrease in the levels of both drugs. This combination has also been associated with hyperammonemia with and without encephalopathy.
Use with **lamotrigine** increases levels by 15%.
The possibility of decreased contraceptive efficacy and increased breakthrough bleeding should be considered in patients taking combination oral contraceptive products with **topiramate.**
Hydrochlorothiazide increased the **topiramate** C_{max} by 27% and AUC by 29%. The addition of **hydrochlorothiazide** to **topiramate** may require an adjustment of the **topiramate** dose.
Decreases the **lithium** AUC and C_{max} by 20%.
Increases the **amitriptyline** AUC and C_{max} by 10-15%. Some patients may experience a large increase in **amitriptyline** concentration, and any adjustments in **amitriptyline** dose should be based on the patient's clinical response and not plasma levels.
Decreases **risperidone** levels by 25%.
Use with other carbonic anhydrase inhibitors (e.g., **acetazolamide, dichlorphenamide**) may create a physiological environment that increases the risk of renal stone formation, and should be avoided.

References

Hunt S, Russell A, Smithson WH, et al. Neurology 2008; 71:272-6.
Ohman I, Vitols S, Luef G, et al. Epilepsia 2002; 43:1157-60.

Summary

Pregnancy Category: C
Lactation Category: S

- **Topiramate** should be used during pregnancy only if alternative therapy fails to provide adequate seizure control.
- **Topiramate** appears to be a human teratogen increasing risk of oral clefting.
- As for most psychotropic drugs, using monotherapy and the lowest effective quantity given in divided doses to minimize the peaks can minimize the risks.
- **Topiramate** appears a good choice for breastfeeding women.
- There are alternative agents for which there is more experience regarding use during pregnancy.

Torsemide—(Demadex; Presaril)

International Brand Name—Toral (Indonesia); Torem (England, Germany, Korea, Sweden, Switzerland); Unat (Chile, Germany, Hong Kong, Indonesia, Portugal, South Africa, Thailand)

Drug Class	Diuretics, loop
Indications	Hypertension, diuresis for CHF, renal failure, hepatic failure
Mechanism	Inhibits Na/K/Cl carriers in ascending loop of Henle
Dosage with Qualifiers	Hypertension—5mg PO qd Diuresis for CHF—10-20mg PO/IV qd, double until desired response; max 200mg/d Diuresis for renal failure—20mg PO/IV qd, double until desired response; max 200mg/d Diuresis for hepatic failure—5-10mg PO/IV qd, double until desired response; max 40mg/d • **Contraindications**—hypersensitivity to drug or class, hypersensitivity to sulfonylureas • **Caution**—hypersensitivity to sulfonamides, hepatic or renal dysfunction
Maternal Considerations	There is no published experience with **torsemide** during pregnancy. Diuretics should not be used for the treatment of physiologic edema of pregnancy. ***Side effects*** include ototoxicity, GI bleeding, arrhythmia, ECG abnormalities, dizziness, headache, N/V, diarrhea, dyspepsia, weakness, rhinitis, cough, arthralgia, hyperglycemia, hyperuricemia, hypokalemia, and insomnia.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **torsemide** crosses the human placenta. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically.
Breastfeeding Safety	There are no adequate reports or well-controlled studies in nursing women. It is unknown whether **torsemide** enters human breast milk.
Drug Interactions	Because it competes with salicylates for secretion by renal tubules, patients receiving high doses of salicylates may experience salicylate toxicity. The natriuretic effect is partially inhibited by **indomethacin** when sodium is restricted (<50mEq/day). Use with **digoxin** is reported to increase the **torsemide** AUC by 50%, but a dose adjustment is not necessary. Absorption may be decreased by use with **cholestyramine.** Thus, simultaneous administration is not recommended. Secretion by the proximal tubule is reduced by **probenecid,** thus decreasing its diuretic activity. May reduce the renal clearance of **lithium,** increasing the risk of **lithium** toxicity. May increase the ototoxic potential of aminoglycoside antibiotics and **ethacrynic acid,** especially in the presence of impaired renal function.

References	There is no published experience in pregnancy or during lactation.
Summary	**Pregnancy Category: B** **Lactation Category: U** • **Torsemide** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk. • There are alternative agents for which there is more experience regarding use during pregnancy and lactation.

Tramadol—(Adamon; Ultram)

International Brand Name—Adamon (Argentina, Costa Rica, Dominican Republic, El Salvador, Guatemala, Honduras, Nicaragua, Panama); Amanda (Thailand); Analab (Malaysia, Thailand); Analdol (Israel); Andalpha (Indonesia); Bellatram (Indonesia); Biodalgic (France); Calmador (Argentina); Calmol (Uruguay); Contramal (Belgium, France, Hungary, India, Italy); Contramal LP (France); Dolana (Indonesia); Dolika (Indonesia); Dolmal (Philippines); Dolotral (Philippines); Dromadol (England); Eufindol (Chile); Exopen (Korea); Katrasic (Indonesia); Kontram XL SR (Korea); Mabron (China, Israel, Singapore, Thailand); Mosepan (Philippines); Newdorphin (Philippines); Nonalges (Indonesia); Omnidol (Colombia); O.P. Pain (Korea); Pengesic (Malaysia, Philippines, Singapore); Penimadol (Korea); Prontofort (Mexico); Radol (Indonesia); Rofy (Thailand); Sefmal (Hong Kong, Singapore); Sensitram (Brazil); Takadol (France); Tamolan (Thailand); Tandol (Korea); Tarol (Israel); Topalgic (France); Trabar (Israel); Trabilan (Malaysia); Trabilin (Costa Rica, El Salvador, Guatemala, Honduras, Nicaragua, Panama); Tradol (Mexico); Tradol-Puren (Germany); Tradonal (Philippines); Tralic (Mexico); Tramada (Malaysia); Tramadex (Israel); Tramagetic (Germany); Tramagit (Germany); Tramahexal (South Africa); Tramake (England, Ireland); Tramal (Austria, Bulgaria, China, Colombia, Czech Republic, Ecuador, Germany, Hong Kong, Israel, Malaysia, Netherlands, Peru, Philippines, Poland, Switzerland, Taiwan, Thailand, Venezuela); Tramal SR (Australia); Tramazac (India, South Africa); Tramed (Taiwan); Tramol (Poland); Trasedal (France); Trasik (Indonesia); TRD-Contin (India); Trexol (Mexico); Tridol (Korea); Unitral (Philippines); Urgendol (India); Zamadol (Brazil, England); Zamudol (France); Zodol (Chile, Paraguay, Peru); Zumatran (Indonesia); Zydol (Australia, England, Ireland); Zytram BD (New Zealand); Zytram XL SR (Korea)

Drug Class	Analgesics, narcotic-like
Indications	Moderate to severe pain
Mechanism	Unknown
Dosage with Qualifiers	Moderate to severe pain—50-100mg PO q4-6h prn *NOTE: renal and hepatic dosing.* • **Contraindications—**hypersensitivity to drug or class, alcohol or drug use • **Caution—**history of substance abuse, CNS depressant use, respiratory depressant use, respiratory depression, seizures, head injury, increase ICP, acute abdomen, hepatic or renal dysfunction
Maternal Considerations	**Tramadol** is a centrally acting analgesic. There are no adequate reports or well-controlled studies of **tramadol** in pregnant women. There are a few studies using it intrathecally. A single study comparing **tramadol** with **meperidine** for labor analgesia concluded it created less maternal sedation and fetal respiratory depression. **Tramadol** reduces postanesthetic shivering with a lower frequency of somnolence than **meperidine.** There is no evidence of a difference between **meperidine** and **tramadol** in terms of pain relief, interval to delivery, or instrumental or operative delivery. It is an excellent oral agent for the relief of significant postoperative pain. However, it is no better than **ibuprofen** for the treatment of postabortal pain. In fact, **ibuprofen** is somewhat more effective at reducing pain 30min after surgical abortion.

Side effects include dependency, seizures, angioedema, bronchospasm, respiratory depression, Stevens-Johnson syndrome, toxic epidermal necrolysis, orthostatic hypotension, serotonin syndrome, hallucinations, suicidal ideation, dizziness, N/V, somnolence, pruritus, nervousness, anxiety, agitation, euphoria, tremor, spasticity, visual disturbances, incoordination, anorexia, rash, and vasodilation.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. **Tramadol** crosses the human placenta, achieving an F:M ratio of 0.83 with the concentrations approaching unity. Chronic use during pregnancy may lead to physical dependence and postpartum withdrawal symptoms in the newborn. Rodent studies are generally reassuring, revealing only embryo and maternal toxicity at high concentrations, and no teratogenicity or IUGR.

Breastfeeding Safety

A small amount of **tramadol** enters human breast milk. The estimated relative infant dose of 2.88% is low.

Drug Interactions

Use with **carbamazepine** may significantly reduce analgesic effect. Since **carbamazepine** increases **tramadol** metabolism and because of the seizure risk associated with **tramadol,** their use together is not recommended.
Quinidine is a selective inhibitor of CYP2D6; its use results in increased concentrations of **tramadol** (50-60%) and reduced concentrations of M1 (50-60%). Other CYP2D6 inhibitors include **amitriptyline, fluoxetine,** and **paroxetine.**
Interactions with MAOIs due to interference with detoxification mechanisms has been reported for some centrally acting drugs.
Post-marketing surveillance reveals rare reports of **digoxin** toxicity and alteration of **warfarin** effect, including elevation of the PT.
Use of CYP3A4 inhibitors (e.g., **erythromycin, ketoconazole**) or inducers (e.g., **rifampin, St. John's Wort**) may affect **tramadol** metabolism leading to altered **tramadol** exposure.

References

Elbourne D, Wiseman RA. Cochrane Database Syst Rev 2000; (2):CD001237.
Fieni S, Angeri F, Kaihura CT, et al. Acta Biomed Ateneo Parmense 2000; 71(Suppl 1):397-400.
Ilett KF, Paich MJ, Page-Sharp M, et al. Br J Clin Pharmacol 2008; 65:661-5.
Frikha N, Ellachtar M, Mebazaa MS, Ben Ammar MS. Middle East J Anesthesiol 2007; 19:87-96.
Romero I, Turok D, Gilliam M. Contraception 2008; 77:56-9.
Siddik-Sayyid S, Aouad-Maroun M, Sleiman D, et al. Can J Anaesth 1999; 46:731-5.
Tsai YC, Chu KS. Anesth Analg 2001; 93:1288-92.

Summary

Pregnancy Category: C
Lactation Category: S (likely)

- **Tramadol** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.
- It is a reasonable oral agent for the management of postoperative pain.

Trandolapril—(Mavik)

International Brand Name—Gopten (Colombia, Czech Republic, Denmark, England, Finland, France, Germany, Italy, Mexico, Netherlands, Portugal, South Africa, Spain, Switzerland, Turkey); Odace (Philippines); Odrik (Denmark, England, Finland, France, Greece, Italy, Peru, Portugal, Spain); Udrik (Germany)

Drug Class	ACEI/A2R-antagonists
Indications	Hypertension, CHF
Mechanism	ACE inhibition
Dosage with Qualifiers	Hypertension—begin 1-2mg PO qd; max 8mg/d CHF—begin 0.5mg PO qd; max 4mg/d *NOTE: renal and hepatic dosing; may be combined with* ***verapamil*** *(Tarka; 1 tab PO qd or bid) for the treatment of hypertension.* • **Contraindications**—hypersensitivity to drug or class; history of ACEI-induced, hereditary, or idiopathic angioedema • **Caution**—severe CHF, renal artery stenosis, collagen vascular disease, renal dysfunction, volume depletion, hyponatremia
Maternal Considerations	There is no published experience with **trandolapril** during pregnancy. Agents that inhibit the renin-angiotensin system should be avoided during pregnancy for fetal indications. ***Side effects*** include angioedema, hypotension, acute renal failure, hyperkalemia, hepatotoxicity, neutropenia, agranulocytosis, pancreatitis, cough, hypotension, dizziness, fatigue, hyperkalemia, N/V, URI symptoms, musculoskeletal pain, and elevated BUN/Cr levels.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **trandolapril** crosses the human placenta. Other drugs of this class do cross the placenta. Adverse fetal effects are reported from drugs that inhibit the renin-angiotensin system throughout pregnancy. Later exposure is associated with cranial hypoplasia, anuria, reversible or irreversible renal failure, death, oligohydramnios, prematurity, IUGR, and PDA. If oligohydramnios is observed, **trandolapril** should be discontinued unless considered lifesaving. Antenatal surveillance (e.g., BPP) may be appropriate, depending upon the week of pregnancy. Oligohydramnios may not appear until after the fetus has sustained irreversible injury. Neonates exposed *in utero* should be closely observed for hypotension, oliguria, and hyperkalemia. Rodent and primate studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically.
Breastfeeding Safety	There is no published experience in nursing women. It is unknown whether **trandolapril** enters human breast milk. It is excreted into rodent milk.
Drug Interactions	Use with **cimetidine** led to an increase of about 44% in C_{max} for **trandolapril,** but no difference in the pharmacokinetics of trandolaprilat or in ACE inhibition. Use with **furosemide** led to an increase of about 25% in the renal clearance of trandolaprilat, but no effect was seen on the pharmacokinetics of **furosemide** or trandolaprilat or on ACE inhibition. Patients on diuretics, especially those on recently instituted diuretic therapy, may experience an excessive reduction

of BP after initiation of therapy with **trandolapril.**
This possibility may be minimized by either discontinuing the diuretic or cautiously increasing salt intake prior to initiation of treatment with **trandolapril.** If it is not possible to discontinue the diuretic, the starting dose of **trandolapril** should be reduced. May attentuate potassium loss caused by thiazide diuretics and increase serum potassium when used alone. Use of potassium-sparing diuretics (e.g., **amiloride, spironolactone, triamterene**), potassium supplements, or potassium-containing salt substitutes concomitantly with ACEIs can increase the risk of hyperkalemia. Increased serum **lithium** levels and symptoms of **lithium** toxicity have been reported. These drugs should be used together with caution, accompanied by frequent monitoring of serum **lithium** levels.

References

Matsuura T, Kurio W, Maeda H, et al. J Toxicol Sci 1993; 18(Suppl 1):107-32.

Summary

Pregnancy Category: C (1st trimester), **D** (2nd and 3rd trimesters)
Lactation Category: U

- **Trandolapril** should not be used at any stage of pregnancy and breastfeeding unless there is no alternative for the control of severe maternal hypertension.
- There are alternative agents for which there is more experience regarding use during pregnancy and lactation.

Tranylcypromine—(Parnate)

International Brand Name—None identified.

Drug Class

Antidepressants, type 3; MAOIs

Indications

Depression

Mechanism

MAO inhibitor, PGI_2 synthetase inhibitor

Dosage with Qualifiers

Depression—30mg PO qd, increase by 10mg/d q1-3w; max 60mg/d

NOTE: withdraw slowly.

- **Contraindications**—hypersensitivity to drug or class, alcoholism, CHF, severe hepatic or renal dysfunction, pheochromocytoma, narcotic use, alcohol use, ingestion of cheese or other foods with a high tyramine content, excessive caffeine intake
- **Caution**—unknown

Maternal Considerations

Depression is common during and after pregnancy, but typically goes unrecognized. Pregnancy is not a reason *a priori* to discontinue psychotropic drugs. **Tranylcypromine** is best suited for patients who have failed to respond to drugs more commonly used for depression. There is no published experience with **tranylcypromine** during pregnancy. Its inhibition of PGI_2 synthetase raises theoretic concerns.
Side effects include hypertensive crisis, blurred vision, orthostatic hypotension, hepatitis, thrombocytopenia, agranulocytosis, CNS stimulation, increased sweating, shakiness, and weakness.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **tranylcypromine** crosses the human placenta. It does cross the rat placenta, but rodent teratogenicity studies have not been performed.

Breastfeeding Safety

There is no published experience in nursing women. It is unknown whether **tranylcypromine** enters human breast milk. It is excreted into rodent milk. As for most psychotropic drugs, monotherapy and the lowest effective quantity given in divided doses to minimize the peaks may minimize the risks.

Drug Interactions

No clinically relevant interactions identified.

References

There is no published experience in pregnancy or during lactation.

Summary

Pregnancy Category: C
Lactation Category: U

- **Tranylcypromine** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.
- There are alternative agents for which there is more experience regarding use during pregnancy and lactation.
- As for most psychotropic drugs, using monotherapy and the lowest effective quantity given in divided doses to minimize the peaks can minimize the risks.

Trazodone—(Desyrel; Sideril; Trazalon; Trazonil)

International Brand Name—Azonz (Finland); Beneficat (Argentina); Bimaran (Argentina); Deprax (Spain); Depresil (Philippines); Depyrel (Israel); Desirel (Thailand); Manegan (Argentina); Molipaxin (England, Ireland, South Africa); Pragmarel (France); Reslin (Japan); Taxagon (Argentina); Thombran (Germany); Trazodil (Israel); Trazolan (Belgium, India, Netherlands); Trazone (Indonesia, Portugal, Taiwan); Trittico (Austria, Colombia, Greece, Hong Kong, Italy, Peru, Switzerland)

Drug Class

Antidepressants, type 4

Indications

Depression

Mechanism

Unknown; serotonin reuptake inhibitor

Dosage with Qualifiers

Depression—begin 150mg PO with meals qd or in divided doses, and increase by 50mg q3d until desired effect; max 400mg/d

- **Contraindications**—hypersensitivity to drug or class, recent acute MI
- **Caution**—suicide risk, CNS depressants, antihypertensive use, electroconvulsive therapy, arrhythmia

Maternal Considerations

Depression is common in reproductive-age women and frequently overlooked or minimized by the care provider. There is no reason *a priori* to deny indicated treatment during pregnancy.
The published experience with **trazodone** during pregnancy is limited but reassuring. In one report, levels were lower in the 1st and 2nd trimesters compared to the 3rd. The elimination t/2 was unchanged though.
Side effects include hypotension, syncope, drowsiness, bitter taste, dry mouth, N/V, headache, blurred vision, fatigue, arthralgia, incoordination, and tremor.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **trazodone** crosses the human placenta. Cohort studies are reassuring, revealing no increase in the prevalence of adverse outcomes. **Trazodone** crosses the rat placenta, and rodent teratogenicity studies reveal an increased risk of embryo absorption and malformations (rabbit) at doses that are multiples of the MRHD.

Breastfeeding Safety

Trazodone enters human breast milk, but the amount ingested by the neonate is not clinically relevant.

Drug Interactions

Trazodone may increase serum **digoxin** or **phenytoin** levels. It is not known whether interactions will occur with MAOIs. Therapy should be initiated cautiously with a gradual increase in dose until the optimal response is achieved.

References

DeVane CL, Boulton DW, Miller LF, Miller RL. Int J Neuropsychopharmacol 1999; 2:17-23.
Einarson A, Bonari L, Voyer-Lavigne S, et al. Can J Psychiatry 2003; 48:106-10.
Klien CM, Mossaheb N, Sania A, et al. J Clin Psychopharmacol 2007; 27:720-2.
Verbeeck RK, Ross SG, McKenna EA. Br J Clin Pharmacol 1986; 22:367-70.

Summary

Pregnancy Category: C
Lactation Category: S

- **Trazodone** should be used during pregnancy only if the benefit justifies the potential perinatal risk.
- There are alternative agents for which there is more experience regarding use during pregnancy.
- As for most psychotropic drugs, monotherapy and the lowest effective quantity given in divided doses to minimize the peaks may minimize the risks.

Treprostinil—(Remodulin)

International Brand Name—Remodulin (Australia, Israel)

Drug Class

Platelet inhibitors; Prostaglandins; Vasodilators

Indications

Pulmonary hypertension, NYHA class II-IV symptoms

Mechanism

Unknown; inhibits platelet aggregation, dilates systemic and pulmonary vasculature

Dosage with Qualifiers

Pulmonary hypertension—begin 1.25ng/kg/min continuous SC infusion; increased in increments no more than 1.25ng/kg/min/w for first 4w, then no more than 2.5ng/kg/min/w for remaining duration depending on clinical response.

NOTE: hepatic dosing.

- **Contraindications**—hypersensitivity to drug or class
- **Caution**—abrupt withdrawal, hepatic or renal dysfunction

Maternal Considerations

Significant pulmonary hypertension is associated with a high maternal mortality rate during the peripartum. There is no published experience with **treprostinil** during pregnancy.

	Side effects include rebound pulmonary hypertension, infusion site reaction, headache, diarrhea, nausea, rash, vasodilation, jaw pain, dizziness, edema, pruritus, and hypotension.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **treprostinil** crosses the human placenta. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically.
Breastfeeding Safety	There is no published experience in nursing women. It is unknown whether **treprostinil** enters human breast milk.
Drug Interactions	Hypotension may be exacerbated by drugs that alone alter the BP (e.g., antihypertensive agents, diuretics, vasodilators). **Treprostinil** inhibits platelet aggregation, and may increase the risk of bleeding, particularly among patients maintained on anticoagulants.
References	There is no published experience in pregnancy or during lactation.
Summary	**Pregnancy Category: B** **Lactation Category: U** • **Treprostinil** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Tretinoin—(Acnavit; Avita; Avitoin; Cordes-Vas; Dermojuventus; Kerlocal; Relief; Renova; Retin-A; Retin-A Micro; Retinoic Acid; SteiVAA; Vesanoid)

International Brand Name—A-Acido (Argentina); Aberel (France); Aberela (Sweden); Acid A Vit (Belgium, Netherlands); Acne Free (Israel); Acta (Hong Kong); Airol (Argentina, Czech Republic, Greece, Italy, Malaysia, Mexico, Norway, Poland, Switzerland, Taiwan); Alquingel (Colombia); Alten (Malaysia, Singapore); Avitcid (Finland); Betarretin (Peru); Derm A (Philippines); Dermairol (Sweden); Dermik A (China); Effederm (France); Eudyna (Hong Kong, India, Indonesia, Malaysia, Taiwan); Facenol (Indonesia); Ilotycin-A (South Africa); Locacid (Israel); Prosome A Cream (Korea); Reacel-A (Mexico); Renova (Malaysia, South Africa); Retacnyl (Costa Rica, Dominican Republic, El Salvador, Guatemala, Honduras, Malaysia, Mexico, Nicaragua, Panama, Peru, Philippines, Singapore, South Africa, Venezuela); Retavit (Israel); Retiderma (Spain); Retin A (Austria, Bulgaria, Czech Republic, France, Greece, Hungary, Israel, Portugal); Retin-A (Bahrain, Canada, China, Colombia, Cyprus, Ecuador, England, Hong Kong, Indonesia, Iran, Ireland, Italy, Jordan, Lebanon, Libya, Malaysia, Peru, Philippines, Switzerland, Syria, Taiwan, Thailand); Retinova (France, New Zealand, Singapore); Retrieve Cream (Australia, Hong Kong); Stieva A (Canada); Stieva-A (Australia, Colombia, Costa Rica, Dominican Republic, El Salvador, Guatemala, Honduras, Korea, Malaysia, Mexico, Nicaragua, Panama, Paraguay, Thailand, Uruguay); Stieva-A forte (Malaysia); Tracne (Indonesia); Trentin (Indonesia); Vesanoid (Argentina, Austria, Belgium, Canada, China, Czech Republic, England, France, Germany, Ireland, Israel, Italy, Japan, Mexico, Netherlands, Paraguay, Peru, Philippines, Poland, South Africa, Switzerland, Taiwan, Thailand, Venezuela); Vitamin A Acid (Canada)

Drug Class	Acne; Antineoplastics; Dermatologics; Retinoids
Indications	Acne vulgaris, acute promyelocytic leukemia
Mechanism	Unknown
Dosage with Qualifiers	Acne vulgaris—apply qhs 30min after washing and drying skin Acute promyelocytic leukemia—45 mg/m^2/d PO given in evenly divided doses bid until complete remission; discontinue 30d after

remission or after 90d of treatment; continue effective contraception during and 1mo after completion of therapy

- **Contraindications**—hypersensitivity to drug or class
- **Caution**—unknown

Maternal Considerations

Some retinoid agents can be highly toxic to the fetus. Within 7d of **tretinoin** therapy, a blood or urine pregnancy test with a sensitivity of at least 50 mIU/L should be performed. When possible, **tretinoin** should be delayed until a negative result from this test is obtained. When a delay is not possible, the patient should be placed on two reliable forms of contraception. Pregnancy testing and contraception counseling should be repeated monthly throughout the period of **tretinoin** treatment. **Tretinoin** inhibits *in vitro* decidualization of endometrial stroma. There are no adequate reports or well-controlled studies of **tretinoin** in pregnant women. The published experience consists of case reports of acute promyelocytic leukemia.
Side effects include peeling, erythema, and blistering after topical therapy; retinoic acid–APL syndrome, hypercholesterolemia and/or hypertriglyceridemia, pseudotumor cerebri, and elevated LFTs after oral therapy.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. **Tretinoin** crosses the human placenta. Epidemiologic data are reassuring: 106 pregnant women with 1st trimester exposure to topical **tretinoin** were reported between 1983 and 2003 and prospectively followed. Birth outcomes were compared to 389 similarly followed women without exposure. There were no significant differences between groups in the proportion of pregnancies ending in spontaneous abortion, or infants with major structural defects. The groups were similar in gestation and size at birth. The prevalence of one or more retinoic acid–specific minor malformations did not differ between groups. Unfortunately, fewer than 10 neonates have been born to women treated with oral **tretinoin** during pregnancy (virtually all after the 1st trimester) for acute promyelocytic leukemia. All had normal growth without apparent complications. **Tretinoin** is a teratogen in rodents and primates when given orally. Reported defects in these species include abnormalities of the CNS, musculoskeletal system, ear, eye, thymus, and great vessels; facial dysmorphia; cleft palate; and PTH deficiency. The offspring of diabetic mice are more prone to develop caudal regression after **tretinoin** exposure. The teratogenic effect of topically applied drug is less clear and is likely low if used as directed.

Breastfeeding Safety

There is no published experience in nursing women. It is unknown whether **tretinoin** enters human breast milk.

Drug Interactions

Metabolized by the hepatic CYP450 system. Medications that induce hepatic CYP450 enzymes include glucocorticoids, **pentobarbital, phenobarbital,** and **rifampicin.** Medications that inhibit hepatic CYP450 enzymes include **cimetidine, cyclosporine, diltiazem, erythromycin, ketoconazole,** and **verapamil.** To date there are no data to indicate whether use with these medications increases or decreases either efficacy or toxicity. Caution should be exercised when the topical form is used with topical OTC acne preparations containing **benzoyl peroxide,** resorcinol, salicylic acid, or sulfur.

References

Brar AK, Kessler CA, Meyer AJ, et al. Mol Hum Reprod 1996; 2:185-93.

Chan BW, Chan KS, Koide T, et al. Diabetes 2002; 51:2811-6.
Loureiro KD, Kao KK, Jones KL, et al. Am J Med Genet A 2005; 136:117-21.
Maeda M, Tyugu H, Okubo T, et al. Rinsho Ketsueki 1997; 38:770-5.
Nau H. J Am Acad Dermatol 2001; 45:S183-7.

■ **Summary**

Pregnancy Category: D (oral), **C** (topical)
Lactation Category: U

- **Tretinoin** should be avoided during pregnancy and lactation unless maternal risk dictates it and there are no alternatives.
- The fetal risk appears low following topical exposure.

Triamcinolone—(Acetocot; Amcort; Aricin; Aristcort; Aristocort; Aristocort Forte; Aristocort Suspension; Aristocort Topical; Aristogel; Aristo-Pak; Aristospan Intralesional; Aristospan Parenteral; Articulose-L.A.; Azmacort; Cenocort A-40; Cenocort Forte; Cinalog; Cinolar; Cinonide 40; Delta-Tritex; Extracort; Flutex; Kenac; Kenacort; Kenaject-40; Kenalog; Kenalog-10; Kenalone; Kena-Plex 40; Kenonel; Nasacort; Oracort; Oralone; Oricort; Sholog A; Sholog K; Tac; Tramacort 40; Tramacort-D; Triacet; Triacort; Triam-A; Triamcinair; Triamcot; Triam-Forte; Triaminoral; Triamolone 40; Triamonide 40; Trianide; Triatex; Triderm; Tri-Kort; Trilog; Trilone; Tri-Med; Tristoject; Tristo-Plex; Trylone A; Trylone D; Trymex; U-Tri-Lone)

International Brand Name—Adcortyl (England, Ireland); Aristocort (Canada); Azmacor (South Africa); Azmacort (Peru); Delphicort (Austria, Germany, Hungary); Kenacort (Argentina, Belgium, Ethiopia, France, India, Indonesia, Italy, Japan, Kenya, Netherlands, Philippines, Sweden, Switzerland, Taiwan, Tanzania, Uganda, Uruguay, Venezuela); Korticoid (Germany); Ledercort (Belgium, Denmark, Ecuador, England, Finland, India, Italy, Japan, Korea, Netherlands, Norway, Paraguay, Spain, Sweden, Switzerland); Simacort (Thailand); Sterocort (Israel); Triamsicort (Mexico); Volon (Austria, Germany)

■ **Drug Class** — Corticosteroids

■ **Indications** — Adrenal insufficiency, inflammatory disorders, chronic asthma, allergic rhinitis, steroid-responsive dermatitis

■ **Mechanism** — Unknown anti-inflammatory; replacement

■ **Dosage with Qualifiers**

Adrenal insufficiency—4-12mg PO qd
Inflammatory disorders—4-48mg PO in divided doses qd
Chronic asthma—2 puffs INH tid or qid, rinse mouth after use; max 16 puffs qd
Allergic rhinitis—1-2 sprays/nostril qd; max 2 sprays/nostril qd; discontinue after 3w if no improvement

Steroid-responsive dermatitis—apply sparingly to affected area bid to qid

NOTE: available in oral, topical, and inhalational forms.

- **Contraindications**—hypersensitivity to drug or class, systemic fungal infection
- **Caution**—CHF, seizures, diabetes mellitus, hypertension, TB, osteoporosis, hepatic dysfunction, respiratory infection (inhalation), nasal surgery, herpes infection (nasal)

Maternal Considerations

Triamcinolone is a fluorinated glucocorticoid. There are no adequate reports or well-controlled studies of **triamcinolone** in pregnant women. **Triamcinolone** appears to be at least as efficacious for the treatment of asthma during pregnancy as **beclomethasone.** The suggestion that chronic topical application might lead to IUGR has yet to be confirmed by others. It is less likely the maternal systemic concentration will reach a clinically relevant level after either topical or inhalational use. In one study, PO **triamcinolone** caused a loss of circadian rhythms of **cortisol,** ACTH, **estradiol,** and unconjugated estriol, and modified the ultradian and circadian patterns of FHR. No differences in hormonal and biophysical parameters were found after the end of treatment, suggesting the inhibition of fetal and maternal adrenal glands modifies FHR patterns.
Side effects vary by route of use and include adrenal insufficiency (long-term therapy [LT]), steroid psychosis (LT), immunosuppression (LT), menstrual irregularities, peptic ulcer, CHF, osteoporosis (LT), cataracts, N/V, dyspepsia, appetite change, edema, headache, dizziness, mood swings, insomnia, anxiety, sinusitis, hypertension, pharyngitis, oral candidiasis, eczema, hyperglycemia, hypokalemia, ecchymoses, acne, folliculitis, dry skin, skin atrophy, and impaired wound healing.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **triamcinolone** crosses the human placenta. However, it does cross the nonhuman primate placenta and is relatively resistant to placental metabolism. The resulting F:M ratio approximates 0.6. Epidemiologic evidence is reassuring. Further, its administration to nonhuman primates at doses 5-60× (10mg/kg) the MRHD increases the prevalence of IUGR and craniofacial defects. The extensive fetoplacental metabolism of **cortisol** to inactive metabolites and the resistance of **triamcinolone** to metabolic conversion result in greater **triamcinolone** than **cortisol** exposure. **Triamcinolone** also crosses the rodent placenta, and its fetal t/2 is significantly prolonged compared to **cortisol.** In several rodent models, **triamcinolone** causes cleft lip and palate, whereas **cortisol** does not. While there is no epidemiologic evidence suggesting PO **triamcinolone** is a teratogen in humans, prescribing caution especially during the 1st trimester seems prudent. It is less likely the maternal systemic concentration will reach a clinically relevant level after either topical or inhalational use.

Breastfeeding Safety

There is no published experience in nursing women. It is unknown whether **triamcinolone** enters human breast milk. Topically applied drug likely poses little risk to the nursing newborn.

Drug Interactions

No clinically relevant interactions identified.

References

Arduini D, Rizzo G, Parlati E, et al. Prenat Diagn 1986; 6:409-17.
Czeizel AE, Rockenbauer M. Teratology 1997; 56:335-40.

Dombrowski MP, Brown CL, Berry SM. J Matern Fetal Med 1996; 5:310-3.
Katz VL, Thorp JM Jr, Bowes WA Jr. Am J Obstet Gynecol 1990; 162:396-7.
Parker RM, Hendrickx AG. Teratology 1983; 28:35-44.
Rahimi R, Nikfar S, Abdollahi M. Hum Exp Toxicol 2006; 25:447-52.
Rowland JM, Althaus ZR, Slikker W Jr, et al. Teratology 1983; 27:333-41.
Rowland JM, Hendrickx AG. Teratog Carcinog Mutagen 1983; 3:313-9.
Slikker W Jr, Althaus ZR, Rowland JM, et al. J Pharmacol Exp Ther 1982; 223:368-74.
Tarara RP, Wheeldon EB, Hendrickx AG. Teratology 1988; 38:259-70.

Summary

Pregnancy Category: C
Lactation Category: U

- **Triamcinolone** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.
- While there is no epidemiologic evidence suggesting PO **triamcinolone** is a human teratogen, prescribing caution seems prudent especially during the 1st trimester.
- It is less likely the maternal systemic concentration will reach a clinically relevant level after either topical or inhalational use.

Triamterene—(Dyrenium)

International Brand Name—Dyrenium (Switzerland); Dytac (Belgium, England, Ireland, Netherlands); Urocaudal (Spain)

Drug Class

Diuretics, potassium sparing

Indications

Peripheral edema associated with CHF, cirrhosis, or nephrotic syndrome or idiopathic

Mechanism

Inhibits aldosterone-induced Na^+ resorption in the distal tubule (K^+ sparing)

Dosage with Qualifiers

Peripheral edema—100mg PO bid pc

- **Contraindications**—hypersensitivity to drug or class, hyperkalemia, other potassium-sparing agents
- **Caution**—hepatic or renal dysfunction, diabetes mellitus

Maternal Considerations

Triamterene has a unique mode of action. In addition to its diuretic effect, **triamterene** is also a folate antagonist. There are no adequate reports or well-controlled studies of **triamterene** in pregnant women.
Side effects include hyperkalemia, ventricular arrhythmia, N/V, fatigue, photosensitivity, rash, dizziness, diarrhea, headache, muscle cramps, dry mouth, weakness, and azotemia.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. **Triamterene** rapidly crosses the human placenta, reaching F:M levels approaching unity. Epidemiologic studies suggest that folate antagonists, including **triamterene,** may increase the risk not only of NTDs, but also of CV defects, oral

clefts, and urinary tract defects. It crosses the rodent placenta. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically.

Breastfeeding Safety

There is no published experience in nursing women. It is unknown whether **triamterene** enters human breast milk. It is excreted into rodent milk.

Drug Interactions

Diuretic-induced sodium loss may reduce the renal clearance of **lithium** and increase serum **lithium** levels with risk of **lithium** toxicity. Patients should be monitored closely and the **lithium** dose adjusted as necessary.
A possible interaction resulting in acute renal failure has been reported when used with an NSAID. Caution is advised.
May potentiate antihypertensive medication, other diuretics, preanesthetic and anesthetic agents, and skeletal muscle relaxants (nondepolarizing).
Use cautiously with ACEIs due to an increased risk of hyperkalemia.
The following may promote serum potassium accumulation and possibly result in hyperkalemia: blood from blood bank (may contain up to 30mEq of potassium/L of plasma or up to 65mEq/L of whole blood when stored for more than 10d); low-salt milk (may contain up to 60mEq of potassium/L); potassium-containing medications (such as parenteral penicillin G potassium); and salt substitutes (most contain substantial amounts of potassium).
May raise blood glucose levels; dose adjustments of hypoglycemic agents may be necessary for adult-onset diabetes.

References

Ching MS, Czuba MA, Mihaly GW, et al. J Pharmacol Exp Ther 1988; 246:1093-7.
Hernandez-Diaz S, Werler MM, Walker AM, Mitchell AA. N Engl J Med 2000; 343:1608-14.

Summary

Pregnancy Category: B
Lactation Category: U

- **Triamterene** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.
- Epidemiologic studies suggest that folate antagonists, including **triamterene,** may increase the risk not only of NTDs, but also of CV defects, oral clefts, and urinary tract defects.
- There are alternative agents for which there is more experience regarding use during pregnancy and lactation.

Triazolam—(Halcion; Somniton; Tialam; Trizam)

International Brand Name—Apo-Triazo (Canada); Arring (Taiwan); Balidon (Chile); Dumozolam (Sweden); Halcion (Brazil, Canada, Costa Rica, Dominican Republic, El Salvador, Guatemala, Honduras, Hong Kong, Indonesia, Israel, Japan, Korea, Mexico, Nicaragua, Panama, Taiwan, Thailand); Hypam (New Zealand); Novidorm (Argentina); Novodorm (Spain); Nuctane (Argentina); Rilamir (Denmark, Finland); Somese (Chile, Colombia, Ecuador, Malaysia, Peru, Venezuela); Songar (Italy); Trialam (Taiwan); Trycam (New Zealand, Thailand); Zolmin (Korea)

Drug Class — Benzodiazepines; Hypnotics; Sedatives

Indications — Insomnia, short-term

Mechanism — Benzodiazepine receptor agonist

Dosage with Qualifiers

Insomnia, short term—0.25mg PO qhs

NOTE: hepatic dosing.

- **Contraindications**—hypersensitivity to drug or class
- **Caution**—hepatic dysfunction, CNS depression, substance abuse

Maternal Considerations

There are no adequate reports or well-controlled studies of **triazolam** in pregnant women. The published literature consists of scattered case reports.
Side effects include dependency, rebound insomnia, behavioral abnormalities, drowsiness, headache, anxiety, lightheadedness, dizziness, confusion, nervousness, ataxia, dry mouth, constipation, diarrhea, tachycardia, chest pain, dermatitis, and blurred vision.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **triazolam** crosses the human placenta. However, neonatal CNS depression has followed its use in the immediate antepartal period. Other benzodiazepines do cross the placenta, and in some rodent models, **diazepam** and **chlordiazepoxide** are associated with cleft lip and palate. Rodent teratogen studies have not been conducted.

Breastfeeding Safety

There is no published experience in nursing women. It is unknown whether **triazolam** enters human breast milk. It is excreted in rodent milk.

Drug Interactions

Produces additive CNS depressant effects when used with other psychotropic medications, anticonvulsants, antihistamines, ethanol, and other drugs that themselves produce CNS depression.
Drugs that inhibit CYP3A may have a profound effect on the clearance of **triazolam.**
Use with **isoniazid** increases the maximum plasma concentration by 20%, decreases clearance by 42%, and increases t/2 by 31%.
Use with oral contraceptives increases the maximum plasma concentration by 6%, decreases clearance by 32%, and increases t/2 by 16%.
Use with grapefruit juice increases the maximum plasma concentration by 25%, the AUC by 48%, and the t/2 by 18%.
Clinical studies of benzodiazepines suggest a possible drug interaction with the following: **amiodarone, cyclosporine, diltiazem, ergotamine, fluvoxamine, nicardipine, nifedipine, paroxetine, sertraline,** and **verapamil.**
Use with **ranitidine** increases the maximum plasma concentration by 30%, the AUC by 27%, and the t/2 by 3.3%. Caution is recommended.

References

Attallah A, Seilanian M, Bavoux F, Choisy H. Rev Fr Gynecol Obstet 1989; 84:47-51.
Sakai T, Matsuda H, Watanabe N. Eur J Pediatr 1996; 155:1065-6.

Summary

Pregnancy Category: X
Lactation Category: U

- **Triazolam** is poorly studied during pregnancy and lactation.
- It is unclear whether **triazolam** is a human teratogen.
- There are alternative agents for which there is more experience regarding use during pregnancy and lactation.

Trifluoperazine—(Calmazine; Flupazine; Novoflurazine; Stelazine; Suprazine; Tfp)

International Brand Name—Eskazine (Spain); Espazine (India); Fluperin (Bulgaria); Flurazin (Taiwan); Iremo-pierol (Greece); Jatroneural (Germany); Jatroneural Retard (Austria); Leptazine (Venezuela); Modalina (Italy); Modiur (Colombia); Nerolet (Argentina); Nylipton (Greece); Operzine (Korea); Oxyperazine (Greece); Psyrazine (Thailand); Sporalon (Greece); Stelazine (Argentina, Brazil, Czech Republic, England, Greece, Indonesia, Ireland, Mexico, Peru, Philippines, Poland, Taiwan); Stelazine Forte Solution (England, Ireland); Terfluzine (Hungary, Netherlands); Triflumed (Thailand); Trinicalm (India); Triozine (Thailand)

Drug Class	Antipsychotics; Phenothiazines
Indications	Schizophrenia, anxiety
Mechanism	Unknown; selective dopamine D_2 antagonist
Dosage with Qualifiers	Schizophrenia—begin 1-2mg PO bid; typical dose 2.5mg PO bid; max 40mg/d Anxiety—1-2mg PO bid; max 6mg/d ×3mo • **Contraindications**—hypersensitivity to drug or class, coma, CNS depression, hepatic disease, bone marrow depression • **Caution**—unknown
Maternal Considerations	**Trifluoperazine** has a number of effects, including the inhibition of calmodulin. There are no adequate reports or well-controlled studies of **trifluoperazine** in pregnant women. **Trifluoperazine** also has antiemetic properties similar to other phenothiazines. The published literature consists of scattered, typically uninformative case reports. ***Side effects*** include neuroleptic malignant syndrome, dry mouth, constipation, orthostatic hypotension, extrapyramidal effects, dizziness, blurred vision, tardive dyskinesia, photosensitivity, rash, nausea, tachycardia, fatigue, headache, weight gain, agranulocytosis, and jaundice.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. **Trifluoperazine** apparently crosses the human placenta, but the kinetics remain to be elucidated. It is oxidized by human placental peroxidase. Calmodulin inhibition has the potential to adversely affect multiple developmentally important pathways. Rodent studies are generally reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically.
Breastfeeding Safety	There are no adequate reports or well-controlled studies in nursing women. **Trifluoperazine** enters human breast milk, but apparently at lower concentrations than **haloperidol** and **chlorpromazine.** As for most psychotropic drugs, monotherapy and the lowest effective quantity given in divided doses to minimize the peaks may minimize the risks.
Drug Interactions	No clinically relevant interactions identified.
References	Boiko SS, Smol'nikova NM. Farmakol Toksikol 1975; 38:701-3. Yang X, Kulkarni AP. Teratog Carcinog Mutagen 1997; 17:139-51. Yoshida K, Smith B, Craggs M, Kumar R. Psychol Med 1998; 28:81-91.

Summary	**Pregnancy Category: C** **Lactation Category: S** (likely) • **Trifluoperazine** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk. • As for most psychotropic drugs, using monotherapy and the lowest effective quantity given in divided doses to minimize the peaks can minimize the risks. • There are alternative agents for which there is more experience regarding use during pregnancy and lactation.

Trimethobenzamide—(Anaus; Arrestin; Benzacot; Bio-Gan; Ibikin; Navogan; Stemetic; Tebamide; Tegamide; T-Gen; Ticon; Tigan; Tiject-20; Ti-Plex; Triban; Tribenzagan; Trimazide)

International Brand Name—None identified.

Drug Class	Anticholinergics; Antiemetics; Antivertigo agents
Indications	N/V
Mechanism	Unknown
Dosage with Qualifiers	N/V—300mg PO tid or qid, or 200mg PR/IM tid or qid • **Contraindications**—hypersensitivity to drug or class • **Caution**—unknown
Maternal Considerations	There are no adequate reports or well-controlled studies of **trimethobenzamide** in pregnant women. It has been used for the treatment of morning sickness. ***Side effects*** include coma, seizures, diarrhea, disorientation, dizziness, drowsiness, and muscle cramps.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **trimethobenzamide** crosses the human placenta. One epidemiologic study several decades old suggested an increased prevalence of major malformations. This observation has not been supported by subsequent study. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically. Embryotoxicity occurred in several animals treated at 50-60× the MRHD.
Breastfeeding Safety	There is no published experience in nursing women. It is unknown whether **trimethobenzamide** enters human breast milk.
Drug Interactions	No clinically relevant interactions identified.
References	Kousen M. Am Fam Physician 1993; 48:1279-84. Miklovich L, van den Berg BJ. Am J Obstet Gynecol 1976; 125:244-8.
Summary	**Pregnancy Category: C** **Lactation Category: U** • **Trimethobenzamide** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk. It is a second-line agent. • There are alternative agents for which there is more experience regarding use during pregnancy and lactation.

Trimethoprim—(Abaprim; Alprim; Bactin; Idotrim; Ipral; Lidaprim; Methoprim; Monotrim; Primosept; Primsol; Proloprim; Syraprim; Tiempe; TMP-Ratiopharm; Trimexazole; Trimopan; Trimpex; Triprim; Unitrim; Wellcoprim)

International Brand Name—Abaprim (Italy); Catin (Taiwan); Giprim (Taiwan); Idotrim (Sweden); Infectotrimet (Germany); Ipral (England, Ireland); Monotrim (Denmark, England, Ireland, Netherlands, South Africa, Switzerland); Motrim (Austria); Primosept (Switzerland); Solotrim (Austria); Syraprim (Spain); Tiempe (England); TMP-Ratiopharm (Germany); Tobyprim (Indonesia); Trimanyl (Germany); Trimesan (Poland); Trimono (Finland, Germany); Trimopan (Denmark, England); Triprim (Czech Republic, New Zealand, South Africa, Taiwan); Utisept (Thailand); Wellcoprim (Belgium, Netherlands)

Drug Class	Antibiotics; Folate antagonists
Indications	UTI, UTI prophylaxis, traveler's diarrhea, PCP treatment
Mechanism	Inhibits bacterial dihydrofolate reductase
Dosage with Qualifiers	UTI—100mg PO q12h ×10d UTI prophylaxis—100mg PO qhs ×6-24w Traveler's diarrhea—200mg PO bid ×5d PCP treatment—20mg/kg/d PO in divided doses *NOTE: renal dosing; often combined with* ***sulfamethoxazole.*** • **Contraindications**—hypersensitivity to drug or class, megaloblastic anemia • **Caution**—hepatic or renal dysfunction, bone marrow depression, folate deficiency
Maternal Considerations	Bacteriuria, with or without clinical symptoms, is common during pregnancy. If left untreated, 20-30% of patients develop acute pyelonephritis, which increases the risk of preterm labor and low-birth-weight infants. Established first-line drugs such as **amoxicillin, ampicillin,** and **trimethoprim-sulfamethoxazole** are associated with a high degree of resistance in *E. coli,* the most common pathogen in the urinary tract. Some 3-4% of women reportedly ingest **trimethoprim** during their pregnacy. **Nitrofurantoin** or a β-lactam agent are also first-line agents for the treatment of asymptomatic bacteriuria. The most powerful study to date documents an increased prevalence of placenta-mediated adverse events when **trimethoprim** is given: preeclampsia, severe preeclampsia, placental abruption, IUGR, and fetal death. A growing number of women are being treated with **trimethoprim** in combination of an array of antivirals for HIV-related complications. The impacts of these combinations are poorly studied. **Trimethoprim-sulfamethoxazole** is used for the treatment of Q fever during pregnancy. Women who develop Q fever should be treated for the duration of pregnancy, specifically if infected during the 1st trimester. ***Side effects*** include thrombocytopenia, leukopenia, megaloblastic anemia, methemoglobinemia, exfoliative dermatitis, Stevens-Johnson syndrome, fever, aseptic meningitis, toxic epidermal necrolysis, rash, erythema multiforme, pruritus, N/V, epigastric pain, glossitis, taste changes, hyperkalemia, hyponatremia, eosinophilia, elevated LFTs and BUN/Cr, and photosensitivity.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. Transfer of **trimethoprim** across the human placenta

is limited. The combination of **trimethoprim-sulfamethoxazole** has been associated with an increased risk of IUGR, CV, NTD, and urinary tract malformations. While there is no solid evidence solo therapy with **trimethoprim** is a human teratogen, the possibility it is a weak human teratogen cannot be excluded. **Trimethoprim** is teratogenic in the rat if given at doses 40× the MRHD.

Breastfeeding Safety

Trimethoprim enters human breast milk with an average level of 2-6mg/L and an M:P of 1.25. The theoretic infant dose can be calculated at 0.8mg/kg/d, which should not pose a risk. Breastfeeding is contraindicated in HIV-infected nursing women where formula is available to reduce the risk of neonatal transmission.

Drug Interactions

Inhibits the hepatic metabolism of **phenytoin,** resulting in a 30% decrease in clearance and a 50% increase in the t/2 of **phenytoin.**

References

Bawdon RE, Maberry MC, Fortunato SJ, et al. Gynecol Obstet Invest 1991; 31:240-2.
Hernandez-Diaz S, Werler MM, Walker AM, Mitchell AA. Am J Epidemiol 2001; 153:961-8.
Raoult D, Fenollar F, Stein A. Arch Intern Med 2002; 162:701-4.
Shepard TH, Brent RL, Friedman JM, et al. Teratology 2002; 65:153-61.
Wen SW, Zhou J, Yang Q, et al. CMAJ 2008; 179:1263-8.
Yang T, Walker MC, Krewski D, et al. Acta Obstet Gynecol Scand 2007; 86:1310-6.

Summary

Pregnancy Category: C
Lactation Category: S

- Epidemiological evidence argues to avoid **trimethoprim** whenever possible during pregnancy.

Trimethoprim-sulfamethoxazole—(Bactrim DS/SS; Cotrim DS/SS; Septra DS/SS/IV)

International Brand Name—None identified.

Drug Class

Folate antagonists; Sulfonamides

Indications

Bacterial infection, PCP treatment and prophylaxis, acute otitis media, shigellosis

Mechanism

See individual drugs

Dosage with Qualifiers

Bacterial infection—2 tab (SS) or 1 tab (DS) PO bid, or 4-5mg/kg **trimethoprim** IV q12h, max 960mg/d
PCP treatment—15-20mg/kg **trimethoprim** PO qd divided qid; or 4-5mg/kg **trimethoprim** IV q6h
PCP prophylaxis—2 tab (SS) or 1 tab (DS) PO qd
Acute otitis media—4-5mg/kg **trimethoprim** IV q12h; max 960mg/d
Shigellosis—4-5mg/kg **trimethoprim** IV q12h; max 960mg/d

*NOTE: SS consists of 80mg **trimethoprim** and 400mg **sulfamethoxazole,** DS is double this concentration; renal dosing.*

- **Contraindications**—hypersensitivity to drug or class, hypersensitivity to sulfonamides, megaloblastic anemia, folate deficiency, G6PD deficiency
- **Caution**—bone marrow suppression, hepatic or renal dysfunction

Maternal Considerations

Bacteriuria, with or without clinical symptoms, is common during pregnancy. If left untreated, 20-30% of patients develop acute pyelonephritis, which increases the risk of preterm labor and low-birth-weight infants. Established first-line drugs such as **amoxicillin, ampicillin,** and **trimethoprim-sulfamethoxazole** are associated with a high degree of resistance in *E. coli,* the most common pathogen in the urinary tract. **Nitrofurantoin** or a β-lactam agent are also first-line agents for the treatment of asymptomatic bacteriuria. There are no adequate reports or well-controlled studies of **trimethoprim-sulfamethoxazole** in pregnant women (see the entries for the individual drugs). However, the most powerful study to date documents an increased prevalence of placenta-mediated adverse events when **trimethoprim** is given: preeclampsia, severe preeclampsia, placental abruption, IUGR, and fetal death. A growing number of women are being treated with **trimethoprim** in combination with an array of antivirals for HIV-related complications. The impacts of these combinations are poorly studied. **Trimethoprim-sulfamethoxazole** is also used for the treatment of Q fever during pregnancy. Women who develop Q fever should be treated for the duration of pregnancy, specifically if infected during the 1st trimester.

Side effects include aplastic anemia, agranulocytosis, blood dyscrasias, Stevens-Johnson syndrome, toxic epidermal necrolysis, fulminant hepatic necrosis, hepatitis, hepatotoxicity, interstitial nephritis, nephrotoxicity, pseudomembranous colitis, aseptic meningitis, bone marrow suppression, methemoglobinemia, hyperkalemia, goiter, SLE, N/V, diarrhea, rash, urticaria, photosensitivity, dizziness, GI upset, headache, and lethargy.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. Transfer of **trimethoprim** across the human placenta is limited. While there is no solid evidence of teratogenicity in humans, the possibility it is a weak human teratogen cannot be excluded. In contrast, **sulfamethoxazole** readily crosses, reaching an F:M ratio approximating unity even in the 1st trimester. (See the entries for the individual drugs.) The combination has been associated with an increased risk of IUGR, CV, NTD, and urinary tract malformations.

Breastfeeding Safety

There are no adequate reports or well-controlled studies in nursing women. **Trimethoprim** enters human breast milk, but the kinetics remain to be elucidated. It is unknown whether **sulfamethoxazole** enters human breast milk. Breastfeeding is contraindicated in HIV-infected nursing women where formula is available to reduce the risk of neonatal transmission.

Drug Interactions

Trimethoprim inhibits the hepatic metabolism of **phenytoin,** resulting in a 30% decrease in clearance and a 50% increase in the t/2 of **phenytoin**.

Sulfamethoxazole may prolong the PT in patients receiving **warfarin.**

Sulfonamides can also displace **methotrexate** from plasma protein binding sites and compete with the renal transport of **methotrexate,** thus increasing toxicity. There is marked but reversible nephrotoxicity when used with **cyclosporine** in renal transplant recipients.

Trimethoprim-sulfamethoxazole may increase **digoxin** blood levels, especially in elderly patients. Serum **digoxin** levels should be monitored.

Blood levels are increased by use with **indomethacin.**

Occasional reports suggest that patients receiving **pyrimethamine** as malaria prophylaxis in doses exceeding 25mg/w may develop megaloblastic anemia.
Trimethoprim-sulfamethoxazole may decrease the efficacy of TCAs.
Like other sulfonamide-containing drugs, **sulfamethoxazole** potentiates the effect of oral hypoglycemics.

References

Bawdon RE, Maberry MC, Fortunato SJ, et al. Gynecol Obstet Invest 1991; 31:240-2.
Czeizel AE, Rockenbauer M, Sorensen HT, Olsen J. Reprod Toxicol 2001; 15:637-46.
Pagliaro LA, Levin (eds). Problems in Pediatric Drug Therapy. Hamilton, IL: Drug Intelligence Publications, 1979.
Prokopczyk J, Raczynski A, Troszynski M, et al. Probl Med Wieku Rozwoj 1979; 9:132-3.
Wen SW, Zhou J, Yang Q, et al. CMAJ 2008; 179:1263-8.
Yang T, Walker MC, Krewski D, et al. Acta Obstet Gynecol Scand 2007; 86:1310-6.

Summary

Pregnancy Category: C
Lactation Category: U
- Epidemiological evidence argues to avoid **trimethoprim** whenever possible during pregnancy.

Trimetrexate—(Neutrexin)

International Brand Name—NeuTrexin (Denmark, England, Ireland, Italy, Thailand)

Drug Class

Antibiotics; Antiprotozoals; Folate antagonists

Indications

PCP treatment

Mechanism

Inhibits protozoal dihydrofolate reductase

Dosage with Qualifiers

PCP treatment—45mg/m^2 IV qd ×21d given with **leucovorin**

- **Contraindications**—hypersensitivity to drug or class
- **Caution**—bone marrow depression, hepatic or renal dysfunction

Maternal Considerations

Trimetrexate with **leucovorin** may have lower toxicity than **trimethoprim-sulfamethoxazole.** There is no published experience with **trimetrexate** during pregnancy. Recent concerns regarding the safety of **trimethoprim** suggest **trimetrexate** should be avoided during pregnancy.
Side effects include neutropenia, thrombocytopenia, anemia, N/V, confusion, GI pain, hepatic dysfunction, peripheral neuropathy, and rash.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **trimetrexate** crosses the human placenta. **Trimetrexate** (without **leucovorin**) is teratogenic in rodents with increased risks of skeletal, visceral, ocular, and CV abnormalities.

Breastfeeding Safety

There is no published experience in nursing women. It is unknown whether **trimetrexate** enters human breast milk.

	Breastfeeding is contraindicated in HIV-infected nursing women where formula is available to reduce the risk of neonatal transmission.
Drug Interactions	Drugs that alter CYP may elicit important drug-drug interactions that may alter **trimetrexate** plasma concentrations. At risk agents that might be co-administered in AIDS patients for other indications, including **erythromycin, fluconazole, ketoconazole, rifabutin,** and **rifampin.**
References	There is no published experience in pregnancy or during lactation.
Summary	**Pregnancy Category: D** **Lactation Category: U** • **Trimetrexate** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk. • There are alternative agents for which there is more experience regarding use during pregnancy and lactation.

Trimipramine—(Surmontil)

International Brand Name—Apo-Trimip (Malaysia); Herphonal (Bulgaria); Rhotrimine (Canada); Sapilent (China, Hungary); Stangyl (Austria, Germany); Sumontil (Japan); Surmontil (Australia, Bahrain, Belgium, Canada, Cyprus, Denmark, Egypt, England, Finland, France, Hong Kong, India, Iraq, Ireland, Italy, Japan, Kuwait, Netherlands, Norway, Oman, Peru, Philippines, Portugal, Republic of Yemen, Spain, Sweden, Switzerland, United Arab Emirates, Venezuela); Tripress (New Zealand); Tydamine (South Africa)

Drug Class	Antidepressants; Tricyclics
Indications	Depression
Mechanism	Unknown; inhibits serotonin and NE reuptake
Dosage with Qualifiers	Depression—begin 50-75mg PO qd; max 300mg/d *NOTE: taper slowly; do not switch rapidly to and from SSRIs.* • **Contraindications**—hypersensitivity to drug or class, acute MI, MAOI <14d • **Caution**—seizures, hepatic dysfunction, glaucoma
Maternal Considerations	Depression is common during and after pregnancy, but typically goes unrecognized. Pregnancy is not a reason *a priori* to discontinue psychotropic drugs. There is no published experience with **trimipramine** during pregnancy. ***Side effects*** include seizures, ventricular arrhythmia, MI, complete AV heart block, stroke, drowsiness, dizziness, orthostatic hypotension, dry mouth, blurred vision, constipation, and diaphoresis.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **trimipramine** crosses the human placenta. Rodent studies are generally reassuring, revealing no evidence of teratogenicity, though embryotoxicity was noted at the highest doses.
Breastfeeding Safety	There is no published experience in nursing women. It is unknown whether **trimipramine** enters human breast milk.

Drug Interactions

Cimetidine may decrease TCA elimination. A decreased dose of **trimipramine** may be required if **cimetidine** therapy is initiated and an increased dose if **cimetidine** is discontinued.
Use with ethanol may exaggerate the CNS effects.
Particular care should be exercised when it is necessary to administer TCAs with sympathomimetic amines, local decongestants, local anesthetics containing **epinephrine, atropine,** or drugs with an anticholinergic effect. In resistant cases of depression in adults, a dose of 2.5mg/kg/d may have to be exceeded. If a higher dose is needed, ECG monitoring should be maintained during the initiation of therapy and at appropriate intervals during stabilization of dose.
Metabolized by CYP2D6 (debrisoquin hydroxylase), which is reduced in a subset of the Caucasian population (about 7-10% of Caucasians are so called "poor metabolizers"). Poor metabolizers have higher than expected plasma concentrations of TCAs. Depending on the fraction of drug metabolized by CYP2D6, the increase in plasma concentration may be small, or quite large (8-fold increase in the AUC).
Some drugs inhibit the activity of CYP2D6 and make normal metabolizers resemble poor metabolizers. An individual who is stable on a given dose of TCA may become abruptly toxic when given one of these inhibiting drugs as concomitant therapy. The drugs include some that are not metabolized by the enzyme (e.g., **cimetidine, quinidine**) and many that are substrates for CYP2D6 (other antidepressants, the class 1C antiarrhythmics **propafenone** and **flecainide,** and phenothiazines). While all SSRIs (e.g., **fluoxetine, paroxetine, sertraline**) inhibit CYP2D6, they may vary in the extent of inhibition. Caution is indicated in the use of TCAs with any of the SSRIs and also in switching from one class to the other.
Use with drugs that can inhibit cytochrome CYP2D6 may require lower doses than usually prescribed for either the TCA or the other drug. Furthermore, whenever one of these other drugs is withdrawn, an increased dose of the TCA may be required. It is desirable to monitor TCA plasma levels.

References

There is no published experience in pregnancy or during lactation.

Summary

Pregnancy Category: C
Lactation Category: U

- **Trimipramine** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.
- As for most psychotropic drugs, monotherapy and the lowest effective quantity given in divided doses to minimize the peaks may minimize the risks.
- There are alternative agents for which there is more experience regarding use during pregnancy and lactation.

Tripelennamine—(PBZ; PBZ-SR; Pelamine; Pyribenzamine; Triplen)

International Brand Name—None identified.

Drug Class

Antihistamines, H_1

Indications

Allergy

Mechanism	Nonselective H_1 antagonist
Dosage with Qualifiers	Allergy—100mg PO bid SR; alternatively, 25-50mg PO q4-6h immediate release • **Contraindications**—hypersensitivity to drug or class, MAOI <14d, narrow-angle glaucoma, asthma, GI obstruction • **Caution**—increased intraocular pressure, hyperthyroidism, CV disease, hypertension
Maternal Considerations	This 1st generation antihistamine is often paired illicitly with **pentazocine** to produce euphoria. Known as T's and Blues, users have a greater risk of adverse pregnancy outcome. There are no adequate reports or well-controlled studies of **tripelennamine** in pregnant women. ***Side effects*** include drowsiness, dry mouth/nose/throat, thickening of bronchial secretions, dizziness, disturbed coordination, epigastric distress, fatigue, chills, confusion, excitation, hysteria, nervousness, irritability, insomnia, anorexia, N/V, diarrhea, constipation, hypotension, wheezing, blurred vision, vertigo, tinnitus, convulsions, headache, palpitations, and tachycardia.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **tripelennamine** crosses the human placenta. However, fetuses of women who abuse T's and Blues have significantly reduced birth weight, length, and head circumference. Withdrawal occurs in about 1/3. Children of mothers who abused T's and Blues throughout pregnancy demonstrate interactive deficits and withdrawal similar to **methadone**-addicted newborns. The limited rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically.
Breastfeeding Safety	There is no published experience in nursing women. It is unknown whether **tripelennamine** enters human breast milk.
Drug Interactions	No clinically relevant interactions identified.
References	Chasnoff IJ, Hatcher R, Burns WJ, Schnoll SH. Dev Pharmacol Ther 1983; 6:162-9. Little BB, Snell LM, Breckenridge JD, et al. Am J Perinatol 1990; 7:359-62. von Almen WF 2nd, Miller JM Jr. J Reprod Med 1986; 31:236-9.
Summary	**Pregnancy Category: C** **Lactation Category: U** • **Tripelennamine** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk. • There are alternative agents for which there is more experience regarding use during pregnancy and lactation.

Trovafloxacin—(Trovan)

International Brand Name—None identified.

Drug Class	Antibiotics; Quinolones
Indications	Bacterial infection due to wide range of gram-negative and gram-positive aerobic and anaerobic bacteria

Mechanism	Bactericidal; inhibits DNA gyrase and topoisomerase IV
Dosage with Qualifiers	Bacterial infection—begin 200-300mg IV qd ×1, then switch to 200mg PO qd ×7-14d *NOTE: hepatic dosing.* • **Contraindications**—hypersensitivity to drug or class • **Caution**—hepatic or renal dysfunction, seizures, CNS disorder, dehydration, diabetes mellitus, sun exposure
Maternal Considerations	There is no published experience with **trovafloxacin** during pregnancy. ***Side effects*** include lethal hepatotoxicity, pseudomembranous colitis, superinfection, increased ICP, seizures, toxic psychosis, tendon rupture, pancreatitis, N/V, diarrhea, abdominal pain, headache, dyspepsia, restlessness, lightheadedness, elevated LFTs, vaginitis, arthralgia, insomnia, pruritus, anxiety, rash, and photosensitivity.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. **Trovafloxacin** crosses the human placenta by simple diffusion and is unlikely to reach toxic levels. Rodent studies conducted with more than 10× the MRHD reveal fetal toxicity and an increased prevalence of skeletal malformations.
Breastfeeding Safety	There is no published experience in nursing women. The manufacturer reports that low levels of **trovafloxacin** are excreted into human breast milk, with levels ranging from 0.3 to 2.1mg/L after 200mg PO preceded by a load of 300mg IV. The theoretic infant dose of 120mcg/kg/d is unlikely to result in a clinically relevant level.
Drug Interactions	Absorption is significantly reduced by use with some antacids containing magnesium or aluminum, citric acid, sodium citrate, and **sucralfate** and iron (ferrous ions). These agents as well as formulations containing divalent and trivalent cations (e.g., **didanosine**) should be taken at least 2h before or 2h after. IV **morphine** significantly reduces the absorption of oral **trovafloxacin** and should be administered at least 2h after in the fasted state or at least 4h after if taken with food. May enhance the effects of **warfarin.** A suitable anticoagulation test should be closely monitored. Do not administer IV with any solution containing multivalent cations (e.g., magnesium) through the same line.
References	Casey B, Bawdon RE. Infect Dis Obstet Gynecol 2000; 8:228-9.
Summary	**Pregnancy Category: C** **Lactation Category: S** (likely) • **Trovafloxacin** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk. • There are alternative agents for which there is more experience regarding use during pregnancy and lactation.

Tubocurarine

International Brand Name—None identified.

Drug Class	Musculoskeletal agents; Neuromuscular blockers, nondepolarizing
Indications	Adjunct to general anesthesia, diagnosis of myasthenia gravis
Mechanism	Competitive cholinergic receptor blocker at the motor end plate, interrupting nerve impulse transmission
Dosage with Qualifiers	Adjunct to general anesthesia—0.5mg/kg IV for abdominal relaxation or nonemergent tracheal intubation; may repeat 0.1mg/kg q40-60min as indicated by response to train-of-4 peripheral nerve stimulation Diagnosis of myasthenia gravis—0.02-0.04mg/kg IV followed by 2mg **neostigmine** • **Contraindications**—hypersensitivity to drug or class • **Caution**—renal or hepatic dysfunction, CV disease, hyperthyroidism
Maternal Considerations	**Tubocurarine** is the active ingredient of the curare-producing plant *Chondodendron tomentosum.* Nondepolarizing relaxants are longer acting than depolarizing muscle relaxants. While there are no adequate reports or well-controlled studies of **tubocurarine** in pregnant women, there is a long clinical experience. **Magnesium sulfate** therapy prolongs the effect of **tubocurarine.** Long-acting agents such as **tubocurarine** or **pancuronium** have generally been abandoned by anesthesiologists/intensivists in favor of synthetic short- to intermediate-acting agents (e.g., **cisatracurium, rocuronium, vecuronium**) that have lesser side effect (e.g., histamine release, tachycardia) profiles. ***Side effects*** include histamine release characterized by erythema, edema, skin rash, flushing, tachycardia, arterial hypotension, bronchospasm, circulatory collapse, cardiac arrhythmias, bradycardia, and prolonged apnea.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. Placental transfer of **tubocurarine** is greater than **atracurium,** with an F:M ratio of 0.09 for **atracurium** and 0.12 for **tubocurarine** ($p < 0.05$). However, it may be more rapidly cleared by the neonate. **Tubocurarine** is well-tolerated by the neonate if used during cesarean delivery, provided the interval between drug and delivery is short (1-10min). One woman treated for tetanus at 10-12w with **tubocurarine** for 10d delivered a term infant with joint contractures. **Tubocurarine** is administered directly to the fetus (3 or 1.5mg/kg SEFW IM/IV) to facilitate fetal therapeutic efforts. It lowers HR and BP in comparison to **pancuronium.** The duration of action of **tubocurarine** is directly related to the relative sensitivities of the different muscle groups, which are ranked from most sensitive to least sensitive as extraocular muscles, nuchal muscle, and diaphragm. Rodent studies reveal an increase in deformations consistent with absent fetal muscle tone.
Breastfeeding Safety	There is no published experience in nursing women. It is unknown whether **tubocurarine** enters human breast milk. However, considering the indication and dosing, one-time **tubocurarine** use is unlikely to pose a clinically significant risk to the breastfeeding neonate.

Drug Interactions

High parenteral doses of certain antibiotics (e.g., aminoglycosides [**gentamicin, kanamycin, neomycin, streptomycin**], **bacitracin,** colistin, **polymyxin B,** tetracyclines) may intensify the neuromuscular blocking action.
IV **clindamycin** plus low pseudocholinesterase levels and abnormal hepatic tests have been associated with prolonged apnea. The patient should be observed closely for respiratory depression if muscle relaxants and antibiotics that may block neuromuscular transmission must be administered together.
Use with volatile liquid anesthetic agents (e.g., cyclopropane, diethyl ether, **enflurane,** fluroxene, **halothane, isoflurane,** methoxyflurane, penthrane) will generate a dose related enhancement of neuromuscular blockade and an increase in the duration of action.
Synergism has been noted when nondepolarizing muscle relaxants (e.g., **gallamine, tubocurarine**) are injected concurrently.
Synergistic or antagonistic effects may result when depolarizing and nondepolarizing muscle relaxants (e.g., **succinylcholine, tubocurarine**) are administered consecutively. The extent and type of interaction depends on the doses and the sequence and timing of injections.
Potentiation of the neuromuscular blockade has been observed in preeclamptic women treated with **magnesium sulfate** prior to cesarean delivery.
Opiate analgesics may enhance respiratory depression.
Potassium-depleting agents (e.g., **amphotericin B,** carbonic anhydrase inhibitors, **chlorthalidone,** corticosteroids, corticotropin, **ethacrynic acid, furosemide,** and thiazide diuretics) may increase sensitivity to neuromuscular blocking agents. Adequate potassium levels should be confirmed prior to elective surgery.
Clinical experience strongly suggests that **quinidine** injected shortly after recovery causes recurrent paralysis in patients who received injections of either depolarizing or nondepolarizing muscle relaxants during surgery.
Calcium salts, **diazepam,** high IV doses of **lidocaine, lithium,** MAOIs, **propranolol, quinine,** and trimethaphan may intensify and/or prolong the effect of curare-containing preparations.

References

Chestnut DH, Weiner CP, Thompson CS, McLaughlin GL. Am J Obstet Gynecol 1989; 160:510-3.
Moise KJ Jr, Carpenter RJ Jr, Deter RL, et al. Am J Obstet Gynecol 1987; 157:874-9.
Perreault C, Guay J, Gaudreault P, et al. Can J Anaesth 1991; 38:587-91.
Szeto HH, Hinman DJ. Am J Obstet Gynecol 1990; 163:202-9.
Weiner CP, Wenstrom KD, Sipes SL, Williamson RA. Am J Obstet Gynecol 1991; 165:1020-5.

Summary

Pregnancy Category: C
Lactation Category: S (likely)

- **Tubocurarine** has been used during pregnancy and lactation as an anesthetic adjunct during surgery for decades.
- Newer synthetic agents may have advantages in specific clinical settings.

Urea—(Ureaphil)

International Brand Names—Alphadrate (Netherlands); Aquadrate (England, Ireland); Aqurea (Singapore); Balisa (Germany); Banjil (Korea); Basodexan (Austria, Germany, Switzerland); Calmurid (Belgium, Germany, Netherlands); Calmuril (Sweden); Carmed (Indonesia); Carmol (Hong Kong); Elacutan (Poland); Euderm (Hong Kong, Singapore); Linola (Germany); Nubral Creme (Germany); Nutraplus (Malaysia, Mexico, New Zealand, Singapore, Switzerland, Taiwan, Thailand); Soft U Derm (Indonesia); Urecare (Australia, Hong Kong); Uremol (Canada); Uricrim (Venezuela)

Drug Class ..... Antihypertensives; Cerebral edema

Indications ..... Increased ICP, increased intraocular pressure, SIADH

Mechanism ..... Osmotic diuretic

Dosage with Qualifiers .....

Increased ICP—1-1.5g/kg IV over 1-3h; max 120g/d
Increased intraocular pressure—1-1.5g/kg IV over 1-3h; max 120g/d
SIADH—80g IV over 6h

- **Contraindications**—hypersensitivity to drug or class, dehydration, hepatic failure, intracranial hemorrhage, renal dysfunction, lower extremity infusion
- **Caution**—CV disease

Maternal Considerations .....

There are no adequate reports or well-controlled studies of **urea** in pregnant women. Intra-amniotic **urea** is a valuable adjunct for late pregnancy termination. There is no published experience in pregnant women for the remaining listed indications.
Side effects include headache, N/V, syncope, disorientation, and injection site reaction.

Fetal Considerations .....

There are no adequate reports or well-controlled studies in human fetuses. **Urea** crosses the human placenta. Intra-amniotic injection of **urea** (80-120g) in combination with a prostaglandin is used for 2nd and 3rd trimester termination. The **urea** is typically lethal when given prior to skin keratinization. Rodent teratogenicity studies have not been conducted.

Breastfeeding Safety .....

There is no published experience in nursing women. **Urea** likely enters human breast milk, but the effect of its use for the listed indications has not been studied. However, most of the **urea** ingested by the infant is not bioavailable. Thus any increase in milk **urea** from maternal treatment should be clinically irrelevant.

Drug Interactions ..... No clinically relevant interactions identified.

References .....

Fomon SJ, Matthews DE, Bier DM, et al. J Pediatr 1987; 111:221-4.
Haning RV Jr, Peckham BM. Am J Obstet Gynecol 1985; 151:92-6.
Hern WM, Zen C, Ferguson KA, et al. Obstet Gynecol 1993; 81:301-6.

Summary .....

Pregnancy Category: C
Lactation Category: S

- **Urea** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.
- The published experience demonstrates that intra-amniotic **urea** is a valuable adjunct for the performance of midtrimester pregnancy termination.

Urokinase—(Abbokinase)

International Brand Name—Abbokinase (Austria, Greece, Israel, Netherlands, Spain, Sweden); Actosolv (Austria, Germany, Italy); Alphakinase (Germany); Medacinase (Netherlands); Persolv (Italy); Ukidan (Austria, Bulgaria, Czech Republic, England, Germany, Greece, Hungary, Israel, Italy, Japan, Korea, Peru, Philippines, Poland, Portugal, Singapore, Sweden, Switzerland, Taiwan, Thailand); Urokine (Korea)

Drug Class	Anticoagulants; Thrombolytics
Indications	PE, coronary artery thrombosis
Mechanism	Converts plasminogen to plasmin
Dosage with Qualifiers	PE—begin 4400IU/kg IV over 10min, then 4400IU/kg qh ×12h within 7d Coronary artery thrombosis—load **heparin** 2500-10,000U IV, then 6000IU/min IV until lysis (up to 2h, average 500,000IU) IV catheter clearance—5000IU contained in 1ml • **Contraindications**—hypersensitivity to drug or class, stroke history, active bleeding, aneurysm, AV malformation, recent trauma, intracranial malignancy, ulcerative colitis, severe uncontrolled hypertension • **Caution**—venipuncture, arterial puncture, IM injections, diabetic retinopathy, CVD, severe hepatic dysfunction, surgery or delivery <10d
Maternal Considerations	**Urokinase** is produced by the kidney and excreted in the urine. **Urokinase** treatment must be instituted as soon as possible after onset of PE, and no later than 7d. Therapy should be instituted within 6h of symptom onset if used to treat coronary artery thrombosis associated with an evolving transmural MI. Any delay instituting lytic therapy, even to evaluate the effect of **heparin,** decreases the potential for optimal efficacy. The diagnosis of a thromboembolus should always be confirmed by objective testing. Concurrent use of anticoagulants with IV administration of **urokinase** is not recommended except as noted. There are no adequate reports or well-controlled studies of **urokinase** in pregnant women. The published literature consists of case reports using **urokinase** to treat MI, PE, and cerebral and ovarian vein thrombosis either during pregnancy or in the puerperium. Hemorrhage is common during pregnancy. In one series of 8 pregnant women with acute ischemic stroke treated, 2 suffered extracranial and 2 asymptomatic intracranial hemorrhages. ***Side effects*** include bleeding, reperfusion arrhythmia, rash, bronchospasm, and injection site phlebitis.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **urokinase** crosses the human placenta. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically.
Breastfeeding Safety	There are no adequate reports or well-controlled studies in nursing women. It is unknown whether **urokinase** enters human breast milk. Plasminogen and plasminogen activator are normal components of breast milk. Considering the indications and dosing, one-time **urokinase** use is unlikely to pose a clinically significant risk to the breastfeeding neonate.

Drug Interactions

Drugs that alter platelet function (e.g., **aspirin, indomethacin, phenylbutazone**) should not be used.
Although **heparin** is recommended prior to intracoronary use, neither oral anticoagulants nor **heparin** should be used with large doses of **urokinase** such as those used for PE because of the risk of hemorrhage.

References

Heegaard CW, Larsen LB, Rasmussen LK, et al. Pediatr Gastroenterol Nutr 1997; 25:159-66.
Lee EH, Im CY, Kim JW. Ultrasound Obstet Gynecol 2001; 18:384-6.
Murugappan A, Coplin WM, Al-Sadat AN, et al. Neurology 2006; 66:768-70.
Wang S, Liang Y, Zhao F. Zhonghua Fu Chan Ke Za Zhi 1998; 33:412-4.
Webber MD, Halligan RE, Schumacher JA. Cathet Cardiovasc Diagn 1997; 42:38-43.

Summary

Pregnancy Category: B
Lactation Category: S (likely)
- **Urokinase** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Ursodiol—(Actigall; Ursacol; Ursodamor)

International Brand Name—Actigall (New Zealand); Cholacid (Germany); Dehychol (Taiwan); Deursil (Italy); Estazor (Indonesia); Pramur (Indonesia); Udihep (Thailand); Urdafalk (Indonesia); Ursacol (Italy); Urso (India); Ursochol (Belgium, Netherlands, Switzerland); Ursodamor (Italy); Ursofalk (Argentina, Canada, Chile, China, Colombia, Ecuador, Germany, Hong Kong, Korea, Malaysia, Mexico, Peru, Philippines, Thailand, Uruguay); Ursolin (Thailand); Ursolit (Israel); Ursolvan (France); Ursopol (Poland); Urso-Ratiopharm (Germany)

Drug Class

Gallstone solubilizers; Gastrointestinals

Indications

Gallstone dissolution or prevention, primary biliary cirrhosis, primary sclerosing cholangitis, nonalcoholic steatohepatitis

Mechanism

Decreases cholesterol synthesis, secretion, and absorption

Dosage with Qualifiers

Gallstone dissolution—8-10mg/kg/d PO in divided doses; monitor response q6mo by ultrasound, and continue drug for 3mo after dissolution
Gallstone prevention—300mg PO bid for obese women losing weight
Primary biliary cirrhosis—13-15mg/kg/d PO in divided doses with food
Primary sclerosing cholangitis—25-30mg/kg/d PO in divided doses with food
Nonalcoholic steatohepatitis—10-15mg/kg/d PO in divided doses with food

- **Contraindications**—hypersensitivity to drug or class, hypersensitivity to bile acids, unremitting acute cholecystitis, acute cholangitis, biliary obstruction, gallstone pancreatitis, biliary-GI fistula, calcified/radiopaque/radiolucent gallstones
- **Caution**—unknown

Maternal Considerations

Ursodiol (ursodeoxycholic acid) is a naturally occurring human bile acid found in small quantities, but found in large quantities

in the bile of certain bears. Small series suggest it can be effective for the treatment of cholestasis of pregnancy (approximately 16mg/kg). Intrahepatic cholestasis of pregnancy is a diagnosis of exclusion. It is associated with increased perinatal morbidity and mortality. Pruritus and postpartum hemorrhage are the main causes of maternal morbidity. Current management focuses on regular fetal and maternal monitoring and delivery at fetal maturity. However, a decrease in bile acids does not necessarily imply improved fetal outcome, and planned delivery remains prudent. One modest RCT concluded its combined use with *S*-adenosyl-L-methionine improved maternal responses. There is a case report of a woman with primary biliary cirrhosis treated throughout pregnancy. **Ursodiol** was effective, though a preterm cesarean delivery was required for uteroplacental dysfunction. ***Side effects*** include N/V, dyspepsia, abdominal pain, diarrhea, constipation, dizziness, alopecia, leukopenia, and URI symptoms.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. **Ursodiol** apparently does not cross the human placenta. It does, however, induce placental MRP2 expression, and reduce bilirubin and bile acid levels in umbilical cord blood.

Breastfeeding Safety

Ursodiol does not enter human breast milk.

Drug Interactions

Bile acid–sequestering agents (e.g., **cholestyramine, colestipol**) may interfere with absorption.
Aluminum-based antacids adsorb bile acids *in vitro* and may be expected to interfere with **ursodiol** in the same manner as the bile acid–sequestering agents.
Clofibrate, estrogens, and oral contraceptives (and perhaps other lipid-lowering drugs) increase hepatic cholesterol secretion, encourage cholesterol gallstone formation, and may counteract the effectiveness of **ursodiol.**

References

Azzaroli F, Mennone A, Feletti V, et al. Aliment Pharmacol Ther 2007; 26:1139-46.
Binder T, Salaj P, Zima T, Vítek L. J Perinat Med 2006; 34:383-91.
Mazzella G, Rizzo N, Azzaroli F, et al. Hepatology 2001; 33:504-8.
Palma J, Reyes, H, Ribalta J, et al. J Hepatol 1997; 27:1022-6.
Paumgartner G, Beuers U. Hepatology 2002; 36:525-31.
Rudi J, Schonig T, Stremmel W. Z Gastroenterol 1996; 34:188-91.
Sentilhes L, Verspyck E, Pia P, Marpeau L. Obstet Gynecol 2006; 107:458-60.

Summary

Pregnancy Category: B
Lactation Category: S

- **Ursodiol** is a first-line agent for the treatment of intrahepatic cholestasis of pregnancy.

Valacyclovir—(Valtrex)

International Brand Name—Rapivir (Mexico); Valcyclor (Colombia); Zelitrex (France, South Africa)

Drug Class	Antivirals
Indications	Genital herpes, herpes zoster
Mechanism	Inhibits DNA polymerase
Dosage with Qualifiers	Genital herpes—*primary:* 1000mg PO bid ×10d; *recurrent:* 500mg PO bid ×3d; *prophylaxis:* 1000mg PO qd Herpes zoster—1000mg PO tid ×7d *NOTE: renal dosing.* • **Contraindications**—hypersensitivity to drug or class, immune compromise • **Caution**—renal dysfunction
Maternal Considerations	After ingestion, **valacyclovir** is metabolized to and actually enhances **acyclovir** bioavailability. It is effective and well tolerated for HSV suppression for up to 10y of continuous use. Neonatal herpes affects 1/15,000 newborns. The vast majority of infected infants are born to women with a primary infection during pregnancy. While there are no adequate reports or well-controlled studies of **valacyclovir** in pregnant women, it is used extensively for the listed indications. If initiated prophylactically at 36w, **acyclovir** reduces both the risk of recurrence and the frequency of a positive cervical culture at delivery in women who experience either a primary infection or at least one secondary episode during pregnancy. There is insufficient evidence to determine if antiviral prophylaxis reduces the incidence of neonatal herpes. However, patients should be counseled that antenatal antiviral prophylaxis reduces viral shedding and recurrences at delivery and reduces the need for cesarean delivery for genital herpes. ***Side effects*** include renal failure, dysmenorrhea, N/V, headache, dizziness, arthralgia, depression, facial edema, hypertension, tachycardia, angioedema, rash, confusion, hallucinations, aplastic anemia, thrombocytopenia, anemia, leukopenia, and erythema multiforme.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. **Valacyclovir** crosses the human placenta. Maternal oral administration of **valacyclovir** leads to therapeutic concentrations in the maternal and fetal compartments, and in the instance of CMV, a decrease in the fetal viral load. However, it is unknown whether this decrease in CMV number is associated with decreased perinatal damage. **Acyclovir** crosses the rodent placenta. Post-marketing surveys suggest no increased frequency of birth defects. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically.
Breastfeeding Safety	**Valacyclovir** is converted to **acyclovir**, which enters human breast milk. However, the amount of **acyclovir** in breast milk during **valacyclovir** administration is <5% of the dose used to treat neonates.
Drug Interactions	No clinically relevant interactions identified.
References	Braig S, Luton D, Sibony O, et al. Eur J Obstet Gynecol Reprod Biol 2001; 96:55-8.

Brown SD, Bartlett MG, White CA. Antimicrob Agents Chemother 2003; 47:991-6.
Hollier LM, Wendel GD. Cochrane Database Syst Rev 2008; (1):CD004946.
Jacquemard F, Yamamoto M, Costa JM, et al. BJOG 2007; 114:1113-21.
Scott LL, Hollier LM, McIntire D, et al. Infect Dis Obstet Gynecol 2001; 9:75-80.
Sheffield JS, Fish DN, Hollier LM, et al. Am J Obstet Gynecol 2002; 186:100-2.
Sheffield JS, Hill JB, Hollier LM, et al. Obstet Gynecol 2006; 108:141-7.
Tyring SK, Baker D, Snowden W. J Infect Dis 2002; 186(Suppl 1):S40-6.
Watts DH, Brown ZA, Money D, et al. Am J Obstet Gynecol 2003; 188:836-43.

Summary

Pregnancy Category: B
Lactation Category: S

- **Valacyclovir** should be used during pregnancy only if the benefit justifies the potential perinatal risk.
- **Valacyclovir** is a first-line agent for the treatment of genital herpes and herpes zoster during pregnancy and lactation.
- Herpes prophylaxis at 36w reduces the risk of recurrence, and as a result, the need for cesarean delivery for recurrence.
- Physicians are encouraged to register pregnant women under the Pregnancy Registry (1-800-336-2176) for a better follow-up of the outcome while under treatment with **valacyclovir.**

Valdecoxib—(NOTE: This drug is no longer marketed in the US.)

International Brand Name—Bextra (Canada, Chile, Colombia, Hong Kong, Indonesia, Malaysia, New Zealand, Peru, Philippines, Singapore, Thailand, Venezuela); Valus (India)

Drug Class

Analgesics, non-narcotic; Antiarthritics; COX-2 inhibitors; NSAID

Indications

Osteoarthritis and rheumatoid arthritis, dysmenorrhea

Mechanism

Selective COX-2 antagonist

Dosage with Qualifiers

NOTE: This drug was removed from the US market in April 2005.

Osteoarthritis—10mg PO qd
Rheumatoid arthritis—10mg PO qd
Dysmenorrhea—20mg PO bid

- **Contraindications**—hypersensitivity to drug or class, hypersensitivity to ASA, NSAIDs, ASA/NSAID-induced asthma or urticaria, hepatic failure, severe renal dysfunction
- **Caution**—CHF, hypertension, nasal polyps, peptic ulcer disease, history of GI bleeding, hepatic or renal dysfunction, dehydration, asthma, fluid retention

Maternal Considerations

Valdecoxib is an NSAID with anti-inflammatory, analgesic, and antipyretic properties. In general, the COX-2 inhibitors are associated with a lower incidence of GI upset but potentially an increase in MI. **Valdecoxib** provides effective relief of dysmenorrhea, but does not appear to be more effective than alternative, nonselective NSAIDs. The manufacturer removed the drug from the US market after

concerns were raised about possible increased risks of MI and CVA. There is no published experience with **valdecoxib** during pregnancy. Its addition after cesarean delivery under spinal anesthesia with intrathecal **morphine** does not improve outcome. It has no effect on the timing of onset of rodent labor.
Side effects include GI bleeding or ulceration, esophagitis, bronchospasm, hypertension, CHF, hepatotoxicity, renal papillary necrosis, anemia, blood dyscrasias, dyspepsia, abdominal pain, N/V, diarrhea, dizziness, and peripheral edema.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **valdecoxib** crosses the human placenta. Other NSAIDs do cross and are associated with gastroschisis (1st trimester exposure), oligohydramnios, and ductal constriction. **Valdecoxib** increases the risk of skeletal malformations in some rodents when given at >70× the MRHD. IUGR is noted with doses >5× the MRHD.

Breastfeeding Safety

There is no published experience in nursing women. It is unknown whether **valdecoxib** enters human breast milk. It is found in rodent milk.

Drug Interactions

Predominantly metabolized by CYP3A4 and 2C9. It is a moderate inhibitor of CYP2C19 and 2C9, and a weak inhibitor of CYP2D6 and 3A4.
Use with **aspirin** may result in an increased risk of GI ulceration and complications. Because of its lack of antiplatelet effect, **valdecoxib** is not a substitute for **aspirin** for CV prophylaxis.
NSAIDs may diminish the antihypertensive effect of ACEIs.
Clinical studies, as well as post-marketing observations, reveal that NSAIDs may reduce the natriuretic effect of **furosemide** and thiazides in some patients. This response has been attributed to inhibition of renal prostaglandin synthesis.
Plasma levels are reduced by 27% when used with **phenytoin** (a CYP3A4 inducer). Patients already stabilized on **valdecoxib** should be closely monitored for loss of symptom control with **phenytoin** co-administration.
Use with **dextromethorphan,** primarily metabolized by CYP2D6 and to a lesser extent by 3A4, caused significantly increased **dextromethorphan** levels, suggesting **valdecoxib** is a weak inhibitor of 2D6. However, a dose adjustment is not necessary.
Decreases **lithium** serum clearance (25%) and renal clearance (30%), with a 34% higher serum exposure compared to **lithium** alone. **Lithium** serum concentrations should be monitored closely.
Fluconazole and **ketoconazole,** predominantly CYP3A4 and 2C9 inhibitors, respectively, increased **valdecoxib** AUC some 62% (**fluconazole**) and 38% (**ketoconazole**).
May increase the **omeprazole** AUC by 46%. Drugs whose absorption is sensitive to pH may be negatively impacted by concomitant administration of **omeprazole** and **valdecoxib.** However, because higher doses (up to 360mg qd) of **omeprazole** are tolerated in Zollinger-Ellison syndrome patients, no dose adjustment for **omeprazole** is recommended at current doses.
Increases **diazepam** levels by 28%. Although the magnitude of change is not sufficient to warrant a dose adjustment, patients may experience enhanced sedative side effects.

References

Carvalho B, Chu L, Fuller A, et al. Anesth Analg 2006; 103:664-70.
Stichtenoth DO, Frolich JC. Drugs 2003; 63:33-45.

Summary	**Pregnancy Category: C** **Lactation Category: U** • **Valdecoxib** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk. • There are alternative agents for which there is more experience regarding use during pregnancy and lactation and circumvent any concerns of increased risks of MI and CVA.

Valganciclovir—(Valcyte)

International Brand Name—Valixa (Colombia)

Drug Class	Antivirals
Indications	CMV retinitis associated with AIDS
Mechanism	Inhibits DNA polymerase
Dosage with Qualifiers	CMV retinitis associated with AIDS—begin 900mg PO bid with food ×21d, then qd *NOTE: renal dosing.* • **Contraindications**—hypersensitivity to drug or class, ANC <500/µl, Hb <8mg/dl, platelets <25,000/µl • **Caution**—bone marrow suppression, concomitant radiation, renal dysfunction
Maternal Considerations	**Valganciclovir** is metabolized to **ganciclovir.** There is no published experience with **valganciclovir** during pregnancy (see **ganciclovir**). ***Side effects*** include leukopenia, neutropenia, thrombocytopenia, aplastic anemia, bone marrow suppression, infertility, nephrotoxicity, peripheral neuropathy, retinal detachment, seizures, psychosis, N/V, diarrhea, fever, insomnia, abdominal pain, confusion, agitation, and increased creatinine.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. **Valganciclovir** crosses the isolated human placenta by passive diffusion. **Ganciclovir** is embryotoxic and teratogenic in various rodent models. Birth defects include cleft palate, craniofacial abnormalities, and pancreas and renal agenesis.
Breastfeeding Safety	There is no published experience in nursing women. It is unknown whether **valganciclovir** enters human breast milk. Breastfeeding is contraindicated in HIV-infected nursing women where formula is available to reduce the risk of neonatal transmission. (See **Ganciclovir.**)
Drug Interactions	See **Ganciclovir.**
References	There is no published experience in pregnancy or during lactation.
Summary	**Pregnancy Category: C** **Lactation Category: U** • **Valganciclovir** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk. • See **Ganciclovir.** • Physicians are encouraged to register pregnant women under the Pregnancy Registry (1-800-336-2176) for a better follow-up of the outcome while under treatment with **valganciclovir.**

Valproate—(Depacon; Epival)

International Brand Name—Convulex (Germany); Depakin (Bulgaria, Turkey); Depakine (Austria, Belgium, France, Greece, Hungary, Israel, Korea, Netherlands, Portugal, Spain, Switzerland, Thailand); Depakine Chrono (Belgium, Hungary, Poland, Portugal, Taiwan, Thailand); Depakine Druppels (Netherlands); Depalept (Israel); Depalept Chrono (Israel); Epilam (Korea); Epilex (Turkey); Epilim (China, England, Hong Kong, Ireland, Malaysia, Puerto Rico); Epilim Chrono (Malaysia); Epival (Costa Rica, Dominican Republic, El Salvador, Guatemala, Honduras, Israel, Nicaragua, Panama); Leptilan (Ecuador, Indonesia, Malaysia, Mexico, Puerto Rico, South Africa, Taiwan); Orfil (Korea); Orfiril (Hong Kong, Israel, Peru); Orfiril Retard (Singapore); Petilin (Israel, Puerto Rico, South Africa); Valcote (Ecuador); Valeptol (Korea); Valoin (Korea); Valpakine (Costa Rica, Dominican Republic, Ecuador, El Salvador, Guatemala, Honduras, Peru); Valparin (Thailand); Valporal (Israel); Valprax (Peru); Valpro (Hong Kong, New Zealand); Valsup (Colombia)

Drug Class	Anticonvulsants
Indications	Seizures
Mechanism	Unknown
Dosage with Qualifiers	Seizures—10-15mg/kg/d IV in divided doses qd to tid, increase by 5-10mg/kg/d q7d to achieve therapeutic trough of 50-100mcg/ml; max 60mg/kg/d *NOTE: switch to PO when feasible.* • **Contraindications**—hypersensitivity to drug or class, hepatic disease or dysfunction • **Caution**—renal dysfunction, bone marrow suppression, bleeding tendencies, congenital metabolic disorders, anticonvulsant use
Maternal Considerations	**Valproate** is the sodium salt of **valproic acid.** There are no adequate reports or well-controlled studies of **valproate** in pregnant women. There is a long clinical experience with **valproate.** It does not alter the efficacy of hormonal contraception. Patients planning pregnancy should be counseled on the risks and the importance of periconceptional folate supplementation. ***Side effects*** include potentially fatal hepatotoxicity, pancreatitis, bone marrow suppression, pancytopenia, aplastic anemia, thrombocytopenia, bleeding, hyponatremia, hyperammonemia, erythema multiforme, Stevens-Johnson syndrome, N/V, appetite and weight changes, dyspepsia, abdominal pain, diarrhea, asthenia, somnolence, tremor, alopecia, rash, peripheral edema, petechiae, blurred vision, nystagmus, tinnitus, SIADH, psychosis, and respiratory disorders.
Fetal Considerations	**Valproate** is a recognized human teratogen, increasing the relative risk by a factor of 4 with an overall prevalence of about 6%. The risk is compounded by a low serum folate. **Valproate** is rapidly and actively transported across the human placenta, reaching an F:M ratio exceeding 2. Recent pregnancy databases suggest valproate is significantly more teratogenic than **carbamazepine,** and the combination of **valproate** and **lamotrigine** is particularly teratogenic. For unknown reasons, **valproate** accumulates in the fetal plasma. A distinct facial appearance, coupled with a cluster of minor and major anomalies and CNS dysfunction, characterize the *fetal* ***valproate*** *syndrome.* The likelihood of the offspring being affected is dose-dependent. Ten percent die in infancy, and 1/4 survivors have either developmental deficits or mental retardation. Affected fetuses may have an increased nuchal translucency measurement. A fetal medicine specialist should

evaluate women taking **valproate** during pregnancy. As for most psychotropic drugs, monotherapy and the lowest effective quantity given in divided doses to minimize the peaks can theoretically minimize the risks. In one recent study, the outcomes of 154 **valproate**-exposed pregnancies (96% at least in the 1st trimester) were compared with those of 1315 unexposed pregnancies. The major anomaly rate in the **valproate** group exposed in the 1st trimester was higher than controls after exclusion of genetic or cytogenetic anomalies (6.7% vs. 2.5%, relative risk [RR] = 2.66). Five of the 8 major anomalies in the **valproate** group were CV, 2/8 were mental retardation, 2/5 male infants with major anomalies had hypospadias and 3/8 were suspected of having fetal **valproate** syndrome. A daily dose >1000mg was associated with the highest teratogenic risk (RR = 8.72). In the subgroup exposed to polytherapy, there was a 4-fold increase in the rate of major anomalies compared with controls. All major anomalies were in the group treated for epilepsy. In another study, those exposed to polytherapy *in utero* had significantly lower developmental quotients than those exposed to monotherapy. Polytherapy was a stronger predictor of lower developmental quotients than dose. Compared with **carbamazepine** monotherapy, **valproate** monotherapy was associated with significantly lower mental and motor developmental scores.

Breastfeeding Safety

Valproate enters human breast milk, but the neonatal concentration is <10% of the maternal.

Drug Interactions

The following information about the potential for several commonly prescribed medications to alter valproate pharmacokinetics is not exhaustive nor could it be, since new interactions are continuously being reported.

Drugs that affect the level of expression of hepatic enzymes, particularly those that elevate levels of glucuronosyltransferases, may increase clearance. For example, **carbamazepine, phenobarbital** (or **primidone**), and **phenytoin** can double **valproate** clearance. Thus, patients on monotherapy will generally have longer t/2s and higher concentrations than patients receiving polytherapy with AEDs.

Aspirin at antipyretic doses may decrease protein binding and inhibit **valproate** metabolism. **Valproate** free fraction was increased 4-fold in the presence of **aspirin** compared to **valproate** alone. Caution is indicated when using **aspirin.**

Felbamate increased the mean **valproate** peak level by 35-50% depending on the dose of **felbamate.** A decrease in the **valproate** dose may be necessary.

Rifampin may increase **valproate** clearance by some 40% and may necessitate a dose adjustment.

May decrease the clearance of both **amitriptyline** by 20% and **nortriptyline** by 30%. Use of **valproate** and **amitriptyline** has rarely been associated with toxicity. Monitoring of **amitriptyline** levels should be considered and consideration given to lowering the dose of **amitriptyline/nortriptyline.**

Decreases **carbamazepine** levels 17% while increasing its 10,11-epoxide metabolite by 45%.

Use with **clonazepam** may induce absence status in patients with a history of absence-type seizures.

Displaces **diazepam** from its plasma albumin binding sites and inhibits its metabolism, resulting in an almost doubling of the **diazepam** free fraction.

Increases by 25% the elimination t/2 of **ethosuximide** and decreases its total clearance by some 15%. Patients using both agents,

especially along with other AEDs, should be monitored for changes in the serum concentrations of both drugs.
Increases the elimination t/2 of **lamotrigine** by 165%. The **lamotrigine** dose should be reduced. Serious skin reactions (such as Stevens-Johnson syndrome and toxic epidermal necrolysis) have been reported in association with this combination.
Increases the t/2 of **phenobarbital** by 50% and decreased the plasma clearance by ⅓. The fraction of **phenobarbital** excreted unchanged increases by 50%.
All patients receiving barbiturate therapy should be closely monitored for neurologic toxicity. Serum barbiturate levels should be obtained, if possible, and the barbiturate dose decreased as appropriate. **Primidone,** which is metabolized to a barbiturate, may have a similar interaction with **valproate.**
Displaces **phenytoin** from its plasma albumin binding sites and inhibits its hepatic metabolism, increasing the free fraction some 60%. Total plasma clearance and apparent volume of distribution of **phenytoin** increase 30% in the presence of **valproate.** As there have been reports of breakthrough seizures occurring with this combination, the dose of **phenytoin** should be adjusted as clinically required.
The clearance of **zidovudine** was decreased by 38% in HIV-seropositive patients.

References

Chaudron LH, Jefferson JW. J Clin Psychiatry 222; 61:79-90.
Crawford P. CNF Drugs 2002; 16:263-72.
Diav-Citrin O, Shechtman S, Bar-Oz B, et al. CNS Drugs 2008; 22:325-34.
Kaaja E, Kaaja R, Hiilesmaa V. Neurology 2003; 60:575-9.
Kozma C. Am J Med Genet 2001; 98:168-75.
Mawer G, Clayton-Smith J, Coyle H, Kini U. Seizure 2002; 11:512-8.
Nakamura H, Ushigome F, Koyabu N, et al. Pharm Res 2002; 19:154-61.
Nau H, Kuhnz W, Egger HJ, et al. Clin Pharmacokinet 1982; 7:508-43.
Philbert A, Pedersen B, Dam M. Acta Neurol Scand 1985; 72:460-3.
Samren EB, van Duijn CM, Koch S, et al. Epilepsia 1997; 38:981-90.
ten Berg K, Lindhout D. Clin Dysmorphol 2002; 11:227-8.
Thomas SV, Ajaykumar B, Sindhu K, et al. Epilepsy Behav 2008; 13:229-36.
Thomas SV, Ajaykumar B, Sindhu K, et al. Pediatr Cardiol 2008 (in press).
Tsuru N, Maeda T, Tsuruoka M. Jpn J Psychiatry 1988; 42:89-96.
Witters I, Van Assche F, Fryns JP. Prenat Diagn 2002; 22:834-5.

Summary

Pregnancy Category: D
Lactation Category: S

- **Valproate** is a recognized human teratogen.
- The risk of a defect is compounded by folate deficiency.
- **Valproate** should be used during pregnancy only if the benefit justifies the potential perinatal risk.
- When **valproate** treatment cannot be avoided in the 1st trimester, the lowest effective dose should be prescribed, preferably as monotherapy in divided doses to minimize the peaks.

Valproic acid—(Depakene; Myproic acid)

International Brand Name—Atemperator (Ecuador); Convulex (Austria, Belgium, Bulgaria, Czech Republic, England, Ireland, Russia, Singapore, South Africa, Switzerland, Taiwan); Depakene (Japan); Depakin (Italy); Depakine (Russia, Taiwan, Venezuela); Epilim (Malaysia); Epilim Chrono 500 (Malaysia); Leptilan (Portugal); Orfiril (Germany); Valpakine (Costa Rica, El Salvador, Guatemala, Honduras); Valporal (Israel); Valprosid (Mexico)

Drug Class ..... Anticonvulsants; Bipolar agents; Migraine agents

Indications ..... Seizures, mania, migraine prophylaxis

Mechanism ..... Unknown

Dosage with Qualifiers .....

Seizures—10-15mg/kg/d PO with meals in divided doses qd to tid, increase by 5-10mg/kg/d q7d to achieve therapeutic trough of 50-100mcg/ml; max 60mg/kg/d
Mania—10-15mg/kg/d PO with meals in divided doses qd to tid, increase by 5-10mg/kg/d q7d to achieve therapeutic trough of 50-100mc/ml; max 60mg/kg/d
Migraine prophylaxis—250-500mg PO with meals bid

- **Contraindications**—hypersensitivity to drug or class, hepatic disease or dysfunction
- **Caution**—renal dysfunction, bone marrow suppression, bleeding tendencies, congenital metabolic disorders, anticonvulsant use

Maternal Considerations .....

Most pregnancies are uneventful in women with epilepsy, and most babies are delivered healthy with no increased risk of obstetric complications in women. There is a long clinical experience with **valproic acid.** It does not alter the efficacy of hormonal contraception. Patients planning pregnancy should be counseled on the risks and the importance of periconceptual folate supplementation.
Side effects include potentially fatal hepatotoxicity, pancreatitis, SIADH, thrombocytopenia, pancytopenia, aplastic anemia, bone marrow suppression, bleeding, hyponatremia, hyperammonemia, erythema multiforme, Stevens-Johnson syndrome, psychosis, N/V, appetite and weight change, dyspepsia, diarrhea, abdominal pain, asthenia, somnolence, tremor, alopecia, rash, peripheral edema, petechiae, blurred vision, nystagmus, tinnitus, and respiratory disorders.

Fetal Considerations .....

Valproate is a recognized human teratogen, increasing the relative risk by a factor of 4 with an overall prevalence of about 6%. The risk is compounded by a low serum folate. **Valproate** is rapidly and actively transported across the human placenta, reaching an F:M ratio exceeding 2. Recent pregnancy databases suggest valproate is significantly more teratogenic than **carbamazepine,** and the combination of **valproate** and **lamotrigine** is particularly teratogenic. For unknown reasons, **valproate** accumulates in the fetal plasma. A distinct facial appearance, coupled with a cluster of minor and major anomalies and CNS dysfunction, characterize the *fetal **valproate** syndrome.* The likelihood of the offspring being affected is dose-dependent. Ten percent die in infancy, and 1/4 survivors have either developmental deficits or mental retardation. Affected fetuses may have an increased nuchal translucency measurement. A fetal medicine specialist should evaluate women taking **valproate** during pregnancy. As for most psychotropic drugs, monotherapy and the lowest effective quantity given in divided doses to minimize the peaks can

theoretically minimize the risks. In one recent study, the outcomes of 154 **valproate**-exposed pregnancies (96% at least in the 1st trimester) were compared with those of 1315 unexposed pregnancies. The major anomaly rate in the **valproate** group exposed in the 1st trimester was higher than controls after exclusion of genetic or cytogenetic anomalies (6.7% vs. 2.5%, relative risk [RR] = 2.66). Five of the 8 major anomalies in the **valproate** group were CV, 2/8 were mental retardation, 2/5 male infants with major anomalies had hypospadias and 3/8 were suspected of having fetal **valproate** syndrome. A daily dose >1000mg was associated with the highest teratogenic risk (RR = 8.72). In the subgroup exposed to polytherapy, there was a 4-fold increase in the rate of major anomalies compared with controls. All major anomalies were in the group treated for epilepsy. In another study, those exposed to polytherapy *in utero* had significantly lower developmental quotients than those exposed to monotherapy. Polytherapy was a stronger predictor of lower developmental quotients than dose. Compared with **carbamazepine** monotherapy, **valproate** monotherapy was associated with significantly lower mental and motor developmental scores.

Breastfeeding Safety

Valproic acid enters human breast milk, but the neonatal concentration is <10% of the maternal.

Drug Interactions

The following information about the potential for several commonly prescribed medications to alter valproate pharmacokinetics is not exhaustive nor could it be, since new interactions are continuously being reported.

Drugs that affect the level of expression of hepatic enzymes, particularly those that elevate levels of glucuronosyltransferases, may increase clearance. For example, **carbamazepine, phenobarbital** (or **primidone**), and **phenytoin** can double **valproate** clearance. Thus, patients on monotherapy will generally have longer t/2s and higher concentrations than patients receiving polytherapy with AEDs.

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May decrease the clearance of both **amitriptyline** by 20% and **nortriptyline** by 30%. Use of **valproate** and **amitriptyline** has rarely been associated with toxicity. Monitoring of **amitriptyline** levels should be considered and consideration given to lowering the dose of **amitriptyline/nortriptyline.**

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Displaces **diazepam** from its plasma albumin binding sites and inhibits its metabolism, resulting in an almost doubling of the **diazepam** free fraction.

Increases by 25% the elimination t/2 of **ethosuximide** and decreases its total clearance by some 15%. Patients using both agents, especially along with other AEDs, should be monitored for changes in the serum concentrations of both drugs.

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References

Chaudron LH, Jefferson JW. J Clin Psychiatry 222; 61:79-90.
Crawford P. CNF Drugs 2002; 16:263-72.
Crawford P. Epilepsia 2005; 46(Suppl 9):117-24.
Diav-Citrin O, Shechtman S, Bar-Oz B, et al. CNS Drugs 2008; 22:325-34.
Kaaja E, Kaaja R, Hiilesmaa V. Neurology 2003; 60:575-9.
Kozma C. Am J Med Genet 2001; 98:168-75.
Mawer G, Clayton-Smith J, Coyle H, Kini U. Seizure 2002; 11:512-8.
Nakamura H, Ushigome F, Koyabu N, et al. Pharm Res 2002; 19:154-61.
Nau H, Kuhnz W, Egger HJ, et al. Clin Pharmacokinet 1982; 7:508-43.
Philbert A, Pedersen B, Dam M. Acta Neurol Scand 1985; 72:460-3.
Samren EB, van Duijn CM, Koch S, et al. Epilepsia 1997; 38:981-90.
ten Berg K, Lindhout D. Clin Dysmorphol 2002; 11:227-8.
Thomas SV, Ajaykumar B, Sindhu K, et al. Epilepsy Behav 2008; 13:229-36.
Thomas SV, Ajaykumar B, Sindhu K, et al. Pediatr Cardiol 2008 (in press).
Tsuru N, Maeda T, Tsuruoka M. Jpn J Psychiatry 1988; 42:89-96.
Witters I, Van Assche F, Fryns JP. Prenat Diagn 2002; 22:834-5.

Summary

Pregnancy Category: D
Lactation Category: S

- **Valproic acid** is a recognized human teratogen.
- The risk of a defect is compounded by folate deficiency.
- **Valproic acid** should be used during pregnancy only if the benefit justifies the potential perinatal risk.
- As for most psychotropic drugs, monotherapy and the lowest effective quantity given in divided doses to minimize the peaks may minimize the risks.

Valsartan—(Diovan)

International Brand Name—Nisis (France); Provas (Germany); Tareg (France)

Drug Class — ACEI/A2R-antagonists

Indications — Hypertension

Mechanism — Selective AT-1 antagonist

Dosage with Qualifiers — Hypertension—begin 80-160mg PO qd if monotherapy; max 320mg/d

- **Contraindications**—hypersensitivity to drug or class
- **Caution**—CHF, history of ACEI-induced angioedema, renal artery stenosis, hepatic or renal dysfunction, volume depletion, hyponatremia

Maternal Considerations — **Valsartan** has no significant advantages over similar agents in its class for which there is more experience. Nor has it been demonstrated to reduce the complications of arterial hypertension. There are no adequate reports or well-controlled studies of **valsartan** in pregnant women. Only a half dozen pregnancy exposures are reported, some with poor outcomes typical of this drug class. Inhibitors of the renin-angiotensin system should be avoided during pregnancy because of their fetal implications.
Side effects include angioedema, severe hypotension, hyperkalemia, URI symptoms, dizziness, fatigue, dyspepsia, back pain, and diarrhea.

Fetal Considerations — There are no adequate reports or well-controlled studies in human fetuses. Drugs that act directly on the renin-angiotensin system can cause perinatal morbidity and death. Adverse outcomes are reported for **valsartan** suggesting it crosses the human placenta. Drugs that inhibit the fetal renin-angiotensin system are now recognized to be potentially teratogenic throughout gestation; the risks are greatest after the 1st trimester. The mechanisms may well be different for ACEIs and AT-1 receptor antagonists. In the 2nd and 3rd trimester, morbidity includes hypotension, neonatal skull hypoplasia, anuria, and reversible or irreversible renal failure. Oligohydramnios may be associated with limb contractures, craniofacial deformation, and hypoplastic lung development. Rarely, an alternative drug is not available. In these cases, the women should be counseled on the hazards, and serial ultrasound examinations should be performed to assess the intra-amniotic environment. If oligohydramnios is observed, the **valsartan** should be discontinued unless lifesaving for the mother. Antenatal surveillance may be appropriate depending upon gestation. Oligohydramnios may not appear until after the fetus has sustained irreversible injury.

Breastfeeding Safety — There is no published experience in nursing women. It is unknown whether **valsartan** enters human breast milk.

Drug Interactions — As with other drugs that block angiotensin II or its effects, potassium-sparing diuretics (e.g., **amiloride, spironolactone, triamterene**), potassium supplements, or salt substitutes containing potassium may increase serum potassium and, in heart failure, increase serum creatinine.

■ **References** ····· Berkone N, Carlier P, Verstraete L, et al. Birth Defects Res A Clin Mol Teratol 2004; 70:547-9.
Biswas PN, Wilton LV, Shakir SW. J Hum Hypertens 2002; 16:795-803.
Briggs GG, Nageotte MP. Ann Pharmacother 2001; 35:859-61.
Roger N, Popovic I, Madelenat P, Mahieu-Caputo D. Gynecol Obstet Fertil 2007; 35:556-60.

■ **Summary** ·····

Pregnancy Category: C (1st trimester), **D** (2nd and 3rd trimesters)
Lactation Category: U

- **Valsartan** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.
- Women should be counseled on the risks and switched to a different class of antihypertensives prior to conception or during the 1st trimester.
- There are alternative agents for which there is more experience regarding use during pregnancy and lactation.

Vancomycin—(Balcorin; Edicin; Ledervan; Lyphocin; Vancocin; Vancoled; Vancor)

International Brand Name—Amplobac (Brazil); Balcorin (Mexico); Diatracin (Spain); Edicin (Thailand); Icoplax (Argentina); Ifavac (Mexico); Vagran (Venezuela); Vanauras (Mexico); Vancam (Mexico); Vanccostacin (Korea); Vanco (Germany); Vancocid (Brazil); Vancocina (Italy, Peru); Vancocina CP (Chile); Vancocin CP (Bulgaria, China, Czech Republic, Hong Kong, Hungary, Malaysia, Mexico, South Africa, Taiwan, Thailand); Vancocine (France); Vancocin HCl (Argentina, Belgium, Canada, Denmark, England, Finland, Hong Kong, Ireland, Korea, New Zealand, Norway, Philippines, Sweden, Switzerland, Taiwan); Vancocin HCl Pulvules (Australia); Vancoled (Israel, Malaysia, Taiwan); Vancomax (Paraguay); Vancomicina (Ecuador); Vanco-Teva (Israel); Vancox (Mexico); Vanmicina (Mexico); Varedet (Uruguay); Voncon (Greece)

■ **Drug Class** ····· Antibiotics; Glycopeptides

■ **Indications** ····· Bacterial infections, endocarditis prophylaxis

■ **Mechanism** ····· Bactericidal—inhibits cell wall and RNA synthesis

■ **Dosage with Qualifiers** ····· Bacterial infections—500mg IV q6h; peak 25-40mcg/ml, trough 5-10mcg/ml
Endocarditis prophylaxis—1g slow IV over 1h

NOTE: renal dosing.

- **Contraindications**—hypersensitivity to drug or class
- **Caution**—hepatic or renal dysfunction, hearing loss, nephrotoxic agents

■ **Maternal Considerations** ····· **Vancomycin** is most commonly used for the treatment of MRSA infections. There are no adequate reports or well-controlled studies of **vancomycin** in pregnant women. In one series, adverse events were common, suggesting that longer infusion times and weight-adjusted doses should be used. It is used as a second-line agent for the treatment of postpartum endomyometritis, and as a first-line agent and alternative to **metronidazole** for the treatment of *C. difficile* diarrhea. Other applications during pregnancy include listeriosis and bacterial endocarditis in IV drug users. ***Side effects*** include neutropenia, Stevens-Johnson syndrome, thrombocytopenia, toxic epidermal necrolysis, nephrotoxicity,

	ototoxicity, chills, fever, nausea, tinnitus, superinfection, urticaria, rash, "red man" syndrome, and phlebitis.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. **Vancomycin** crosses the human placenta in a predictable manner, achieving concentrations that exceed the usual GBS inhibitory level. In contrast, transplacental passage of **vancomycin** was minimal in an *ex vivo* human placental perfusion model, yielding no detectable accumulation. There is no obvious explanation. Concern that **vancomycin** exposure might cause ototoxicity has not been substantiated. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically.
Breastfeeding Safety	There are no adequate reports or well-controlled studies in nursing women. **Vancomycin** enters human breast milk, but the kinetics remain to be elucidated. Considering the poor oral absorption, it is unlikely the breastfed neonate would ingest a clinically relevant amount.
Drug Interactions	Use with anesthetic agents has been associated with erythema and histamine-like flushing and anaphylactoid reactions. Concurrent and/or sequential systemic or topical use of other potentially neurotoxic and/or nephrotoxic drugs (e.g., aminoglycosides, **amphotericin B, bacitracin, cisplatin,** colistin, **polymyxin B,** viomycin) requires careful monitoring.
References	Bonacorsi S, Doit C, Aujard Y, et al. Clin Infect Dis 1993; 17:139-40. Bourget P, Fernandez H, Delouis C, Ribou F. Obstet Gynecol 1991; 78:908-11. Hnat MD, Gainer J, Bawdon RE, Wendel GD Jr. Infect Dis Obstet Gynecol 2004; 12:57-61. James AH, Katz VL, Dotters DJ, Rogers RG. South Med J 1997; 90:889-92. Laiprasert J, Klein K, Mueller BA, Pearlman MD. Obstet Gynecol 2007; 109:1105-10. Reyes MP, Ostrea EM Jr, Cabinian AE, et al. Am J Obstet Gynecol 1989; 161:977-81.
Summary	**Pregnancy Category: B** **Lactation Category: S** • **Vancomycin** should be used during pregnancy only if the benefit justifies the potential perinatal risk. • It should probably be reserved for antibiotic-resistant bacterial infections.

Varicella vaccine—(Varivax)

International Brand Name—Okavax (Hong Kong); Suduvax (Korea); Vaccin Varilrix (France); Varilrix (Argentina, Brazil, Chile, Colombia, Costa Rica, Denmark, Dominican Republic, El Salvador, England, Guatemala, Honduras, Hong Kong, Hungary, India, Indonesia, Ireland, Israel, Korea, Mexico, Nicaragua, Panama, Paraguay, Peru, Philippines, Taiwan, Thailand, Uruguay); Varipox (India); Varivax (Canada, England, Hong Kong, Ireland, Philippines); Varivax II (Australia); V-Z Vax (Philippines)

Drug Class	Vaccines
Indications	Varicella susceptibility
Mechanism	Active immunity

Dosage with Qualifiers

Varicella susceptibility—0.5ml SC and a second 0.5ml SC in 4-8w

- **Contraindications**—hypersensitivity to drug or class; blood dyscrasias; leukemia, lymphomas, or other malignant neoplasms affecting the bone marrow or lymphatic systems; immune suppression or compromise (acquired or congenital); febrile illness; active TB
- **Caution**—acute lymphocytic leukemia in remission

Maternal Considerations

Varicella is a cause of significant maternal and fetal morbidity and mortality. The attack rate of natural varicella after household exposure among healthy susceptible people approaches 90%. **Varicella vaccine** is a live, attenuated preparation, and as such is usually contraindicated during pregnancy. Most adverse events associated with **varicella vaccine** are minor, and serious complications rare. If vaccine virus transmission occurs, it does so at a very low rate and possibly without recognizable clinical disease. Most complications are instead associated with wild-type virus. Seventy percent of women in North America who do not remember having childhood varicella are actually immune. It is wise to test women of reproductive age planning pregnancy, and selectively immunize preconception if indicated. It is estimated that selective serologic screening of pregnant women with postpartum vaccination of susceptible women is cost-effective and would prevent half the cases of congenital varicella. There are no adequate reports or well-controlled studies of **varicella vaccine** in pregnant women. Inadvertent administration during pregnancy produces maternal immunity. There are reports of its erroneous administration when **varicella-zoster immune globulin** was ordered.

Side effects include fever, injection site reactions, vesicular lesions, upper respiratory illness, headache, fatigue, cough, myalgia, disturbed sleep, N/V, malaise, diarrhea, stiff neck, irritability/nervousness, lymphadenopathy, chills, eye complaints, abdominal pain, loss of appetite, arthralgia, otitis, itching, other rashes, constipation, lower respiratory illness, and allergic reactions.

Fetal Considerations

Varicella is a human teratogen. Abnormalities are usually related to CNS and peripheral nerve infection. They include skin lesions in dermatomal distribution, neurologic disease, and skeletal anomalies. The frequency of the syndrome is low (0.4-1.2% of infected cases) and gestational age related. There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether the attenuated virus comprising the **varicella vaccine** crosses the human placenta. Wild-type virus does cross. Inadvertent immunization during pregnancy is unassociated with fetal pathology and is not *a priori* an indication for pregnancy termination. A voluntary Pregnancy Registry established by the manufacturer (Merck & Co.) recorded 981 women inadvertently vaccinated during the 1st trimester between 1995 and 2005, among whom the pregnancy outcomes were known. There was no evidence of congenital varicella syndrome and the major birth defect rate was 3.7%. Longitudinal study demonstrates the fetal immunologic response to congenital varicella may not be sustained. Molecular testing is recommended. Rodent teratogenicity studies have not been performed.

Breastfeeding Safety

There is no published experience with **varicella vaccine** in nursing women. According to one study by the manufacturer, it does not appear to enter human breast milk. Twelve women were enrolled postpartum; all seroconverted after the first vaccine dose. Varicella DNA was not detected by polymerase chain reaction

(PCR) in any of the 217 postvaccination breast milk specimens. None of the infants was seropositive. Samples from 6 infants were tested for varicella-zoster virus DNA by PCR, and all were negative. In contrast, wild-type virus is excreted into human breast milk and can cause neonatal infection.

Drug Interactions ..... No clinically relevant interactions identified.

References .....

Bohlke K, Galil K, Jackson LA, et al. Obstet Gynecol 2003; 102:970-7.
Gidai J, Bács E, Czeizel E. Orv Hetil 2007; 148:1373-9.
Harger JH, Ernest JM, Thurnau GR, et al. Obstet Gynecol 2002; 100:260-5.
Salzman MB, Sharrar RG, Steinberg S, LaRussa P. J Pediatr 1997; 131:151-4.
Shields KE, Galil K, Seward RG, et al. Obstet Gynecol 2001; 98:14-9.
Smith WJ, Jackson LA, Watts, DH, Koepsell TD. Obstet Gynecol 1998; 92:535-45.
Wilson E, Goss MA, Marin M, et al. J Infect Dis 2008; 197 (Suppl2):S178-84.
Wise RP, Braum MM, Seward JF, et al. Pharmacoepidemiol Drug Saf 2002; 11:651-4.
Wise RP, Salive ME, Braum MM, et al. JAMA 2000; 284:3129.
Yoshida M, Yamagami N, Tezuka T, Hondo R. J Med Virol 1992; 38:108-10.

Summary .....

Pregnancy Category: C
Lactation Category: NS (possibly)

- **Varicella vaccine** administration is contraindicated during pregnancy.
- A cogent societal cost:benefit argument can be made for selective serologic screening during pregnancy and postpartum vaccination of susceptible women.
- Inadvertent immunization during pregnancy is not associated with fetal pathology and is not *a priori* an indication for pregnancy termination.

Varicella-zoster immune globulin—(VZIG; Varitect)

International Brand Name—Varitect (Hong Kong, Taiwan, Thailand)

Drug Class ..... Immune globulins

Indications ..... Varicella susceptibility and exposure

Mechanism ..... Passive immunization

Dosage with Qualifiers .....

Varicella susceptibility and exposure—625U IM ×1

- **Contraindications**—hypersensitivity to drug or class, severe thrombocytopenia if IM
- **Caution**—avoid intravascular injection

Maternal Considerations .....

Varicella is a cause of significant maternal and fetal morbidity and mortality. Varicella pneumonia is perhaps the most serious maternal complication, with mortality rates in excess of 10%. Current smokers and women with more than 100 lesions are at particularly high risk. There are no adequate reports or

well-controlled studies of **varicella-zoster immune globulin** in pregnant women. There is no evidence that administration to a susceptible, pregnant woman prevents viremia, fetal infection, or congenital varicella syndrome. The goal is to reduce the maternal sequelae of varicella rather than to prevent intrauterine infection. Women with no history of varicella and an unknown immune status should be tested as soon as the exposure is recognized. Seventy percent of women with no history of childhood varicella are immune. **Varicella-zoster immune globulin** administered within 24h of exposure may reduce the severity of maternal disease and is typically coupled with a course of **acyclovir.** The newer IV form achieves higher initial anti-varicella antibodies than the IM format. Though the effectiveness of this practice is unclear, case series indicate improved outcomes. Neonatal studies suggest the combination of immune globulin and **acyclovir** is more effective than monotherapy.
Side effects include pain, redness, or swelling at the injection site; GI symptoms; malaise; headache; rash; respiratory symptoms; and angioneurotic edema.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. It is likely **varicella-zoster immune globulin** crosses the human placenta, but it is unknown whether such transfer conveys a level of passive immunity. Neonatal varicella is more likely severe when the maternal rash appears 5d prior to or 2d after delivery. These newborns should receive immune globulin immediately. Intravenous **acyclovir** is recommended for severely affected neonate. Unlike primary varicella infection in pregnancy, herpes zoster has not been documented to cause complications unless in the disseminated form. Newborns of women who develop varicella 7d before or up to 28d after delivery should be given **varicella-zoster immune globulin** and possibly **acyclovir.**

Breastfeeding Safety

There are no adequate reports or well-controlled studies in nursing women. It is unknown whether **varicella-zoster immune globulin** enters human breast milk. Other IgG immunoglobulins do, and breastfeeding is encouraged as a potential source of neonatal passive immunization.

Drug Interactions

Varicella-zoster immune globulin may reduce the response to live vaccines.

References

Gregorakos L, Myrianthefs, Markou N, et al. Respiration 2002; 69:330-4.
Harger JH, Ernest JM, Thurnau GR, et al. J Infect Dis 2002; 185:422-7.
Heuchan AM, Issacs D. Med J Aust 2001; 174:288-92.
Koren G, Money D, Boucher M, et al. J Clin Pharmacol 2002; 42:267-74.
Wise RP, Braun MM, Seward JF, et al. Pharmacoepidemiol Drug Saf 2002; 11:651-4.

Summary

Pregnancy Category: C
Lactation Category: S

- Varicella is a cause of significant maternal and fetal morbidity and death.
- **Varicella-zoster immune globulin** should be used during pregnancy only if the benefit justifies the potential perinatal risk.
- 70% of pregnant women who do not recall childhood varicella are immune.
- Susceptible women may benefit from **varicella-zoster immune globulin** and **acyclovir** given within 24-48h of exposure.

Vasopressin—(Pitressin)

International Brand Name—Pitressin (Australia, England, Germany, Hong Kong, Indonesia, Ireland, Taiwan); Pressyn (Canada); Vasopin (India)

Drug Class	Antidiuretics; Hormones
Indications	Diabetes insipidus, abdominal distention, abdominal radiographs, renal biopsy, GI hemorrhage, ACLS, VF/pulseless ventricular tachycardia
Mechanism	Smooth muscle V1 agonist
Dosage with Qualifiers	Diabetes insipidus—5-10U IM/SC bid to qid; max 60U/d Abdominal distention—5-10U IM q3-4h prn Abdominal radiographs—5-15U IM/IV 2h and 30min preoperatively Renal biopsy—5-15U IM/IV 2h and 30min preoperatively GI hemorrhage—0.2-0.4U/min IV ACLS, VF/pulseless ventricular tachycardia—40U IV ×1 • **Contraindications**—hypersensitivity to drug or class • **Caution**—CHF, CAD, severe hepatic disease, renal dysfunction, asthma, migraine
Maternal Considerations	V1 receptors are widely distributed in smooth muscle, including the myometrium. Women with dysmenorrhea have higher vasopressin levels. There are no adequate reports or well-controlled studies of **vasopressin** in pregnant women. Doses of **vasopressin** sufficient for an antidiuretic effect are unlikely to produce tonic uterine contractions deleterious to the fetus or threaten the continuation of the pregnancy. DDAVP is now the first choice for the treatment of diabetes insipidus and von Willebrand's disease. It has also been used to treat gestational diabetes insipidus. ***Side effects*** include MI, water intoxication, arrhythmia, bradycardia, angina, hypertension, headache, uterine cramping, bronchospasm, angioedema, venous thrombosis, N/V, abdominal pain, flatulence, diarrhea, sweating, tremor, pallor, vertigo, rash, fever, and urticaria.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **vasopressin** crosses the human placenta. Rodent teratogenicity studies have not been performed.
Breastfeeding Safety	There are no adequate reports or well-controlled studies in nursing women. Little **vasopressin** enters human breast milk, and it does not pose a significant risk to the breastfeeding neonate.
Drug Interactions	Antidiuretic effect may be enhanced when used with **carbamazepine, chlorpropamide, clofibrate, fludrocortisone,** TCAs, and **urea.** Antidiuretic effect may be decreased by **demeclocycline,** ethanol, **heparin, lithium,** and NE. Ganglionic blocking agents may produce a marked increase in sensitivity to the pressor effects.
References	Burrow GN, Wassenaar W, Robertson GL, Sehl H. Acta Endocrinol 1981; 97:23-5.

Silcox J, Schultz P, Horbay GL, Wassenaar W. Obstet Gynecol 1993; 82:456-9.

Summary

Pregnancy Category: C
Lactation Category: S

- **Vasopressin** should be used during pregnancy only if the benefit justifies the potential perinatal risk.
- Pregnancy should not preclude its use for diagnostic or lifesaving procedures.

Vecuronium—(Musculax; Norcuron)

International Brand Name—Musculax (Japan); Norcuron (Argentina, Brazil, Canada, Chile, China, Ecuador, Hong Kong, India, Indonesia, Malaysia, Mexico, Philippines, South Africa, Taiwan, Venezuela); Vecron (Korea); Vecural (Paraguay, Uruguay); Vecuron (Thailand)

Drug Class

Anesthetics, adjunct; Neuromuscular blockers, nondepolarizing; Skeletal muscle relaxants

Indications

Paralysis

Mechanism

Competitive ACh motor end plate antagonist

Dosage with Qualifiers

Paralysis—begin 0.08-0.1mg/kg IV, then 25-45min after load, 0.01-0.015mg/kg IV q15-30min as indicated by train-of-4 peripheral nerve stimulation

- **Contraindications**—hypersensitivity to drug or class, bronchogenic carcinoma
- **Caution**—hepatic dysfunction, hypovolemia

Maternal Considerations

Vecuronium is a nondepolarizing neuromuscular blocker. There are no adequate reports or well-controlled studies of **vecuronium** in pregnant women. Popular during cesarean delivery as an adjunct to general anesthesia, its effect may be prolonged by the concurrent administration of **magnesium sulfate** and possibly **clindamycin.**
Side effects include arrhythmia, tachycardia, bradycardia, hypotension, bronchospasm, and flushing.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. A limited amount of **vecuronium** crosses the human placenta within 5min, achieving a fetal concentration of 79ng/ml and an F:M ratio <0.07. It is administered directly to the fetus as an alternative to **pancuronium** during fetal procedures. In contrast to **pancuronium, vecuronium** has no effect on the FHR. This is an advantage for many procedures, but a potential drawback when used with fetal intravascular transfusion. Fetal paralysis modestly reduces oxygen consumption. Rodent teratogenicity studies have not been performed.

Breastfeeding Safety

There is no published experience in nursing women. It is unknown whether **vecuronium** enters human breast milk. Though similar to **pancuronium, vercuronium's** clearance is faster and t/2 shorter. Considering the indication and dosing, limited **vecuronium** use is unlikely to pose a clinically significant risk to the breastfeeding neonate.

Drug Interactions

Succinylcholine may enhance the neuromuscular blocking effect and prolong its duration. If **succinylcholine** is to be used, the **vecuronium** should be delayed until the **succinylcholine** shows signs of wearing off.
Other nondepolarizing neuromuscular blocking agents (e.g., **gallamine, metocurine, pancuronium,** *d*-**tubocurarine**) may have an additive effect when used together. There are insufficient data to support concomitant use of **vecuronium** and other competitive muscle relaxants in the same patient.
Use with volatile inhalational anesthetics (e.g., **enflurane, halothane, isoflurane**) will enhance neuromuscular blockade. Potentiation is most prominent with **enflurane** and **isoflurane.**
High parenteral doses of certain antibiotics (e.g., aminoglycosides [**dihydrostreptomycin, gentamicin, kanamycin, neomycin, streptomycin**], **bacitracin,** colistin, colistimethate, **polymyxin B,** tetracyclines) may intensify or produce neuromuscular block on their own.
Recurrent paralysis may occur after **quinidine** injection.
Magnesium sulfate, administered for the management of preeclampsia, may enhance the neuromuscular blockade.

References

Kaneko T, Iwama H, Tobishima S, et al. Masui 1997; 46:750-4.
Sloan PA, Rasul M. Anesth Analg 2002; 94:123-4.
Watson WJ, Atchison SR, Harlass FE. J Matern Fetal Med 1996; 5:151-4.
Weiner CP, Anderson TL. Obstet Gynecol 1989; 73:219-24.
Yoshida A, Itoh Y, Nagaya K, et al. J Anesth 2006; 20:33-5.

Summary

Pregnancy Category: C
Lactation Category: S

- **Vecuronium** is a useful adjunct to general anesthesia during pregnancy and lactation and for fetal procedures.
- **Vecuronium** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Venlafaxine—(Effexor; Trewilor)

International Brand Name—Efectin (Bulgaria, Czech Republic, Hungary, Poland); Efexor (Argentina, Austria, Belgium, Brazil, Canada, Colombia, Costa Rica, Denmark, Dominican Republic, El Salvador, England, Greece, Guatemala, Honduras, Hong Kong, Ireland, Italy, Korea, Mexico, Netherlands, Nicaragua, Panama, Peru, Philippines, South Africa, Sweden, Switzerland, Thailand); Efexor XR (Argentina, Brazil, Canada, Chile, Colombia, Ecuador, Israel, Malaysia, Mexico, Peru, Philippines, Singapore, Thailand, Venezuela); Efexor-XR SR (Korea); Effexor (France); Elafax (Paraguay, Uruguay); Elafax XR (Paraguay, Uruguay); Trevilor (Germany, Switzerland); Trewilor (Austria); Vaxor (Israel); Venix-XR (India); Venla (Israel); Venlax (Chile); Venlax Retard (Chile); Viepax (Israel); Viepax XR (Israel)

Drug Class

Antidepressants, miscellaneous

Indications

Depression

Mechanism

Inhibits NE, serotonin, and dopamine reuptake

Dosage with Qualifiers

Depression—begin 37.5mg PO with meals bid and increase q4h as needed; max 375mg/d

NOTE: hepatic and renal dosing; taper over 2w.

- **Contraindications**—hypersensitivity to drug or class, MAOI <14d
- **Caution**—hepatic or renal dysfunction, seizures, history of mania, suicide risk

Maternal Considerations

Depression is common during and after pregnancy, but typically goes unrecognized. Pregnancy is not a reason *a priori* to discontinue psychotropic drugs. There are no adequate reports or well-controlled studies of **venlafaxine** in pregnant women. In one woman, the elimination t/2 declined from 8.7h to 3.2h from the 1st to 3rd trimesters. Plasma levels likewise declined.
Venlafaxine may be effective for the treatment of other disorders, including OCD, panic disorder, eating disorders, substance abuse, headaches, hot flashes, and chronic pain (including neuropathic pain).
Side effects include seizures, headache, N/V, diarrhea, somnolence, anorexia, weight loss, constipation, anxiety, blurred vision, dizziness, dry mouth, insomnia, hypertension, and sweating.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. **Venlafaxine** and its active metabolites cross the human placenta and enter the AF, where it is actually concentrated. The M:F ratio approaches unity. Case-control study suggests it is unassociated with an increased prevalence of fetal malformations. Neonatal behavioral signs are noted in exposed more frequently than unexposed newborns, but symptoms are described as transient and self-limited. Premature infants could be more susceptible to the effects of SSRIs and **venlafaxine.**
Rodent studies are generally reassuring, revealing no evidence of teratogenicity despite the use of doses higher than those used clinically. IUGR is seen in some models.

Breastfeeding Safety

Venlafaxine enters human breast milk, achieving an M:P ratio approximating 2.5, and 2.7 for its active metabolite. Yet, the mean total drug exposure of breastfed infants is only 6.4%. Though this level of exposure should be safe, measurable levels are achieved in about ½ of the exposed neonates, suggesting the need for close monitoring.

Drug Interactions

Cimetidine inhibits first-pass metabolism, reducing the oral clearance of **venlafaxine** by about 43%; the AUC and C_{max} were each increased by about 60%. However, for patients with preexisting hypertension, and for elderly patients or patients with hepatic dysfunction, the interaction between **venlafaxine** and **cimetidine** is not known and potentially could be more pronounced. Caution is advised.
Decreases the clearance of **haloperidol** by 42%, resulting in a 70% increase in the **haloperidol** AUC and an 88% increase in the **haloperidol** C_{max}.
Metabolized to its active metabolite by CYP2D6. Although **imipramine** partially inhibited the CYP2D6-mediated metabolism of **venlafaxine,** resulting in higher plasma levels of **venlafaxine** and lower plasma concentrations of its active metabolite, the total concentration of active compounds was unaffected. Therefore, no dose adjustment is required when **venlafaxine** is co-administered with a CYP2D6 inhibitor.
Decreases the **indinavir** AUC 28% and its C_{max} 36%. The clinical significance of this finding is unknown.
Based on the mechanism of action and the potential for serotonin syndrome, caution is advised when **venlafaxine** is used with other drugs that may affect the serotonergic neurotransmitter systems (e.g., **lithium,** SSRIs, triptans).

References

Berle JØ, Steen VM, Aamo TO, et al. J Clin Psychiatry 2004; 65:1228-34.

Einarson A, Fatoye B, Sarkar M, et al. Am J Psychiatry 2001; 158:1728-30.
Ferreira E, Carceller AM, Agogué C, et al. Pediatrics 2007; 119:52-9.
Hostetter A, Ritchie JC, Stowe ZN. Biol Psychiatry 2000; 48:1032-4.
Ilett KF, Kristensen JH, Hackett LP, et al. Br J Clin Pharmacol 2002; 53:17-22.
Klien CM, Mossaheb N, Sania A, et al. J Clin Psychopharmacol 2007; 27:720-2.
Loughhead AM, Fisher AD, Newport DJ, et al. Am J Psychiatry 2006; 163:145-7.
Rampono J, Proud S, Hackett LP, et al. Int J Neuropsychopharmacol 2004; 7:329-34.

Summary

Pregnancy Category: C
Lactation Category: S (possibly)

- **Venlafaxine** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.
- As for most psychotropic drugs, monotherapy and the lowest effective quantity given in divided doses to minimize the peaks can minimize the risks.

Verapamil—(Calan; Calan SR; Cardiabeltin; Covera-HS; Isoptin; Isoptin SR; Verelan; Verpal)

International Brand Name—Akilen (Hong Kong); Anpec (Australia, Taiwan); Apoacor (Israel); Apo-Verap (Canada); Azupamil (Germany); Berkatens (England, Ireland); Calaptin (India); Calaptin 240 SR (India); Cardiolen (Chile); Cardiover (Indonesia); Caveril (Ethiopia, Ghana, Kenya, Mauritius, Puerto Rico, Tanzania); Cintsu (Malaysia); Civicor (Thailand); Coraver (Sweden); Cordilat (Brazil); Cordilox (England, Ireland); Cordilox SR (Australia); Corpamil (Indonesia); Dilacoran (Brazil, Mexico); Dilacoran HTA (Mexico); Flamon (Malaysia, Puerto Rico, Switzerland); Geangin (Denmark, England, Ireland, Netherlands, Norway); Hexasoptin (Denmark, Finland); Hexasoptin Retard (Denmark); Ikacor (Israel); Ikapress (Israel); Iso-Card SR (South Africa); Isoptin (Austria, Bulgaria, Canada, China, Colombia, Czech Republic, Denmark, Ecuador, Finland, Germany, Greece, Hong Kong, Indonesia, Ireland, Italy, Korea, Malaysia, Netherlands, Norway, Peru, Philippines, Poland, Portugal, South Africa, Sweden, Switzerland, Thailand); Isoptine (Belgium, France); Isoptino (Argentina, Paraguay, Uruguay); Isoptin Retard (Austria, Costa Rica, Denmark, Dominican Republic, Ecuador, El Salvador, Finland, Germany, Greece, Guatemala, Honduras, Italy, Nicaragua, Panama, Peru, Portugal, Sweden, Switzerland); Isoptin SR (China, Costa Rica, Czech Republic, Dominican Republic, El Salvador, Guatemala, Honduras, Hong Kong, Hungary, Korea, Netherlands, Nicaragua, Panama, South Africa, Taiwan); Manidon (Spain, Venezuela); Manidon Retard (Spain); Napamil (Taiwan); Novopressan (China); Novo-Veramil (Canada); Quasar (Italy); Ravamil SR (South Africa); Securon (England, Ireland); Vasolan (Japan); Vasomil (South Africa); Vasopten (India, Thailand); Veracaps SR (Australia); Veracor (Israel); Verahexal (Australia, Germany); Veraloc (Denmark, Sweden, Switzerland); Veramex (Germany); Veramil (India); Verapin (Thailand); Verapress 240 SR (Israel); Veratad (Colombia); Verdilac (Mexico); Verelan (Philippines); Vetrimil (Taiwan); Zolvera (England, Ireland)

Drug Class

Antiarrhythmics, class IV; Antihypertensives; Calcium channel blockers

Indications

Angina, hypertension, supraventricular arrhythmia, atrial flutter/fibrillation, migraine prophylaxis

Mechanism

Inhibits Ca^{2+} influx into muscle

Dosage with Qualifiers

Angina—80-480mg PO tid; max 480mg/d
Hypertension—begin 80mg PO tid; max 480mg/d
Supraventricular arrhythmia—80-120mg PO tid; max 480mg/d; *alternative for paroxysmal SVT:* 2.5-5mg IV push, may repeat as dictated by response
Atrial flutter/fibrillation—80-120mg PO tid or qid; max 480mg/d
Migraine prophylaxis—80mg PO tid; adjust dose based on effect

NOTE: renal dosing.

- **Contraindications**—hypersensitivity to drug or class, severe hypotension, cardiogenic shock, severe LV dysfunction, 2nd or 3rd degree AV block, atrial fibrillation/flutter with bypass tract, sick sinus syndrome
- **Caution**—bradycardia, CHF, hepatic or renal dysfunction, muscular dystrophy, myasthenia gravis, GERD

■ Maternal Considerations

In addition to the listed indications, **verapamil** is used in some locales for the treatment of bipolar disorder and for tocolysis in women with preterm labor. There are no adequate reports or well-controlled studies of **verapamil** in pregnant women. There is no randomized or case-control study using **verapamil** as the primary tocolytic, and the practice of combining it with a β-blocker has been appropriately abandoned. Isolated case reports describe its successful use to treat maternal SVT. There are also rare reports of its use to treat preeclamptic hypertension, though there is no suggestion it offers advantages over other, more commonly used antihypertensives. Clearance is not altered in the rabbit pregnancy. Recently, a relationship between oral **erythromycin** and sudden cardiac death was reported in patients also receiving strong inhibitors of CYP3A (e.g., **diltiazem,** nitroimidazole antifungal agents, **troleandomycin**, **verapamil**); each doubles, at least, the AUC for a CYP3A substrate. Caution is advised.
Side effects include CHF, severe hypotension, AV block, severe bradycardia, constipation, dizziness, nausea, headache, edema, and fatigue.

■ Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. **Verapamil** readily crosses the human placenta, achieving an F:M ratio of 0.7. Similar levels are found in AF. Relaxation of precontracted placental arteries by **verapamil** is reduced in placentas obtained from preeclamptic women. Doppler-determined fetal blood flow resistances in preeclamptic women are unaltered by **verapamil. Verapamil** has been used as transplacental therapy for fetal SVT with unclear efficacy. **Flecainide** remains the drug of choice for SVT and fetal hydrops. Direct fetal administration has been reported with success. **Verapamil** crosses the rabbit placenta, though the kinetics remain to be elucidated. Rodent studies are generally reassuring, revealing no teratogenicity despite the use of doses higher than those used clinically. However, IUGR and embryotoxicity occur.

■ Breastfeeding Safety

There are no adequate reports or well-controlled studies in nursing women. **Verapamil** enters human breast milk, but the amount excreted is <0.05% and does not result in measurable levels in the nursing newborn.

■ Drug Interactions

Metabolized by CYP3A4, CYP1A2, and CYP2C. Clinically significant interactions have been reported with inhibitors of CYP3A4 (e.g., **erythromycin, ritonavir**) causing elevation of plasma levels of **verapamil,** while inducers of CYP3A4 (e.g., **rifampin**) have caused a lowering of plasma levels of **verapamil.** May increase blood ethanol concentrations and prolong its effects.
Use with β-adrenergic blockers may result in additive negative effects on HR, AV conduction, and/or cardiac contractility. Close surveillance of clinical status should be maintained if combined therapy is used. Combined therapy should usually be avoided in patients with AV conduction abnormalities and those with depressed LV function.

Asymptomatic bradycardia (36bpm) with a wandering atrial pacemaker has been observed in a patient receiving concomitant **timolol** (a β-adrenergic blocker) eyedrops and oral **verapamil.**
May decrease in the clearance of **metoprolol** and **propranolol** clearance; the effect on **atenolol** is variable.
Chronic use with **digoxin** can increase serum **digoxin** levels by 50-75% during the first week of therapy, causing **digitalis** toxicity. The influence of **verapamil** on **digoxin** kinetics is magnified in patients with hepatic cirrhosis. Maintenance and digitalization doses should be reduced and the patient reassessed to avoid over- or underdigitalization.
Use with oral antihypertensive agents (e.g., ACE inhibitors, β-blockers, diuretics, vasodilators) will usually have an additive effect on lowering BP. Patients receiving these combinations should be appropriately monitored.
Until data on possible interactions between **verapamil** and **disopyramide** are obtained, **disopyramide** should not be administered within 48h before or 24h after **verapamil** administration.
Use with **flecainide** may have additive negative inotropic effects and prolong AV conduction.
In a small number of patients with hypertrophic cardiomyopathy (IHSS), concomitant use of **verapamil** and **quinidine** resulted in significant hypotension. Until further data are obtained, this combination should probably be avoided in women with IHSS.
Counteracts the effects of **quinidine** on AV conduction. There has been a report of increased **quinidine** levels during **verapamil** therapy.
Lithium toxicity has been reported with concomitant use; **lithium** levels have been observed sometimes to increase, sometimes to decrease, and sometimes to be unchanged. Patients receiving both drugs must be monitored carefully.
May increase **carbamazepine** concentrations, producing diplopia, headache, ataxia, or dizziness.
Phenobarbital therapy may increase **verapamil** clearance.
May increase serum levels of **cyclosporine.**
May inhibit the clearance and increase the plasma levels of **theophylline.**
Clinical data and animal studies suggest that **verapamil** may potentiate the activity of neuromuscular blocking agents (curare-like and depolarizing). It may be necessary to decrease the dose of **verapamil** and/or the dose of the neuromuscular blocking agent when the drugs are used together.

References

Anderson P, Bondesson U, Mattiasson I, Johansson BW. Eur J Clin Pharmacol 1987; 31:625-7.
Belfort M, Akovic K, Anthony J, et al. J Clin Ultrasound 1994; 22:317-25.
Belfort MA, Anthony J, Buccimazza A, Davey DA. Obstet Gynecol 1990; 75:970-4.
Byerly WG, Hartmann A, Foster DE, Tannenbaum AK. Ann Emerg Med 1991; 20:552-4.
Gembruch U, Hansmann M, Redel DA, Bald R. J Perinat Med 1988; 16:39-44.
Kook H, Yoon YD, Baik YH. J Korean Med Sci 1996; 11:250-7.
Ray WA, Murray KT, Meredith S, et al. N Engl J Med 2004; 351:1089-96.
Simpson JM, Sharland GK. Heart 1998; 79:576-81.
Solans C, Bregante MA, Aramayona JJ, et al. Xenobiotica 2000; 30:93-102.
Szymanski W, Skublicki S, Jankowski A, Kotzbach R. Ginekol Pol 1992; 63:166-71.
Wisner KL, Peindl KS, Perel JM, et al. Biol Psychiatry 2002; 51:745-52.

Summary	**Pregnancy Category: C** **Lactation Category: S** • **Verapamil** should be used during pregnancy only if the benefit justifies the potential perinatal risk. • There are alternative agents for which there is more experience regarding use during pregnancy and lactation. • Oral **erythromycin** should be avoided in women receiving **verapamil. Ampicillin** plus **sulbactam** would be preferred in women with PPROM.

Vidarabine—(Vira-A)

International Brand Name—Adena A ungena (Mexico); Arasena-A (Japan)

Drug Class	Antivirals; Ophthalmics
Indications	HSV epithelial keratitis, keratoconjunctivitis, encephalitis
Mechanism	Inhibits DNA synthesis
Dosage with Qualifiers	HSV epithelial keratitis—apply 0.5in ribbon OS/OD 5×/d HSV keratoconjunctivitis—apply 0.5in ribbon OS/OD 5×/d HSV encephalitis—15mg/kg/d ×10d IV *NOTE: IV preparation no longer marketed in the US.* • **Contraindications**—hypersensitivity to drug or class, sterile trophic ulcers • **Caution**—unknown
Maternal Considerations	**Vidarabine** is a purine nucleoside obtained from fermentation cultures of *Streptomyces antibioticus*. There is no published experience with **vidarabine** for the above indications during pregnancy. Treatment for encephalitis should be discontinued when the brain biopsy is negative for HSV in cell culture. Many of the previous uses for **vidarabine** have been superceded by **acyclovir**. ***Side effects*** include tearing, foreign body sensation, burning, photophobia, and superficial punctuate keratitis.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **vidarabine** crosses the human placenta. **Vidarabine** is teratogenic in rodents after parenteral administration, where it appears to interfere with placental transport of uridine and adenosine. Though this concern remains for topical administration, it is unlikely the maternal systemic concentration will reach clinically relevant level. **Vidarabine** is used for neonatal treatment.
Breastfeeding Safety	There is no published experience in nursing women. It is unknown whether **vidarabine** enters human breast milk. It is unlikely to pose a clinically significant risk to the breastfeeding neonate after topical use.
Drug Interactions	No clinically relevant interactions identified.
References	Chishu T, Sai Y, Nishimura T, et al. Placenta. 2008; 29:461-7.

Summary

Pregnancy Category: C
Lactation Category: S (likely, topical), **U** (IV)
- **Vidarabine** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Vinblastine—(Velban; Velsar)

International Brand Name—Blastovin (Israel, Paraguay); Cytoblastin (India); Lemblastine (Mexico); Velban (Brazil); Velbastine (Korea); Velbe (Argentina, Australia, Canada, Chile, China, Hungary, Malaysia, New Zealand, Peru, South Africa, Spain, Turkey); Xintoprost (Argentina)

Drug Class

Antineoplastics, antimitotic

Indications

Ovarian or breast cancer, choriocarcinoma, Hodgkin's disease, lymphoma, Kaposi's sarcoma, mycosis fungoides

Mechanism

Arrests mitosis in metaphase by inhibiting microtubule formation

Dosage with Qualifiers

Chemotherapy—dosing protocols vary; usually combined with other agents

- **Contraindications**—hypersensitivity to drug or class, bacterial infection, granulocytopenia, intrathecal use, intestinal obstruction, paralytic ileus
- **Caution**—bone marrow depression, neuropathy, neuromuscular disease, neurotoxic agents, ototoxic agents, pulmonary disease, hepatic dysfunction, CYP3A4 interactions

Maternal Considerations

Vinblastine is a vinca alkaloid. Fertility is retained when **vinblastine** is used for either GTD or ovarian cancer after ovary-sparing surgery. There are no adequate reports or well-controlled studies of **vinblastine** in pregnant women. The literature consists of numerous but isolated case reports of its use for the treatment of various malignancies.
Side effects include myelosuppression, peripheral neuropathy, paralytic ileus, intestinal obstruction, intestinal necrosis, hemorrhagic enterocolitis, loss of or decreased DTRs, severe neuromuscular impairment, bronchospasm, infertility, SIADH, extravasation necrosis, leukopenia, anorexia, N/V, alopecia, constipation, paresthesias, stomatitis, anemia, malaise, headache, diarrhea, dizziness, bone pain, injection site reaction, thrombophlebitis, and BP changes.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **vinblastine** crosses the human placenta. *In vitro,* its transfer involves P-glycoprotein, whose back-transfer of **vinblastine** may help protect the fetus. Most fetuses exposed deliver without apparent adverse effects. The risk of birth defects in pregnant women previously treated is similar to the background rate. **Vinblastine** is teratogenic and embryotoxic in rodents. Exposed fetuses should be evaluated in a fetal medicine unit.

Breastfeeding Safety

There is no published experience in nursing women. It is unknown whether **vinblastine** enters human breast milk.

Drug Interactions

Vinblastine may reduce **phenytoin** levels and increase seizure activity. Dose adjustment should be based on serial blood level monitoring.

Caution should be exercised in patients taking drugs known to inhibit CYP3A drug metabolism or in patients with hepatic dysfunction. Concurrent use of **vinblastine** with inhibitors of this metabolic pathway may cause an earlier onset and/or an increased severity of side effects. Enhanced toxicity has been reported in patients receiving concomitant **erythromycin.**

References

Motegi M, Takakura S, Takano H, et al. Obstet Gynecol 2007; 109:537-40.
Nisce LZ, Tome MA, He S, et al. Am J Clin Oncol 1986; 9:146-51.
Ross GT. Cancer 1976; 37:1043-7.
Sudhakaran S, Rayner CR, Li J, et al. Br J Clin Pharmacol 2008; 65:667-73.
Ushigome F, Takanaga H, Matsuo H, et al. Eur J Pharmacol 2000; 408:1-10.
Yoshinaka A, Fukasawa I, Sakamoto T, et al. Arch Gynecol Obstet 2000; 264:124-7.

Summary

Pregnancy Category: D
Lactation Category: U

- **Vinblastine** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.
- *In utero* exposure appears for the most part well-tolerated, and is not *a priori* an indication for pregnancy termination.

Vincristine—(Citomid; Oncovin; Vincasar PFS; Vincrex)

International Brand Name—Citomid (Mexico); Citomid RU (Mexico); Cytocristin (India); Farmistin CS (Germany); Krebin (Indonesia); Neocristin (India); Nevexitin (Philippines); Oncovin (Australia, Brazil, Chile, China, Peru); Vinces (Argentina); Vincrina (Paraguay); Vincristina (Italy); Vincrisul (Spain); Vinracine (Malaysia); Vintec (Mexico)

Drug Class

Antineoplastics, antimitotic

Indications

Trophoblastic disease, Hodgkin's disease, leukemia, non-Hodgkin's lymphoma, neuroblastoma, rhabdomyosarcoma, Wilms' tumor

Mechanism

Arrests mitosis in metaphase by inhibiting microtubule formation

Dosage with Qualifiers

Chemotherapy—multiple protocols; typically 1.4mg/m^2, max 2mg/dose; usually combined with other agents

- **Contraindications**—hypersensitivity to drug or class, acute bacterial infection, intestinal obstruction, paralytic ileus, demyelinating Charcot-Marie-Tooth disease
- **Caution**—bone marrow suppression, neuromuscular disease, neurotoxic agents, ototoxic agents, pulmonary disease, hepatic dysfunction, CYP3A4 interactions

Maternal Considerations

Vincristine is a vinca alkaloid. There are no adequate reports or well-controlled studies of **vincristine** in pregnant women. The literature consists of isolated case reports and series of women typically treated during pregnancy for leukemia or lymphoma. ***Side effects*** include myelosuppression, peripheral neuropathy, paralytic ileus, intestinal necrosis, cranial nerve palsy, decreased DTRs, severe neuromuscular impairment, seizures, bronchospasm, MI, SIADH, infertility, extravasation necrosis, tumor lysis

syndrome, uric acid nephropathy, alopecia, N/V, anorexia, constipation, diarrhea, fatigue, paresthesias, peripheral neuropathy, dizziness, nystagmus, thrombophlebitis, ataxia, BP changes, weakness, and electrolyte abnormalities.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **vincristine** crosses the human placenta. *In vitro,* its transfer involves P-glycoprotein, whose back-transfer may help protect the fetus. Most fetuses exposed deliver without apparent adverse effects. **Vincristine** is teratogenic and embryotoxic in rodents, and in limited study teratogenic in a subhuman primate. Exposed fetuses should be evaluated in a fetal medicine unit.

Breastfeeding Safety

There is no published experience in nursing women. It is unknown whether **vincristine** enters human breast milk. It inhibits goat milk production in a dose-dependent manner.

Drug Interactions

Vincristine may reduce **phenytoin** blood levels and increase seizure activity. Dosage adjustment should be based on serial blood level monitoring.

References

Aviles N, Neri N. Clin Lymphoma 2001; 2:173-7.
Fassas A, Kartalis G, Klearchou N, et al. Nouv Rev Fr Hematol 1984; 26:19-24.
Henderson AJ, Faulkner A. Q J Exp Physiol 1985; 70:15-22.
Kisacik B, Akdogan A, Maras Y, et al. Rheumatol Int 2008; 28:909-11.
Ushigome F, Takanaga H, Matsuo H, et al. Eur J Pharmacol 2000; 408:1-10.

Summary

Pregnancy Category: D
Lactation Category: U

- **Vincristine** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.
- *In utero* exposure appears for the most part well-tolerated, and is not *a priori* an indication for pregnancy termination.

Vinorelbine—(Navelbine)

International Brand Name—Navelbin (Bulgaria, Hungary); Navelbine (Argentina, Austria, Brazil, Canada, Chile, China, Czech Republic, Ecuador, England, France, Italy, Korea, Malaysia, Mexico, Philippines, Poland, Russia, South Africa, Spain, Switzerland, Taiwan, Thailand); Vinbine (India); Vinelbine (Thailand)

Drug Class

Antineoplastics, antimitotic

Indications

Breast, cervical, and non–small cell lung cancers; Kaposi's sarcoma

Mechanism

Inhibits microtubule formation in metaphase, arresting mitosis

Dosage with Qualifiers

Chemotherapy—multiple protocols alone or in combination with **cisplatin**

- **Contraindications**—hypersensitivity to drug or class, acute bacterial infection, granulocytopenia, intrathecal administration, GI obstruction, paralytic ileus
- **Caution**—bone marrow depression, neuropathy, neuromuscular disease, neurotoxic agents, pulmonary disease, hepatic dysfunction, CYP3A4 interactions

Maternal Considerations	**Vinorelbine** is a vinca alkaloid. There are no adequate reports or well-controlled studies of **vinorelbine** in pregnant women. The literature consists of multiple case reports of women treated during pregnancy. ***Side effects*** include myelosuppression, peripheral neuropathy, paralytic ileus, intestinal necrosis, radiation recall reaction, severe neuromuscular impairment, interstitial pulmonary disease, dyspnea, MI, SIADH, infertility, extravasation necrosis, leukopenia, granulocytopenia, anemia, increased LFTs, infusion site reactions, constipation, anorexia, alopecia, peripheral neuropathy, diarrhea, dizziness, N/V, nystagmus, thrombophlebitis, and thrombocytopenia.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **vinorelbine** crosses the human placenta, though in vitro studies suggest a role for P-glycoprotein. The case reports of its use during pregnancy usually note no adverse effects on the perinate attributable to treatment.
Breastfeeding Safety	There is no published experience in nursing women. It is unknown whether **vinorelbine** enters human breast milk.
Drug Interactions	Acute pulmonary reactions have been reported with **vinorelbine** and other anticancer vinca alkaloids used in conjunction with **mitomycin.** Although the pharmacokinetics are not influenced by use with **cisplatin,** the incidence of granulocytopenia is significantly higher than with single-agent **vinorelbine.** Patients who receive **vinorelbine** and **paclitaxel,** either together or sequentially, should be monitored for signs and symptoms of neuropathy. Use in patients with prior or concomitant radiation therapy may result in radiosensitizing effects. Caution should be exercised in patients concurrently taking drugs known to inhibit CYP3A, or in patients with hepatic dysfunction. This combination may cause an earlier onset and/or an increased severity of side effects.
References	Cuvier C, Espie M, Extra JM, Marty M. Eur J Cancer 1997; 33:168-9. Janne PA, Rodriguez-Thompson D, Metcalf DR, et al. Oncology 2001; 61:175-83. Mir O, Berveiller P, Ropert S, et al. Ann Oncol 2008; 19:607-13.
Summary	**Pregnancy Category: D** **Lactation Category: U** • **Vinorelbine** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Voriconazole—(Vfend)

International Brand Name—VFEND (Argentina, Belize, Brazil, Colombia, Costa Rica, El Salvador, Guatemala, Honduras, Hong Kong, Indonesia, Israel, Malaysia, Mexico, Nicaragua, Panama, Peru, Singapore, Taiwan)

Drug Class	Antifungals
Indications	Invasive aspergillosis, severe fungal infections
Mechanism	Inhibits sterol C-14 α-demethylation and CYP

Dosage with Qualifiers

Invasive aspergillosis—begin 6mg/kg IV q12h, then 4mg/kg IV q12h or convert to PO
Severe fungal infections—begin 6mg/kg IV q12h, then 4mg/kg IV q12h or convert to PO

NOTE: renal and hepatic dosing.
NOTE: check LFTs at baseline and periodically during treatment; monitor visual fields if >28d treatment.

- **Contraindications**—hypersensitivity to drug or class; use of either **astemizole, carbamazepine, cisapride,** long-acting barbiturates, **pimozide, quinidine, rifabutin, rifampin, sirolimus,** or **terfenadine;** galactose intolerance
- **Caution**—hepatic or renal dysfunction, hematologic malignancy, prolonged use

Maternal Considerations

There are no adequate reports or well-controlled studies of **voriconazole** in pregnant women. The published experience is limited to case reports of its use post–cesarean section for the treatment of *Aspergillus.*
Side effects include cholecystitis, hepatitis, fulminant hepatic necrosis, acute renal failure, Stevens-Johnson syndrome, photosensitivity, angioedema, blood dyscrasias, fever, N/V, rash, chills, headache, increased LFTs, hallucinations, visual changes, blurred vision, and photophobia.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **voriconazole** crosses the human placenta.

Breastfeeding Safety

There is no published experience in nursing women. It is unknown whether **voriconazole** enters human breast milk.

Drug Interactions

Use with **efavirenz, rifabutin,** and **rifampin** decreases the **voriconazole** C_{max} and AUC; the combinations should not be used.
Use with high-dose **ritonavir** (400mg q12h) significantly reduces the **voriconazole** C_{max} and AUC; the combination should not be used. Low-dose **ritonavir** (100mg q12h) should also be avoided unless the risk:benefit ratio justifies it.
Carbamazepine and long-acting barbiturates have not been studied, but likely reduce the **voriconazole** C_{max} and AUC; the combination is best avoided.
Phenytoin significantly reduces the **voriconazole** C_{max} and AUC. Increase the **voriconazole** maintenance dose from 4 to 5mg/kg IV q12h or from 200 to 400mg orally q12h.
Increases the **sirolimus** (CYP3A4 inhibitor) C_{max} and AUC; this combination is considered contraindicated.
Use with **astemizole, cisapride, pimozide, quinidine,** and **terfenadine** (each CYP3A4 inhibitors) is considered contraindicated because of the potential for QT prolongation and rare occurrence of torsades de pointes.
Cyclosporine is a CYP3A4 inhibitor; reduce the **cyclosporine** dose to ½ the starting dose when beginning **voriconazole,** and follow with frequent monitoring of **cyclosporine** blood levels. Increased **cyclosporine** levels have been associated with nephrotoxicity. When **voriconazole** is discontinued, **cyclosporine** concentrations must be frequently monitored and the dose increased as necessary.
Increases the C_{max} and AUC of **methadone,** a CYP3A4 inhibitor. Increased plasma concentrations of **methadone** have been associated with toxicity, including QT prolongation. Frequent monitoring for adverse events and toxicity is recommended. Dose reduction of **methadone** may be needed.

Increases **tacrolimus** (a CYP3A4 inhibitor); reduce the **tacrolimus** dose to ⅓ the starting dose when beginning **voriconazole** and follow with frequent monitoring of **tacrolimus** blood levels. Increased **tacrolimus** levels have been associated with nephrotoxicity. When **voriconazole** is discontinued, the dose of **tacrolimus** may need to be increased.
Increases the **phenytoin** level (CYP2C9 inhibition), necessitating frequent monitoring of **phenytoin** levels.
Increases the levels of **ethinyl estradiol** and **norethindrone** in oral contraceptives (CYP3A4 inhibition). Monitoring closely for adverse events related to oral contraceptives.
Increases the effect of **warfarin** (CYP2C9 inhibition). Monitor the PT or INR and adjust dose as needed to achieve target.
Increases the level of **omeprazole** (CYP2C19/3A4 inhibition). Reduce the **omeprazole** dose by ½ when initiating therapy with **voriconazole** in patients already receiving **omeprazole** doses of ≥40mg. The metabolism of other proton pump inhibitors that are CYP2C19 substrates may also be inhibited by **voriconazole** and may result in increased plasma concentrations of those agents.
May inhibit benzodiazepine (e.g., **alprazolam, midazolam, triazolam**) metabolism (CYP3A4 inhibition) and increase plasma levels. Monitor closely for adverse effects.
May inhibit HMG-CoA reductase inhibitor (statins) (CYP3A4 inhibition) metabolism and increase the plasma levels. Monitor closely for adverse events and toxicity related to statins. A statin dose adjustment may be needed.
May inhibit dihydropyridine calcium channel blockers (CYP3A4 inhibition). An adjustment of calcium channel blocker dose may be needed.

References

Gunaratne PS, Wijeyaratne CN, Chandrasiri P, et al. Ceylon Med J 2006; 51:137-42.
Rodrigo N, Perera KN, Ranwala R, et al. Int J Obstet Anesth 2007; 16:256-60.

Summary

Pregnancy Category: D
Lactation Category: U

- **Voriconazole** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk

Warfarin—(Coumadin; Jantoven)

International Brand Name—Aldocumar (Spain); Befarin (Thailand); Circuvit (Argentina); Coumadan (Argentina); Coumadan Sodico (Argentina); Coumadin (Canada, Chile, Ecuador, Germany, Italy, Korea, Malaysia, Paraguay, Peru, Philippines, Portugal, Singapore, Venezuela); Coumadine (France); Dagonal (Uruguay); Farin (Thailand); Maforan (Thailand); Marevan (Belgium, Brazil, China, Denmark, England, Finland, Ireland, Norway, Singapore); Orfarin (Malaysia, Thailand); Panwarfin (Greece); Simarc-2 (Indonesia); UniWarfin (India); Waran (Sweden); Warfar (Colombia); Warfil 5 (Dominican Republic); Warfilone (Canada)

Drug Class	Anticoagulants; Thrombolytics
Indications	Anticoagulation, therapeutic and prophylactic
Mechanism	Inhibits vitamin K–dependent clotting factor synthesis (II, VII, IX, X, proteins C and S)
Dosage with Qualifiers	Chronic treatment of thrombophilia—5-10mg PO qd; keep INR >3 Acute therapy of thromboembolic disease—begin 2.5mg, increase gradually over 2-4d to achieve desired INR Prosthetic cardiac valves or atrial fibrillation—2.5-10mg PO qd; INR should be maintained between 2.5 and 3.0 depending on the valve type • **Contraindications**—hypersensitivity to drug or class, active bleeding, recent surgery, esophageal varices, thrombocytopenia, vitamin K deficiency, concurrent thrombolytics, recent lumbar puncture, congenital clotting defect • **Caution**—recent surgery, acute infection, heparin induced thrombocytopenia, Protein C or S deficiency, hepatic dysfunction, hypertension, CHF
Maternal Considerations	Thromboembolic disease remains a major cause of maternal morbidity and mortality. There are no adequate reports or well-controlled studies in pregnant women. It is most likely that a woman with a prior thromboembolic event unrelated to a permanent risk factor does not require prophylaxis during a subsequent pregnancy. The risk of a bleeding complication during pregnancy approximates 18% with **warfarin.** An INR of 3.0 is sufficient for either prophylaxis or treatment of venous thromboembolism, thus minimizing the risk of hemorrhage associated with higher INRs. Women on **warfarin** planning pregnancy should switch to a heparinoid agent prior to conception if possible. However, therapeutic **heparin** is not effective prophylaxis in women with a prosthetic heart valve, though some recommend replacement with **heparin** between 6 and 12w. A daily dose >5mg is associated with a greater risk of an adverse pregnancy outcome. If the mother's condition requires anticoagulation with **warfarin,** it should be substituted with **heparin** at 36w to decrease the risk to the fetus. Neuraxial anesthesia is contraindicated because of the risk of puncture-associated bleeding. **Warfarin** treatment is resumed postpartum. There is consensus those women with APL syndrome and their first DVT should be treated with **warfarin** to a target INR of 2.3-3.0. However, a recent systematic review including observational studies found patients with APL syndrome and stroke to be at a high risk of recurrent events. It may be reasonable to a target an INR>3.0 in this group. Likewise, the optimal approach for women with obstetric manifestations of APL syndrome is not well defined. Some recommend universal **aspirin** plus **heparin,** while others consider **aspirin**

in monotherapy useful for women with recurrent early miscarriage only.
Anticoagulation was evaluated in 60 pregnancies with a mechanical heart valve prosthesis and 45 with a tissue valve. All women had **warfarin** in the 2nd trimester and **heparin** for delivery. The 1st trimester was divided among **warfarin** only, **heparin** and LMWH. Live births occurred in 60% of tissue valves and 30% of mechanical valves. Likewise, spontaneous abortion rates differed with 2% in the tissue valves and 37% in the mechanical valves. The worst outcomes were with **warfarin** in the 1st trimester.
Side effects include hemorrhage, skin necrosis, rash, major hemorrhage, diarrhea, nausea, abdominal pain, hepatitis, dermatitis, and blue toe syndrome.

Fetal Considerations

Warfarin is a known teratogen. While there are no adequate reports or well-controlled studies in human fetuses, exposure from 6 to 10w gestation is associated with an embryopathy, and exposure subsequently with a fetopathy. The *fetal* ***warfarin*** *syndrome* includes nasal hypoplasia (failure of nasal septum development), microphthalmia, hypoplasia of the extremities, IUGR, heart disease, scoliosis, deafness, and mental retardation. While the embryopathy appears secondary to a fetal vitamin K deficiency, the fetopathy results from microhemorrhages.
The most common CNS malformations include agenesis of the corpus callosum, Dandy-Walker malformation, and optic atrophy. In a large series of women treated the duration of pregnancy for a prosthetic valve, the overall incidence of fetal **warfarin** syndrome was 5.6%. The pregnancy loss rate was 32% and the stillbirth rate 10% of pregnancies achieving at least 20w.
School-age children exposed *in utero* have an increased frequency of mild neurologic dysfunction and an IQ <80.

Breastfeeding Safety

Warfarin does not enter human breast milk and is compatible with breastfeeding.

Drug Interactions

The following factors, alone or in combination, may be responsible for *increased* PT/INR response:
Endogenous Factors: Cancer, collagen vascular disease, CHF, diarrhea, elevated temperature, hyperthyroidism, poor nutritional state, steatorrhea and vitamin K deficiency.
Hepatic Disorders: Infectious hepatitis and jaundice.
Certain Classes of Drugs: 5-lipoxygenase inhibitors, adrenergic stimulants (central), analgesics, inhalation anesthetics, antiandrogens, antiarrhythmics, anticoagulants, anticonvulsants, antidepressants, antimalarial agents, antineoplastics, antiparasitics/antimicrobials, antiplatelet drugs/effects, antithyroid drugs, β-adrenergic blockers, cholelitholytic agents, oral hypoglycemic agents, diuretics, systemic fungal medications, gastric acidity and peptic ulcer agents, GIs (prokinetic agents and ulcerative colitis agents), gout treatment agents, hepatotoxic drugs, hyperglycemic agents, hypertensive emergency agents, hypnotics, leukotriene receptor antagonist, MAOIs, prolonged narcotics, NSAIDs, pyschostimulants, pyrazolones, salicylates, SSRIs, corticosteroids, anabolic steroids (17-alkyl testosterone derivatives), thrombolytics, thyroid drugs, TB agents, uricosuric agents, vaccines, vitamins.
Antibiotics: Oral aminoglycosides, parenteral cephalosporins, macrolides, miscellaneous, penicillins (IV, high dose), quinolones (fluoroquinolones), sulfonamides (long-acting), and tetracyclines.

Hypolipidemics: Bile acid–binding resins, fibric acid derivatives, HMG-CoA reductase inhibitors.
Specific Drugs Reported:
Acetaminophen, allopurinol, aminosalicylic acid, amiodarone, aspirin, atorvastatin, azithromycin, capecitabine, cefamandole, cefazolin, cefoperazone, cefotetan, cefoxitin, ceftriaxone, celecoxib, cerivastatin, **chenodiol, chloramphenicol, chloral hydrate, chlorpropamide, cholestyramine, cimetidine, ciprofloxacin, cisapride, clarithromycin, clofibrate, cyclophosphamide, danazol, dextran, dextrothyroxine, diazoxide, diclofenac, diflunisal, disulfiram, doxycycline, erythromycin, ethacrynic acid,** ethanol, **fenofibrate, fenoprofen, fluconazole, fluorouracil, fluoxetine,** flutamide, **fluvastatin, fluvoxamine, gemfibrozil, glucagon, halothane, heparin, ibuprofen,** ifosfamide, **indomethacin, influenza vaccine, itraconazole, ketoprofen, ketorolac, levamisole, levofloxacin, levothyroxine, liothyronine, lovastatin, mefenamic acid, methimazole, methyldopa, methylphenidate, metronidazole, miconazole** (intravaginal, systemic), **moricizine, nalidixic acid, naproxen, neomycin, norfloxacin, ofloxacin, olsalazine, omeprazole, oxaprozin,** oxymetholone, **paroxetine,** penicillin G (IV), **pentoxifylline, phenylbutazone, phenytoin, piperacillin, piroxicam, pravastatin, prednisone, propafenone, propoxyphene, propranolol, propylthiouracil, quinidine, quinine, ranitidine, rofecoxib, sertraline, simvastatin,** stanozolol, **streptokinase,** sulfamethizole, **sulfamethoxazole, sulfinpyrazone, sulfisoxazole, sulindac, tamoxifen, tetracycline, ticarcillin, ticlopidine,** tissue plasminogen activator, **tolbutamide, tramadol, trimethoprim-sulfamethoxazole, urokinase, valproate,** vitamin E, **zafirlukast,** and **zileuton.**
The following factors, alone or in combination, may be responsible for *decreased* PT/INR response:
Endogenous Factors: Edema, hereditary warfarin sodium resistance, hyperlipemia, hypothyroidism, and nephrotic syndrome.
Certain Classes of Drugs: antacids, antianxiety agents, antiarrhythmics, antibiotics, anticonvulsants, antidepressants, antihistamines, antineoplastics, antipsychotic medications, antithyroid drugs, barbiturates, diuretics, enteral nutritional supplements, systemic fungal medications, gastric acidity and peptic ulcer agents, hypnotics, immunosuppressives, oral contraceptives (estrogen containing), SERMs, corticosteroids, TB agents, vitamins.
Hypolipidemics: Bile acid–binding resins and HMG-CoA reductase inhibitors.
Specific Drugs Reported:
Aminoglutethimide, amobarbital, aquamephyton**, ascorbic acid** (high dose), **atorvastatin, azathioprine,** butabarbital, **butalbital, carbamazepine, chloral hydrate, chlordiazepoxide, chlorthalidone, cholestyramine, clozapine,** corticotropin, **cortisone, cyclophosphamide, dicloxacillin,** ethanol, **glutethimide, griseofulvin, haloperidol, meprobamate, mercaptopurine, methimazole, moricizine, nafcillin, pentobarbital, phenobarbital, phenytoin, pravastatin, prednisone, primidone, propylthiouracil, raloxifene, ranitidine, rifampin, secobarbital, spironolactone,** and **trazodone.**
Caution should be exercised when botanical medicines are taken concomitantly with **warfarin**. The amount of active ingredients may vary due to a lack of manufacturing standardization with botanical medicinal preparations. It is good practice to monitor the patient's response with additional PT/INR determinations when initiating or discontinuing botanicals.
*Specific botanicals reported to affect **warfarin** therapy include the following:*

Bromelains, danshen, dong quai *(Angelica sinensis),* garlic, and *Ginkgo biloba* are most often associated with an *increase* in the effects of **warfarin**.
Coenzyme Q_{10} (ubidecarenone) and **St. John's wort** are most often associated with a *decrease* in the effects of **warfarin.**
Botanicals that contain coumarins with potential anticoagulant effects: Alfalfa, angelica (dong quai), aniseed, arnica, asa foetida, bogbean, boldo, buchu, capsicum, cassia, celery, chamomile (German and Roman), dandelion, fenugreek, horse chestnut, horseradish, licorice, meadowsweet, nettle, parsley, passion flower, prickly ash (Northern), quassia, red clover, sweet clover, sweet woodruff, tonka beans, wild carrot, wild lettuce.
Miscellaneous botanicals with anticoagulant properties: Bladder wrack *(Fucus),* pau d'arco.
Botanicals that contain salicylate and/or have antiplatelet properties: Agrimony, aloe gel, aspen, black cohosh, black haw, bogbean, cassia, clove, dandelion, feverfew, garlic, German sarsaparilla, ginger, *Ginkgo biloba,* ginseng *(Panax),* licorice, meadowsweet, onion, policosanol, poplar, senega, tamarind, willow, wintergreen.
Botanicals with fibrinolytic properties: Bromelains, capsicum, garlic, ginseng *(Panax),* inositol nicotinate, onion.
Botanicals with coagulant properties: Agrimony, goldenseal, mistletoe, yarrow.
Caution should be observed when used with NSAIDs, including **aspirin,** to be certain no change in the **warfarin** dose is required.
Acquired or inherited **warfarin** resistance should be suspected if large daily doses are required to maintain a patient's PT/INR within a normal therapeutic range.

References

Akhtar RP, Abid AR, Zafar H, et al. Asian Cardiovasc Thorac Ann 2007; 15:497-501.
Brill-Edwards P, Ginsberg JS, Gent M, et al. N Engl Med 2000; 343:1439-44.
Clark SL, Porter TF, West FG. Obstet Gynecol 2000; 95:938-40.
Cotrufo M, De Feo M, De Santo LS, et al. Obstet Gynecol 2002; 99:35-40.
Cotrufo M, de Luca TS, Calabro R, et al. Eur J Cardiothorac Surg 1991; 5:300-4.
Rosove MH, Brewer PM. Ann Intern Med 1992; 117:303-8.
Ruiz-Irastorza G, Khamashta MA. Best Pract Res Clin Rheumatol 2007; 21:1079-92.
Suri V, Sawhney H, Vasishta K, et al. Int J Gynaecol Obstet 1999; 64:239-46.
Wesseling J, Van Driel D, Heymans HS, et al. Thromb Haemost 2001; 85:609-13.
Wesseling J, Van Driel D, Smrkovsky M, et al. Early Hum Dev 2001; 63:83-95.

Summary

Pregnancy Category: X
Lactation Category: S

- **Warfarin** may cause an embryopathy in the 1st trimester, and a fetopathy in the 2nd and 3rd trimesters. A daily dose > 5 mg conveys the highest risk.
- It is probably best to substitute **heparin** (therapeutic levels) for **warfarin** during the 1st trimester in women with replacement heart valves.
- Heparinoids are the preferred substitutes for most anticoagulant needs during pregnancy except when the prophylaxis is for a mechanical heart valve.
- **Warfarin** should be used during pregnancy only if the benefit justifies the potential perinatal risk.

Zafirlukast—(Accolate)

International Brand Name—Zuvair (India)

Drug Class — Antiasthmatics; Leukotriene antagonists

Indications — Asthma prophylaxis

Mechanism — Leukotriene D4 and E4 receptor antagonist

Dosage with Qualifiers — Asthma prophylaxis—20mg PO 1h ac or 2h pc bid

NOTE: hepatic dosing.

- **Contraindications**—hypersensitivity to drug or class, acute asthma
- **Caution**—hepatic dysfunction, systemic corticosteroid taper

Maternal Considerations — There is only limited published experience with **zafirlukast** during pregnancy. Leukotriene receptor antagonists are probably safe during pregnancy but should be limited to special circumstances, where they are viewed essential for asthma control. ***Side effects*** include Churg-Strauss syndrome, headache, rhinitis, N/V, diarrhea, pain, asthenia, abdominal pain, dizziness, myalgia, fever, back pain, increased hepatic transaminases, and dyspepsia.

Fetal Considerations — There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **zafirlukast** crosses the human placenta. In one recent report, the subjects were participants of the Organization of Teratology Information Specialists Asthma Medications in Pregnancy Study. Perinatal outcomes among 96 women who took leukotriene receptor antagonists (LTRAs) (**montelukast** or **zafirlukast**) were compared with women who exclusively took short-acting β-agonists (n = 122) and women without asthma (n = 346). LTRAs use was not associated with an increased risk of pregnancy loss, gestational diabetes, preeclampsia, low maternal weight gain, preterm delivery, low Apgar scores, or reduced measures of birth length and head circumference in infants. The prevalence of major structural defects in the LTRA group (5.95%) was higher compared with nonasthmatic controls (p = 0.007), but not different from the comparison group with asthma (p = 0.524). Furthermore, the defects observed in the LTRA group did not represent a consistent pattern. These findings suggests LTRAs are not a major human teratogen. Rodent and primate studies are reassuring, revealing no evidence of teratogenicity or IUGR (unless there was maternal toxicity) despite the use of doses higher than those used clinically.

Breastfeeding Safety — There is no published experience in nursing women. **Zafirlukast** is excreted into human breast milk with an M:P ratio of 0.2.

Drug Interactions — Increases the t/2 and AUC of **warfarin.** The mean PT increased by approximately 35%. This interaction is probably due to an inhibition by **zafirlukast** of the CYP2C9. Monitor anticoagulant therapy closely.
Other drugs metabolized by CYP2C9 include **carbamazepine, phenytoin,** and **tolbutamide.** These combinations have not been studied.
Use with **erythromycin** decreases mean plasma levels of **zafirlukast** by approximately 40%.

Use with **theophylline** may decrease mean plasma levels of **zafirlukast** by some 30%. Rare instances of patients experiencing increased **theophylline** levels with or without clinical signs or symptoms of **theophylline** toxicity after the addition of **zafirlukast** have been reported. The mechanism of the interaction is unknown. **Aspirin** increases plasma levels of **zafirlukast** by approximately 45%.

References

Bakhireva LN, Jones KL, Schatz M, et al; Organization of Teratology Information Specialists Collaborative Research Group. J Allergy Clin Immunol 2007; 119:618-25.
Spector SL. Ann Allergy Asthma Immunol 2001; 86:18-23.

Summary

Pregnancy Category: B
Lactation Category: S (likely)

- **Zafirlukast** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.
- Leukotriene receptor antagonists are probably safe during pregnancy but should be limited to special circumstances, where they are viewed essential for asthma control.
- There are alternative agents for which there is more experience regarding use during pregnancy and lactation.

Zalcitabine—(DDC; ddC; Dideoxycytidine; Hivid)

International Brand Name—Hivid (Argentina, Australia, Brazil, Canada, Chile, Ecuador, Hong Kong, Israel, Malaysia, Mexico, Peru, Philippines, Taiwan, Thailand, Venezuela); Virorich (Paraguay, Uruguay)

Drug Class

Antivirals; NRTIs

Indications

Advanced HIV infection

Mechanism

Nucleoside reverse transcriptase inhibition

Dosage with Qualifiers

Advanced HIV infection—0.75mg PO q8h

- **Contraindications**—hypersensitivity to drug or class
- **Caution**—hepatic or renal dysfunction, peripheral neuropathy, CHF, history of pancreatitis

Maternal Considerations

There are no adequate reports or well-controlled studies of **zalcitabine** in pregnant women. The treatment of HIV during pregnancy significantly reduces the risk of mother-to-child transmission. Triple therapy (**lamivudine, nevirapine, zidovudine**) remains the standard of care for management of HIV infection in adults. The FDA has approved only 4 nucleoside analog reverse transcriptase inhibitors: **didanosine, stavudine, zalcitabine,** and **zidovudine. Zalcitabine** is a 2nd selection should the patient not respond to **zidovudine.**
Side effects include seizures, lactic acidosis, thrombocytopenia, leukopenia, anemia, eosinophilia, peripheral neuropathy, hepatic dysfunction, fatigue, N/V, abdominal pain, diarrhea, constipation, rash, pruritus, urticaria, oral lesions, depression, headache, fever, cough, and rhinitis.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **zalcitabine** crosses the human placenta. It does cross the primate (*Macaca nemestrina*) placenta. Rodent studies revealed evidence of teratogenicity at doses >1000× the MRHD.

Breastfeeding Safety

There are no adequate reports or well-controlled studies in nursing women. It is unknown whether **zalcitabine** enters human breast milk. However, breastfeeding is contraindicated in HIV-infected nursing women where formula is available to reduce the risk of neonatal transmission.

Drug Interactions

In vitro studies suggest use with **lamivudine** may result in subtherapeutic levels of the active phosphorylated **zalcitabine,** which may lead to a decreased antiretroviral effect. While it is unknown whether these *in vitro* findings translate into clinical consequences, concomitant use of **zalcitabine** and **lamivudine** is not recommended.

Use with drugs that have the potential to cause peripheral neuropathy (e.g., antiretroviral nucleoside analogues, **chloramphenicol, cisplatin, dapsone, disulfiram, ethionamide, glutethimide,** gold, **hydralazine, iodoquinol, isoniazid, metronidazole, nitrofurantoin, phenytoin, ribavirin, vincristine**) should be avoided where possible.

Use with **didanosine** is not recommended.

Discontinue when a drug that has the potential to cause pancreatitis (e.g., **pentamidine**). Death due to fulminant pancreatitis possibly related to IV **pentamidine** and **zalcitabine** has been reported.

Amphotericin, foscarnet, and aminoglycosides may increase the risk of peripheral neuropathy (or other **zalcitabine**-associated adverse events) by interfering with the renal clearance of **zalcitabine.** Patients who require one of these drugs should have frequent clinical and laboratory monitoring with dose adjustment for any significant change in renal function.

Use with **probenecid** or **cimetidine** decreases the elimination of **zalcitabine,** most likely by inhibition of its renal tubular secretion. Monitor closely for signs of toxicity.

Absorption is moderately reduced (approximately 25%) when given with magnesium/aluminum-containing antacid products.

References

Matthews SJ, Cersosimo RJ, Spivack ML. Pharmacotherapy 1991; 11:419-48.

Spector SA. AIDS 1994; 8(Suppl 3):S15-8.

Temesgen Z, Wright AJ. Mayo Clin Proc 1999; 74:1284-301.

Tuntland T, Nosbisch C, Baughman WL, et al. Am J Obstet Gynecol 1996; 174:856-63.

Summary

Pregnancy Category: C
Lactation Category: NS

- Combination therapy with **zidovudine, lamivudine,** and **nevirapine** significantly reduces the risk of mother-to-child transmission and remains the standard of care for management of HIV infection in adults.
- **Zalcitabine** is an alternative reverse transcriptase inhibitor in patients unresponsive to **zidovudine.**
- Physicians are encouraged to register pregnant women under the Antiretroviral Pregnancy Registry (1-800-258-4263) for a better follow-up of the outcome while under treatment with **zalcitabine.**

Zaleplon—(Sonata)

International Brand Name—Hegon (Argentina); Hipnodem (Argentina); Noctiplon (Chile); Plenidon (Chile, Peru); Prox (Uruguay); Sonata (Mexico); Starnoc (Canada); Zaplon (India)

Drug Class	Anxiolytics; Hypnotics
Indications	Short-term treatment of insomnia
Mechanism	Interacts with GABA/benzodiazepine receptor complex
Dosage with Qualifiers	Short-term treatment of insomnia—5-10mg PO qhs prn; onset 60min, duration <5h • **Contraindications**—hypersensitivity to drug or class • **Caution**—hepatic dysfunction, history of substance abuse, pulmonary disease
Maternal Considerations	There is no published experience with **zaleplon** during pregnancy. ***Side effects*** include dependency, drowsiness, amnesia, paresthesias, abnormal vision, dizziness, headache, hangover, rebound insomnia, and confusion.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **zaleplon** crosses the human placenta.
Breastfeeding Safety	Small quantities of **zaleplon** are excreted into human breast milk. It is calculated that the breastfeeding neonate would ingest approximately 0.015% of the maternal dose. This quantity is unlikely to result in a clinically relevant level.
Drug Interactions	Potentiates the CNS-impairing effects of ethanol. Use with either **imipramine** or **thioridazine** may have additive effects on decreased alertness and impaired psychomotor performance for 2-4h after administration. The potent CYP3A4 inducer **rifampin** may reduce zaleplon C_{max} and AUC by approximately 80%, and its use may decrease the efficacy of **zaleplon.** An alternative non-CYP3A4 substrate hypnotic agent may be considered in patients taking CYP3A4 inducers such as **carbamazepine, phenobarbital, phenytoin,** and **rifampin.** **Cimetidine** inhibits both aldehyde oxidase and CYP3A4, the primary and secondary enzymes responsible for **zaleplon** metabolism. Cimetidine increased the mean C_{max} and AUC of **zaleplon** by 85%. As a result, an initial dose of 5mg should be given to patients who are concomitantly being treated with **cimetidine.**
References	Darwish M, Martin PT, Cevallos WH, et al. J Clin Pharmacol 1999; 39:670-4.
Summary	**Pregnancy Category: C** **Lactation Category: S** • **Zaleplon** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk. • There are alternative agents for which there is more experience during pregnancy and lactation.

Zanamivir—(Relenza)

International Brand Name—Relenza (Argentina, Canada, Costa Rica, Dominican Republic, El Salvador, France, Germany, Guatemala, Honduras, Hong Kong, Korea, Mexico, Nicaragua, Panama)

Drug Class	Antivirals
Indications	Uncomplicated influenza
Mechanism	Inhibits influenza neuraminidase
Dosage with Qualifiers	Uncomplicated influenza—begin within 48h of symptoms, 10mg INH q2-4h ×2, then q12h ×5d • **Contraindications**—hypersensitivity to drug or class, COPD, asthma, unable to use inhaler • **Caution**—unknown
Maternal Considerations	There is no published experience with **zanamivir** during pregnancy. Pregnant women should consider vaccination prior to influenza season. ***Side effects*** include bronchospasm, nausea, dizziness, headache, bronchitis, cough, nasal symptoms, and ear/nose/throat infection.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **zanamivir** crosses the human placenta. It does cross the rodent placenta. Rodent studies are for the most part reassuring, with only minor skeletal abnormalities occurring in one strain of rat when the dose exceeded 1000× the MRHD.
Breastfeeding Safety	There is no published experience in nursing women. It is unknown whether **zanamivir** enters human breast milk. It is excreted into rodent milk.
Drug Interactions	No clinically relevant interactions identified.
References	There is no published experience in pregnancy or during lactation.
Summary	**Pregnancy Category: C** **Lactation Category: U** • **Zanamivir** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Zidovudine—(Aviral; AZT; Retrovir; Retrovis)

International Brand Name—Adovi (Indonesia); Apo-Zidovudine (Canada); Aviral (Colombia); Avirzid (Indonesia); Azidomine (Korea); Novo-AZT (Canada); Pranadox (Mexico); Retrocar (Peru); Retrovir (Argentina, Canada, Ecuador, Hong Kong, India, Indonesia, Japan, Malaysia, Paraguay, Philippines, South Africa, Taiwan, Thailand, Uruguay, Venezuela); Retrovir-AZT (Brazil, Chile, Costa Rica, Dominican Republic, El Salvador, Guatemala, Honduras, Mexico, Nicaragua, Panama, Peru); T-Za (Thailand); Zidis (Thailand); Zidovir (India); Zydowin (South Africa)

Drug Class ..... Antivirals; NRTIs

Indications ..... HIV infection

Mechanism ..... Nucleoside reverse transcriptase inhibition

Dosage with Qualifiers .....

HIV infection during pregnancy—begin 100mg PO 5×/d after 14w until onset of labor; in intrapartum period: 2mg/kg IV over 1h, then 1mg/kg/h until cord clamping
HIV infection in nonpregnant women—300mg PO q12h, or 1mg/kg IV q4h

- **Contraindications**—hypersensitivity to drug or class, severe bone marrow suppression
- **Caution**—hepatic or renal dysfunction

Maternal Considerations .....

The treatment of HIV infection during pregnancy significantly reduces the risk of mother-child transmission. Combination therapy (**lamivudine, nevirapine, zidovudine**) remains the standard of care for management of HIV infection in adults due to its high efficacy. The Pediatric AIDS Clinical Trials Group (protocol 076) documented that **zidovudine** chemoprophylaxis reduced perinatal HIV-1 transmission by nearly 70%. Since then, multiple randomized studies confirm **zidovudine** monotherapy is extremely effective in preventing vertical transmission of the virus. Shorter regimens reduced the risk of transmission by 50% in a non-breastfeeding population, and by about 37% in breastfeeding populations. When **zidovudine** is combined with other antiretroviral drugs (protease inhibitors), the effectiveness is almost 90%. The addition of **nevirapine** to the standard IV **zidovudine** labor regimen further reduces perinatal HIV transmission in women not already receiving antenatal antiretroviral therapy. The addition of **nevirapine** is not beneficial when the patient has been using "triple therapy" prenatally. It is possible in developed countries to lower the transmission rate below 4% using combinations of available medications and, for the selective patient, elective cesarean section before labor. Thus, it is important to encourage women to undergo testing for HIV during pregnancy, maximizing opportunities for offering antiretroviral therapy. Unfortunately, adherence to **zidovudine** therapy may be relatively low during the last 3w of gestation and during the first 3w postpartum. For women with HIV RNA levels of <1000copies/ml, a 3-part **zidovudine** prophylaxis regimen (prenatal, intrapartum, and neonatal) should be used alone or in combination with other antiretroviral drugs. **Zidovudine** prophylaxis is not associated with the development of resistance. Women should be monitored closely for hepatotoxicity after initiation of **zidovudine.**

Side effects include agranulocytosis, thrombocytopenia, bone marrow suppression, seizures, anemia, pancreatitis, myopathy, lactic acidosis, granulocytopenia, hepatotoxicity, N/V, abdominal pain, diarrhea, headache, asthenia, rash, fever, anorexia,

somnolence, myalgia, malaise, dyspepsia, diaphoresis, dyspnea, taste changes, pigmented nails, and paresthesias.

Fetal Considerations

Zidovudine and its major metabolites rapidly cross the human placenta, achieving concentrations that approach unity even in the 1st trimester. Maternal antiretroviral drug therapy during pregnancy and labor, followed by 6w of neonatal **zidovudine,** significantly reduces the risk of vertical transmission. Additional antiretroviral drugs may be needed in some high-risk newborns. Asymptomatic women with HIV who lack a social support network are more likely not to comply with the recommended neonatal prophylactic regimen of antiretroviral therapy. Elective cesarean section prior to the onset of labor also reduces the rate of vertical transmission if there is a detectable maternal viral load. Mitochondrial disorders are described in children exposed to **zidovudine** *in utero.* MRIs observed in children with antiretroviral-induced mitochondrial dysfunction are similar to those in children with congenital mitochondrial diseases and even in exposed children without symptoms of systemic mitochondrial dysfunction. Fetuses exposed to triple therapy may be at increased risk for malformations.

Breastfeeding Safety

There is no published experience in nursing women. It is unknown whether **zidovudine** enters human breast milk. It is excreted into rodent milk. However, breastfeeding is contraindicated in HIV-infected nursing women where formula is available to reduce the risk of neonatal transmission.

Drug Interactions

Use with either **stavudine** or **doxorubicin** should be avoided since an antagonistic relationship has been demonstrated *in vitro.* Some nucleoside analogues affecting DNA replication, such as **ribavirin,** antagonize the *in vitro* antiviral activity of **zidovudine** against HIV, and their concomitant use should be avoided. Use with **ganciclovir,** interferon-alfa, or other bone marrow suppressive or cytotoxic agents may increase the hematologic toxicity of **zidovudine.**

References

Bhana N, Ormrod D, Perry CM, et al. Paediatr Drugs 2002; 4:515-53.
Chappuy H, Treluyer JM, Jullien V, et al. Antimicrob Agents Chemother 2004; 48:4332-6.
Cooper ER, Charurat M, Mofenson L, et al. J Acquir Immune Defic Syndr 2002; 29:484-94.
Cote HC, Raboud J, Bitnum A, et al. J Infect Dis 2008; 198:851-9.
Demas PA, Webber MP, Schoenbaum EE, et al. Pediatrics 2002; 110:e35.
Dorenbaum A, Cunningham CK, Gelber RD, et al. JAMA 2002; 288:189-98.
Ekpini RA, Nkengasong JN, Sibailly T, et al. AIDS 2002; 16:625-30.
El Beitune P, Duarte G. Eur J Obstet Gynecol Reprod Biol 2006; 128:59-63.
Hill JB, Sheffield JS, Zeeman GG, Wendel GD Jr. Obstet Gynecol 2001; 98:909-11.
Ickovics JR, Wilson TE, Royce RA, et al. J Acquir Immune Defic Syndr 2002; 30:311-5.
Jamieson DJ, Clark J, Kourtis AP, et al. Am J Obstet Gynecol 2007; 197(3 Suppl):S26-32.
Lansky A, Jones JL, Frey RL, Lindegren ML. Am J Public Health 2001; 91:1291-3.
Mofenson LM. MMWR Recomm Rep 2002; 51(RR-18):1-38.
[No authors]. Arch Pediatr Adolesc Med 2002; 156:915-21.
[No authors]. Lancet 2002; 359:1178-86.

Nolan M, Fowler MG, Mofenson LM. J Acquir Immune Defic Syndr 2002; 30:216-29.
Rovira MT, Antorn MT, Paya A, et al. Eur J Obstet Gynecol Reprod Biol 2001; 97:46-9.
Rutstein RM. Curr Opin Pediatr 2001; 13:408-16.
Simon T, Funke AM, Hero B, et al. Zentralbl Gynakol 2002; 124:413-7.
Siu SS, Yeung JH, Pang MW, et al. Obstet Gynecol 2005; 106:824-7.
Sperling RS, Roboz J, Dische R, et al. Am J Perinatol 1992; 9:247-9.
Tardieu M, Brunelle F, Raybaud C, et al. AJNR Am J Neuroradiol 2005; 26:695-701.
Volmink J, Siegfried NL, van del Merwe L, Brocklehurst P. Cochrane Database Syst Rev 2007; (1):CD003510.

Summary

Pregnancy Category: C
Lactation Category: NS

- "Triple therapy" consisting of **zidovudine, lamivudine,** and **nevirapine** significantly reduces the risk of mother-child transmission; it is the standard of care for HIV infection in adults.
- A short course of **zidovudine** or a single dose of **nevirapine** is an effective therapy to reduce mother-child transmission of HIV.
- Breastfeeding is not recommended.
- Physicians are encouraged to register pregnant women under the Antiretroviral Pregnancy Registry (1-800-258-4263) for a better follow-up of the outcome while under treatment with **zidovudine.**

Zileuton—(Zyflo)

International Brand Name—None identified.

Drug Class — Antiasthmatics; Leukotriene antagonists

Indications — Asthma

Mechanism — 5-Lipoxygenase inhibitor reducing leukotrienes

Dosage with Qualifiers

Asthma—600mg PO qid; max 2400mg/d

NOTE: check LFTs baseline, qmo ×3mo, then q3mo ×1y.

- **Contraindications**—hypersensitivity to drug or class, acute asthma, hepatotoxicity
- **Caution**—alcohol abuse, hepatic dysfunction

Maternal Considerations

There is no published experience with **zileuton** during pregnancy. ***Side effects*** include hepatotoxicity, insomnia, headache, dizziness, nausea, dyspepsia, abdominal pain, neutropenia, and elevated LFTs.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **zileuton** crosses the human placenta. Rodent studies revealed evidence for an increased prevalence of IUGR, skeletal abnormalities, and cleft palate.

Breastfeeding Safety	There is no published experience in nursing women. It is unknown whether **zileuton** enters human breast milk. It is excreted into rodent milk.
Drug Interactions	May decrease **theophylline** clearance by half, doubling the **theophylline** AUC and increasing its C_{max} by 73%. Thus, the **theophylline** dosage should be reduced by ½ upon initiation of **zileuton** and plasma **theophylline** concentrations monitored. Similarly, the maintenance dose and/or dosing interval of **theophylline** should be adjusted accordingly when initiating therapy with **theophylline** in a patient receiving **zileuton.** May increase the anticoagulant effect of **warfarin.** Monitor the PT or INR closely. Decreases **propranolol** clearance by 40%, increasing the **propranolol** C_{max}, AUC, and elimination t/2 by 52%, 104%, and 25%, respectively. Patients on **zileuton** and **propranolol** should be closely monitored.
References	[No authors]. Ann Allergy Asthma Immunol 2000; 84:475-80. Spector SL. Ann Allergy Asthma Immunol 2001; 86:18-23.
Summary	**Pregnancy Category: C** **Lactation Category: U** • **Zileuton** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk. • There are alternative agents for which there is more experience regarding use during pregnancy and lactation.

Ziprasidone—(Aygestin; Geodon; Milligynon; Norcolut; Nordron; Norlutate; Shiton)

International Brand Name—Geodon (Brazil, Colombia, Israel, Mexico, Taiwan, Venezuela); Zeldox (Argentina, Brazil, Chile, Germany, Hong Kong, Malaysia, Peru, Philippines, Singapore, Thailand, Uruguay); Zipsydon (India)

Drug Class	Antipsychotics
Indications	Schizophrenia
Mechanism	Unknown; antagonizes dopamine D_2 and 5-HT_2 receptors
Dosage with Qualifiers	Schizophrenia—begin 20mg PO with meals bid, adjust to response; max 160mg/d • **Contraindications**—hypersensitivity to drug or class, prolonged QT interval, recent MI, uncompensated CHF, hypokalemia, hypomagnesemia, history of arrhythmia • **Caution**—hepatic dysfunction, seizures, cerebrovascular disease, CV disease, hypotension, hypovolemia, dehydration, agents that prolong the QT interval, risk for aspiration pneumonia
Maternal Considerations	There is no published experience with **ziprasidone** during pregnancy. ***Side effects*** include neuroleptic malignant syndrome, tardive dyskinesia, hypertension, QT interval prolongation, syncope, extrapyramidal symptoms, irregular menses, somnolence, nausea,

	constipation, dyspepsia, akathisia, dizziness, respiratory disorders, asthenia, diarrhea, weight gain, rash, urticaria, visual disturbances, tachycardia, hyperglycemia, and hyperprolactinemia.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **ziprasidone** crosses the human placenta. Rodent studies reveal evidence of embryotoxicity, IUGR, and an increased prevalence of malformation (cardiac, renal, and skeletal depending upon species and model) at doses similar to the MRHD.
Breastfeeding Safety	There is no published experience in nursing women. It is unknown whether **ziprasidone** enters human breast milk.
Drug Interactions	Should not be used with any drug that prolongs the QT interval. May enhance the effects of certain antihypertensive agents. May antagonize the effects of **levodopa** and dopamine agonists. **Carbamazepine** is an inducer of CYP3A4 and can decrease the **ziprasidone** AUC by more than ⅓. This effect may be greater with higher doses of **carbamazepine.** **Ketoconazole,** a potent inhibitor of CYP3A4, increases the **ziprasidone** AUC and C_{max} by 35-40%. Other inhibitors of CYP3A4 would be expected to have similar effects.
References	There is no published experience in pregnancy or during lactation.
Summary	**Pregnancy Category: C** **Lactation Category: U** • **Ziprasidone** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk. • There are alternative agents for which there is more experience regarding use during pregnancy and lactation.

Zolmitriptan—(Zomig; Zomigoro)

International Brand Name—Ascotop (Germany); Myslee (Japan); Zomig (Australia, Austria, Belgium, Brazil, Canada, China, Costa Rica, Denmark, Dominican Republic, Ecuador, El Salvador, England, France, Guatemala, Honduras, Hong Kong, Hungary, Ireland, Israel, Italy, Korea, Mexico, Netherlands, Nicaragua, Panama, Peru, Philippines, Poland, Singapore, Thailand, Venezuela); Zomigon (Argentina, Uruguay); Zomigoro (France); Zomig Rapimelt (Canada, Hong Kong, Israel)

Drug Class	Migraine agents; Serotonin receptor agonists
Indications	Migraine headache
Mechanism	Selective 5-HT_1 receptor agonist
Dosage with Qualifiers	Migraine headache—1.25-2.5mg PO ×1, may repeat after 2h prn; max 10mg/24h; alternatively, use the same dose of the nasal spray • **Contraindications**—hypersensitivity to drug or class, CAD, coronary vasospasm, history of MI, uncontrolled hypertension, 5-HT_1 agonist <24h, MAOI <14d, ergot <24h, basilar migraine, hemiplegic migraine, Wolff-Parkinson-White syndrome with symptoms • **Caution**—cardiac risk factors, hepatic dysfunction, severe renal disease, PVD, CVD

Maternal Considerations

Pregnancy has a beneficial effect on migraine in 55-90% of women, mainly during the 2nd and 3rd trimesters. A higher percentage of women with menstrual migraine compared to other migraines improve during pregnancy. There is no published experience with **zolmitriptan** during pregnancy. Mean plasma concentrations of **zolmitriptan** are up to 1.5-fold higher in females than males. It is not known whether pregnancy alters clearance.

Side effects include acute MI, arrhythmias, coronary vasospasm, cerebral hemorrhage, stroke, hypertensive crisis, peripheral vascular ischemia, bowel ischemia, asthenia, N/V, dizziness, chest pain, neck and jaw tightness, somnolence, sweating, palpitations, and myalgia.

Fetal Considerations

There are no adequate reports or well-controlled studies in human fetuses. It is unknown whether **zolmitriptan** crosses the human placenta. Rodent studies revealed embryotoxicity and skeletal abnormalities at doses more than 500× the MRHD.

Breastfeeding Safety

There is no published experience in nursing women. It is unknown whether **zolmitriptan** enters human breast milk. It is excreted into rodent milk. However, considering the indication and dosing, one-time or occasional **zolmitriptan** use is unlikely to pose a clinically significant risk to the breastfeeding neonate. If desired, the patient may pump her breasts for 24h and then resume breastfeeding.

Drug Interactions

Ergot-containing drugs have been reported to cause prolonged vasospastic reactions. Because there is a theoretical basis that these effects may be additive, use with ergotamine-containing or ergot-type medications (e.g., **dihydroergotamine, methysergide**) within 24h of each other should be avoided.

MAO-A inhibitors increase the systemic exposure of **zolmitriptan.** Therefore, its use with MAO-A inhibitors is contraindicated.

Cimetidine almost doubles the **zolmitriptan** t/2 and AUC.

SSRIs (e.g., **fluoxetine, fluvoxamine, paroxetine, sertraline**) have been reported, rarely, to cause weakness, hyperreflexia, and incoordination when used with 5-HT_1 agonists.

References

Diener HC, Limmroth V. Expert Opin Investig Drugs 2001; 10:1831-45.

Pfaffenrath V, Rehm M. Drug Saf 1998; 19:383-8.

Summary

Pregnancy Category: C

Lactation Category: U

- **Zolmitriptan** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.
- There are alternative agents for which there is more experience regarding use during pregnancy and lactation.

Zolpidem—(Ambien)

International Brand Name—Adormix (Chile); Amsic (Germany); Durnit (Argentina); Niotal (Italy); Nitrest (India); Somit (Argentina, Paraguay, Uruguay); Somnil (Colombia); Somno (Ecuador, Peru); Stilnix (Israel); Stilnoct (Belgium, Denmark, England, Ireland, Netherlands); Stilnox (Australia, Austria, Belgium, Brazil, China, Colombia, Costa Rica, Czech Republic, Dominican Republic, Ecuador, El Salvador, France, Germany, Greece, Guatemala, Honduras, Hong Kong, Hungary, Israel, Italy, Korea, Malaysia, Mexico, Nicaragua, Panama, Peru, Philippines, Poland, Spain, Switzerland, Taiwan, Thailand, Venezuela); Stilpidem (Hong Kong); Supedal (Peru); Ziohex (Philippines); Zodorm (Israel); Zolpinox (Germany); Zopidem (Taiwan); Zopim (Taiwan)

Drug Class	Anxiolytics; Hypnotics
Indications	Short-term treatment of insomnia
Mechanism	Interacts with GABA/benzodiazepine receptor complex
Dosage with Qualifiers	Short-term treatment of insomnia—5-10mg PO qhs prn • **Contraindications**—hypersensitivity to drug or class • **Caution**—depression, substance abuse, impaired respiratory function
Maternal Considerations	There are no adequate reports or well-controlled studies of **zolpidem** in pregnant women. **Zolpidem** significantly inhibits smooth muscle contractility *in vitro*. ***Side effects*** include ataxia, hallucinations, headache, drowsiness, lethargy, depression, dizziness, URI, sinusitis, pharyngitis, dry mouth, nausea, dyspepsia, diarrhea, constipation, palpitations, arthralgia, back pain, and myalgias.
Fetal Considerations	There are no adequate reports or well-controlled studies in human fetuses. **Zolpidem** crosses the human placenta, but the kinetics have yet to be elucidated. Typical maternal peak levels after 5 or 10mg are 59 and 121ng/ml respectively. In one case report, the cord blood level at least 14h after maternal ingestion was 41ng/ml. Rodent studies are reassuring, revealing no evidence of teratogenicity or IUGR despite the use of doses higher than those used clinically. Prenatal exposure to **diazepam** and **alprazolam,** but not to **zolpidem,** affects behavioral stress reactivity in adult male rats.
Breastfeeding Safety	Less than 0.02% of the total administered maternal dose is excreted into milk, but the effect of **zolpidem** on the infant is unknown. It seems unlikely the occasional use of **zolpidem** would pose a clinically insignificant risk to the breastfeeding neonate. If desired, the patient may pump her breasts for 8h and then resume breastfeeding.
Drug Interactions	There is an additive effect on psychomotor performance when used with ethanol. **Fluoxetine** may increase the **zolpidem** t/2 by 15-20%. **Sertraline** may increase the **zolpidem** C_{max} (43%) and decrease the T_{max} (53%). Since the systematic evaluations of **zolpidem** in combination with other CNS-active drugs have been limited, careful consideration should be given to the pharmacology of any CNS-active drug to be used with **zolpidem.** Any drug with CNS-depressant effects could potentially enhance the CNS-depressant effects of **zolpidem.** **Rifampin** reduces the AUC (−73%), C_{max} (−58%), and t/2 (−36%) of **zolpidem.** The sedative-hypnotic effect is reversed by **flumazenil.**

■ **References** ····· Alvarez de Sotomayor M, Herrera MD, et al. Z Naturforsch 1997; 52:687-93.
Askew JP. Pharmacotherapy 2007; 27:306-8.
Cannizzaro C, Martire M, Steardo L, et al. Brain Res 2002; 953:170-80.

■ **Summary** ····· **Pregnancy Category: B**
Lactation Category: S
- **Zolpidem** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Zonisamide—(Zonegran)

International Brand Name—None identified.

■ **Drug Class** ····· Anticonvulsants

■ **Indications** ····· Partial seizures

■ **Mechanism** ····· Unknown

■ **Dosage with Qualifiers** ····· Partial seizures—begin 100mg PO qd, increasing q2w or greater for control; max dose 600mg/d in divided doses if necessary

- **Contraindications**—hypersensitivity to drug or class, hypersensitivity to sulfonamides
- **Caution**—hepatic or renal dysfunction, hot weather, history of nephrolithiasis

■ **Maternal Considerations** ····· There are no interactions between **zonisamide** and the combined OCP, progesterone-only pill, **medroxyprogesterone** injections, or **levonorgestrel** implants. There are no adequate reports or well-controlled studies of **zonisamide** in pregnant women. Levels may decline with advancing gestation.
Side effects include Stevens-Johnson syndrome, toxic epidermal necrolysis, agranulocytosis, heat stroke, withdrawal seizures, aplastic anemia, somnolence, fatigue, anorexia, dizziness, headache, irritability, agitation, impaired concentration, speech disturbance, impaired memory, mental slowing, confusion, depression, insomnia, diplopia, tremor, and incoordination.

■ **Fetal Considerations** ····· There are no adequate reports or well-controlled studies in human fetuses. **Zonisamide** crosses the human placenta, achieving F:M ratios of 0.92. The current data do not indicate an increased risk of teratogenicity in humans. However, studies in rodents, dogs, and nonhuman primates reveal embryotoxicity and an increased prevalence of malformations when **zonisamide** is given at doses within the human range during organogenesis.

■ **Breastfeeding Safety** ····· There are no adequate reports or well-controlled studies in nursing women. **Zonisamide** enters human milk, achieving an M:P ratio between 0.6 and 1.03. Using the available data, the theoretic infant dose would approximate 1.4mg/kg/d.

■ **Drug Interactions** ····· Drugs that induce liver enzymes increase the metabolism and clearance of **zonisamide** and decrease its t/2. The t/2 of **zonisamide** following a 400mg dose in patients concurrently on enzyme-inducing AEDs (e.g., **carbamazepine, phenobarbital,**

phenytoin) was between 27 and 38h compared to the non–enzyme-inducing AED, **valproate,** which was 46h. Concurrent medication with drugs that either induce or inhibit CYP3A4 would be expected to alter serum concentrations of **zonisamide.**

References

Kawada K, Itoh S, Kusaka T, et al. Brain Dev 2002; 24:95-7.
Kondo T, Kaneko S, Amano Y, Egawa I. Epilepsia 1996; 37:1242-4.
Oles KS, Bell WL. Ann Pharmacother 2008; 42:1139-41.
Shimoyama A, Ohkubo T, Sugawara K. Biomed Chromatogr 1999; 13:370-2.

Summary

Pregnancy Category: C
Lactation Category: U

- **Zonisamide** should be used during pregnancy and lactation only if the benefit justifies the potential perinatal risk.

Abbreviations

ABG	arterial blood gases
ac	before meals
ACE	angiotensin-converting enzyme
ACEI	angiotensin-converting enzyme inhibitor
ACh	acetylcholine
ACLS	Advanced Cardiac Life Support
ACOG	American College of Obstetricians and Gynecologists
ACTH	adrenocorticotropic hormone
ADD	attention deficit disorder
ADHD	attention deficit/hyperactivity disorder
ADP	adenosine diphosphate
AED	antiepileptic drug
AF	amniotic fluid
AF:M ratio	amniotic fluid:maternal plasma ratio
AGA	average for gestational age
AIDS	acquired immunodeficiency syndrome
Al	aluminum
ALS	amyotrophic lateral sclerosis
ALT	alanine aminotransferase
AML	acute myelogenous leukemia
ANC	absolute neutrophil count
APL	antiphospholipid
aPTT	activated partial thromboplastin time
A2R-antagonist	angiotensin-2 receptor antagonist
ARDS	adult respiratory distress syndrome
ASA	acetylsalicylic acid (aspirin)
ASAP	as soon as possible
AST	aspartate aminotransferase
ATIII	antithrombin III

ATP	adenosine triphosphate
ATPase	adenosine triphosphatase
AUC	area under the time-versus-concentration curve
AV	atrioventricular
AVM	arteriovenous malformation
AZT	3′-azido-3′-deoxythymidine (zidovudine; azidothymidine)
B.	*Bacillus; Bacteroides*
β-hCG	β-human chorionic gonadotropin
bid	twice a day
BNP	B-type natriuretic peptide
BP	blood pressure
bpm	beats per minute
BPP	biophysical profile
BUN	blood urea nitrogen
BV	bacterial vaginosis
C.	*Candida; Clostridium*
Ca	calcium
CAD	coronary artery disease
cAMP	cyclic adenosine monophosphate
CBC	complete blood count
CD_4	type of white blood cell
CDC	Centers for Disease Control and Prevention
cGMP	cyclic guanosine monophosphate
CHB	congenital heart block
chemo	chemotherapy
CHF	congestive heart failure
CI	confidence interval
CK	creatine kinase
Cl^-	chloride

cm	centimeter(s)
cm^2	square centimeter(s)
C_{max}	maximum concentration
C_{min}	minimum concentration
CML	chronic myelocytic leukemia
cml	cubic milliliter(s)
CMV	cytomegalovirus
CN^-	cyanide anion
CNS	central nervous system
CO_2	carbon dioxide
COPD	chronic obstructive pulmonary disease
COX-2	cyclooxygenase-2
CPD	cephalopelvic disproportion
CPK	creatine phosphokinase
Cr	creatinine
CrCl	creatinine clearance
CSF	cerebrospinal fluid
CT	computed tomography
CV	cardiovascular
CVA	cerebrovascular accident
CVD	cerebrovascular disease
CVS	chorionic villus sampling
CYP	cytochrome P-450
d	day(s)
Da	Dalton(s)
DDAVP	1-deamino(8-D-arginine) vasopressin
DIC	disseminated intravascular coagulation
DKA	diabetic ketoacidosis
dl	deciliter
DNA	deoxyribonucleic acid

DPT	diphtheria, pertussis, and tetanus
DS	double-strength
DSM-IV	*Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*
D_5W	5% dextrose in water
DTIC	dimethyltriazenoimidazole carboxamide (dacarbazine)
DTP	diphtheria-tetanus-pertussis vaccine
DTR	deep tendon reflex
DVT	deep vein thrombosis
E.	*Escherichia*
EBV	Epstein-Barr virus
ECG	electrocardiogram
EDC	estimated date of confinement
EEG	electroencephalogram
ER^+	estrogen receptor–positive
ET	endotracheal
FDA	Food and Drug Administration
FDP	fibrin degradation products
Fe	iron
FEV_1	forced expiratory volume in 1 second
FFP	fresh frozen plasma
FHR	fetal heart rate
F:M ratio	fetal:maternal ratio
FSH	follicle-stimulating hormone
g	gram(s)
G6PD	glucose-6-phosphate dehydrogenase
GABA	γ-aminobutyric acid
GBS	group B streptococcus (streptococci)
GERD	gastroesophageal reflux disease
GFR	glomerular filtration rate

GH	growth hormone
GI	gastrointestinal
GIFT	gamete intrafallopian transfer
GnRH	gonadotropin-releasing hormone
GPIIb/IIIa	glycoprotein IIb/IIIa
GTD	gestational trophoblastic disease
gt(t)	drop(s)
GU	genitourinary
h	hour(s)
H.	*Haemophilus; Helicobacter*
HAART	highly active antiretroviral therapy
HAV	hepatitis A virus
Hb	hemoglobin
HBV	hepatitis B virus
hCG	human chorionic gonadotropin
HCV	hepatitis C virus
HDL	high-density lipoprotein
HELLP	hemolysis, elevated liver enzymes, and low platelets
HIB	*Haemophilus influenzae* type B
HIV	human immunodeficiency virus
HIV-1	human immunodeficiency virus type 1
HMG-CoA	3-hydroxy-3-methylglutaryl coenzyme A
HPA	hypothalamic-pituitary-adrenal
HPLC	high-performance liquid chromatography
HR	heart rate
HRT	hormone replacement therapy
hs	at bedtime
HSV	herpes simplex virus
5-HT	5-hydroxytryptamine
HUVEC	human umbilical vein endothelial cell

ICAM	intracellular adhesion molecule
ICP	intracranial pressure
ICU	intensive care unit
IDDM	insulin-dependent diabetes mellitus
IgA	immunoglobulin A
IGF-I	insulin-like growth factor-I
IgG	immunoglobulin G
IgM	immunoglobulin M
IHSS	idiopathic hypertrophic subaortic stenosis
I_{Kr}	inwardly delayed rectified potassium channel
IL	interleukin
IM	intramuscular
IN	intranasal
INH	inhalation
INR	International Normalized Ratio
IQ	intelligence quotient
ITP	immune thrombocytopenic purpura
IU	International Unit(s)
IUD	intrauterine device
IUGR	intrauterine growth restriction
IUI	intrauterine insemination
IV	intravenous
IVF	in vitro fertilization
IVH	intraventricular hemorrhage
IVIG	intravenous immune globulin
IVP	intravenous pyelogram
K	potassium
kg	kilogram(s)
L	liter(s)
L2	second lumbar vertebra

L4	fourth lumbar vertebra
lb	pound(s)
LDL	low-density lipoprotein
LDL-C	low-density lipoprotein cholesterol
LFTs	liver function tests
LH	luteinizing hormone
LMP	last menstrual period
LMWH	low-molecular-weight heparin
L:S ratio	lecithin:sphingomyelin ratio
LV	left ventricular
M	molar
M.	*Microsporum*
m^2	square meter(s) [body surface area]
MAC	*Mycobacterium avium* complex
M:AF ratio	maternal:amniotic fluid ratio
MAO	monoamine oxidase
MAOI	monoamine oxidase inhibitor
MAP	mean arterial pressure
max	maximum
mcg	microgram(s)
MDI	metered-dose inhaler
MDR	minimum daily requirement
mEq	milliequivalent
M:F ratio	maternal:fetal ratio
Mg	magnesium
mg	milligram(s)
mGy	milligray(s)
MI	myocardial infarction
MIC	minimum inhibitory concentration
min	minute

mIU	milli–International unit(s)
ml	milliliter(s)
mm^3	cubic millimeter(s)
μM	micromolar
mmHg	millimeter(s) of mercury
mmol	millimole(s)
MMP	matrix metalloproteinase
mo	month(s)
M:P ratio	milk:maternal plasma ratio
MRHD	maximal recommended human dose
MRI	magnetic resonance imaging
MS	multiple sclerosis
msec	millisecond(s)
MSRA	methicillin-resistant *Staphylococcus aureus*
MSSA	methicillin-sensitive *Staphylococcus aureus*
MTHFR	5,10-methylenetetrahydrofolate reductase
MW	molecular weight
N.	*Neisseria*
Na	sodium
NaCl	sodium chloride
NAPA	*N*-acetyl-procainamide
NAS	nasal
NE	norepinephrine
NEB	nebulizer spray
NEC	necrotizing enterocolitis
NG	nasogastric
ng	nanogram(s)
NICU	neonatal intensive care unit
NIDDM	non–insulin-dependent diabetes mellitus
NMDA	*N*-methyl-D-aspartate

NNRTI	non-nucleoside reverse transcriptase inhibitor
NO	nitric oxide
NRT	nicotine replacement therapy
NRTI	nucleoside/nucleotide reverse transcriptase inhibitor
NS	normal saline
NSAID	nonsteroid anti-inflammatory drug
NST	nonstress test
NTD	neural tube defect
N/V	nausea and vomiting
NYHA	New York Heart Association
OCD	obsessive-compulsive disorder
OCT	oxytocin challenge test
OD	right eye
$25(OH)D_3$	25-hydroxyvitamin D_3
OPV	oral polio vaccine
OR	odds ratio
OS	left eye
OTC	over-the-counter
p	probability value
P.	*Pasteurella; Plasmodium; Proteus*
PaO_2	partial pressure of oxygen in arterial blood
pc	after meals
PCA	patient-controlled analgesia
PCEA	patient-controlled epidural analgesia
PCOS	polycystic ovary syndrome
PCP	*Pneumocystis jiroveci (carinii)* pneumonia
PDA	patent ductus arteriosus
PDE	phosphodiesterase
PE	pulmonary embolism

PEMA	phenylethylmalonamide
PGI_2	prostacyclin
PGE	prostaglandin E
PGF	prostaglandin F
PGHS-II	prostaglandin H synthase-II
pH	hydrogen ion concentration
PID	pelvic inflammatory disease
pK	negative logarithm of the dissociation constant
PKU	phenylketonuria
PMS	premenstrual syndrome
PO	by mouth
PPAR	peroxisome proliferator activated receptor
ppb	parts per billion
PPH	primary pulmonary hypertension
PPROM	prolonged premature rupture of membranes
PR	by way of the rectum
PRBCs	packed red blood cells
prn	as required
PROM	premature rupture of membranes
PT	prothrombin time
PTH	parathyroid hormone
PTT	partial thromboplastin time
PUPPP	pruritic urticarial papules and plaques of pregnancy
PUVA	psoralen and ultraviolet A
PV	through the vagina
PVC	premature ventricular contraction
PVD	peripheral vascular disease
q	every
qac	before every meal
qam	every morning

qd	every day
qhs	every hour of sleep
qid	four times daily
qmo	every month
qnoon	every noon
qod	every other day
qpm	every night
QT	the Q-T interval on an electrocardiogram
QTc	corrected Q-T interval
qw	every week
r^2	coefficient of determination
RBC(s)	red blood cell(s)
RCT	randomized controlled trial
RDA	recommended daily allowance
rDNA	ribosomal deoxyribonucleic acid
RDS	respiratory distress syndrome
REM	rapid eye movement
Rh	Rhesus [factor]
RNA	ribonucleic acid
ROM	rupture of membranes
RSV	respiratory syncytial virus
rt-PA	recombinant tissue plasminogen activator
S.	*Staphylococcus; Streptococcus*
SA	sinoatrial
SC	subcutaneous
SD	standard deviation
S/D	systolic/diastolic
sec	second(s)
SEFW	sonographic estimate of fetal weight

SEM	standard error of the mean
SERM	selective estrogen receptor modulators
SGA	small for gestational age
SIADH	syndrome of inappropriate antidiuretic hormone
SIDS	sudden infant death syndrome
SL	sublingual
SLE	systemic lupus erythematosus
SOB	shortness of breath
SR	slow-release
SSRI	selective serotonin reuptake inhibitor
STD	sexually transmitted disease
SVT	supraventricular tachycardia
T.	*Treponema; Trichomonas; Trichophyton*
t/2	half-life
T_3	triiodothyronine
T_4	thyroxine
tab(s)	tablet(s)
TAT	thrombin-antithrombin
TB	tuberculosis
tbsp	tablespoon(s)
TCA	tricyclic antidepressant
TIA	transient ischemic attack
tid	three times a day
T_{max}	time to peak plasma concentration
TNF	tumor necrosis factor
TSH	thyroid-stimulating hormone
tsp	teaspoon(s)
TT	thrombin time
TTP	thrombotic thrombocytopenic purpura
U	unit(s)

URI	upper respiratory infection
USP	United States Pharmacopeia
UTI	urinary tract infection
UV	ultraviolet
UVA	ultraviolet A
UVB	ultraviolet B
V.	*Vibrio*
VACTERL	vertebral, anal, cardiac, tracheoesophageal, renal, and limb malformations
VATER	vertebral defects, imperforate anus, tracheoesophageal fistula, and radial and renal dysplasia
VBAC	vaginal birth after cesarean section
VCAM	vascular cell adhesion molecule
VF	ventricular fibrillation
VIP	vasoactive intestinal polypeptide
VLDL	very-low-density lipoprotein
VSD	ventricular septal defect
VTE	venous thromboembolism
vWD	von Willebrand's disease
VZV	varicella-zoster virus
w	week(s)
WBC	white blood cell count
WHO	World Health Organization
×	times
Xa	activated factor X
XR	extended-release
y	year(s)

Appendix I List of Pregnancy Registries

Table 1: Pregnancy Registries Enrolling Pregnant Women for Specific Medical Conditions (as of May 2008)

Medical Condition	Medical Products Covered	Registry Name	Contact Information
HIV/AIDS	HIV/AIDS medicines	Antiretroviral Pregnancy Registry	**Kendle International** *North America:* Phone: 1-800-258-4263 (toll-free) Fax: 1-800-800-1052 *Outside North America:* Phone: 910-256-0238 (call collect) Fax: 910-256-0637 Website: *http://www.kendle.com/registries/*
Cancer	Cancer medicines	Cancer and Childbirth Registry	**Cooper Health** Phone: 1-877-635-4499 (toll-free) Phone: 856-757-7876 Phone: 856-342-2491 Website: *http://www.cooperhealth.org/content/pregnancyandcancer.htm*
Epilepsy	Epilepsy medicines	AED (antiepileptic drug) Pregnancy Registry	**Genetics and Teratology Unit** **Massachusetts General Hospital** Phone: 1-888-233-2334 (toll-free) Fax: 617-724-8307 Website: *http://www.massgeneral.org/aed/*
Transplant	Antirejection medicines	National Transplantation Pregnancy Registry (NTPR)	**National Transplantation Pregnancy Registry (NTPR)** **Thomas Jefferson University** 1025 Walnut St. 605 College Bldg. Philadelphia, PA 19107 Phone: 215-955-4820 Fax: 215-923-1420 E-mail: *NTPR.Registry@jefferson.edu* Website: *http://www.tju.edu/NTPR/*
Rheumatoid arthritis, Ankylosing spondylitis, Psoriatic arthritis, and Psoriasis	Autoimmune medicines	OTIS Autoimmune Diseases Study	**Organization of Teratology Information Specialists (OTIS)** Phone: 1-877-311-8972 (toll-free) Website: *http://otispregnancy.org/otis_study_ra.asp*

Table 2: Specific Medical Products (generic drug name)

Medical Products Studied	Medical Condition	Registry Name	Contact Information
Aldurazyme (laronidase)	Mucopolysaccharidosis I (MPS I) Hurler's syndrome Hurler-Scheie syndrome Scheie's syndrome	Fabry Registry	**Genzyme Corporation** *In North America*: Phone: +617-591-5500 E-mail: *help@FabryRegistry.com* *In Europe:* Phone: +31-35-699-1232 E-mail: *europe@FabryRegistry.com* *In Latin America:* Phone: +617-591-5500 E-mail: *help@FabryRegistry.com* *In Asia-Pacific*: Phone: +852 2810 1613 Website: *http://www.lsdregistry.net/fabryregistry/*
Amerge (naratriptan) Imitrex (sumatriptan)	Migraine headaches	Sumatriptan and Naratriptan Pregnancy Registry	**Kendle International** *North America:* Phone: 1-800-336-2176 (toll-free) Phone: 910-256-0549 (call collect) Fax: 1-800-800-1052 *Outside North America:* Phone: 910-256-0549 (call collect) Fax: 910-256-0637 Website: *http://www.kendle.com/registries/*
Amevive (alefacept)	Chronic plaque psoriasis, candidates for systemic therapy	Amevive Pregnancy Registry	**Astellas Pharma U.S. Inc**. Research Park 1011 Ashes Drive Wilmington, NC 28405 Phone: 1-866-834-7223 (toll-free) Fax: 1-800-800-1052 (toll-free fax) Website: *http://www.kendle.com/registries/*
Arava (leflunomide)	Rheumatoid arthritis	Arava Pregnancy Registry	**Organization of Teratology Information Specialists (OTIS)** Phone: 1-877-311-8972 (toll-free) Website: *http://otispregnancy.org/otis_study_ra.asp*
Avonex (interferon beta-1a)	Relapsing forms of multiple sclerosis	Avonex Pregnancy Registry	**Avonex Pregnancy Registries** Research Park 1011 Ashes Drive Wilmington, NC 28405 Phone: 1-800-811-0104 Fax: 1-800-800-1052 (toll-free fax) Website: *http://www.kendle.com/registries/*

Table 2: Specific Medical Products (generic drug name)—cont'd

Medical Products Studied	Medical Condition	Registry Name	Contact Information
Betaseron (interferon beta-1b)	Relapsing forms of multiple sclerosis	Betaseron Pregnancy Registry	**Kendle International** Research Park 1011 Ashes Drive Wilmington, NC 28405 Phone: 1-800-478-7049 Website: *http://www.betaseronpregnancyregistry.com/*
Enbrel (etanercept)	Rheumatoid arthritis Psoriatic arthritis Ankylosing spondylitis Psoriasis	OTIS AutoImmune Diseases Study	**Organization of Teratology Information Specialists (OTIS)** Phone: 1-877-311-8972 (toll-free) Website: *http://otispregnancy.org/otis_study_ra.asp*
Fabrazyme (agalsidase beta)	Fabry's disease	Fabry Registry	**Genzyme Corporation** *In North America:* Phone: +617-591-5500 E-mail: *help@FabryRegistry.com* *In Europe:* Phone: +31-35-699-1232 E-mail: *europe@FabryRegistry.com* *In Latin America:* Phone: +617-591-5500 E-mail: *help@FabryRegistry.com* *In Asia-Pacific:* Phone: +852 2810 1613 Website: *http://www.lsdregistry.net/fabryregistry/*
Gardasil vaccine	Human papillomavirus vaccine	Gardasil Registry	**Merck Gardasil Pregnancy Registry*** Phone: 1-800-986-8999 Website: *http://www.merckpregnancyregistries.com/gardasil.html*
Hepatitis B vaccine (Includes Twinrix, Engerix-B, Recombivax HB, Comvax)	Hepatitis B vaccine	Hepatitis B Vaccine in Pregnancy	Motherisk Program Phone: 1-800-670-6126 Website: *http://www.motherisk.org/*
Humira (adalimumab)	Rheumatoid arthritis Psoriatic arthritis Ankylosing spondylitis Crohn's disease	OTIS AutoImmune Diseases Study	Organization of Teratology Information Specialists (OTSI) Phone: 1-877-311-8972 (toll-free) Website: *http://otispregnancy.org/otis_study_ra.asp*
Janumet (sitagliptin plus metformin)	Type 2 diabetes mellitus	Merck Pregnancy Registry Program	**Merck & Company, Inc.** Merck National Service Center Phone: 1-800-986-8999 (toll-free) Fax: 215-993-1220

Table 2: Specific Medical Products (generic drug name)—cont'd

Medical Products Studied	Medical Condition	Registry Name	Contact Information
			Website: *http://www.merckpregnancyregistries.com/januvia.html*
Januvia (sitagliptin)	Type 2 diabetes mellitus	Merck Pregnancy Registry Program	**Merck & Company, Inc.** Merck National Service Center Phone: 1-800-986-8999 (toll-free) Fax: 215-993-1220 Website: *http://www.merckpregnancyregistries.com/januvia.html*
Keppra (levetiracetam)	Partial-onset seizures	Keppra Pregnancy Registry	**Kendle International** Phone: 1-888-537-7734 or 1-888-KEPPREG Phone: 910-509-4970 (call collect) Website: *http://www.kendle.com/registries/*
Lamictal (lamotrigine)	Partial seizure in adults with epilepsy	Lamotrigine Pregnancy Registry	**Kendle International for GlaxoSmithKline** *North America:* Phone: 1-800-336-2176 (toll-free) Phone: 910-256-0549 (call collect) *Pregnant women may contact:* North American AED Registry Phone: 1-888-233-2334 (toll-free) *Outside North America:* Phone: 910-256-0549 (call collect) Fax: 910-256-0637 Website: *http://www.kendle.com/registries/*
Lamisil (terbinafine)	Toe and nail fungal infections	Motherisk: Lamisil in Pregnancy	**Motherisk Program** Phone: 1-800-670-6126 Website: *http://www.motherisk.org/*
Maxalt (rizatriptan)	Migraine headaches	Merck Pregnancy Registry Program	**Merck & Company, Inc.** Merck National Service Center Phone: 1-800-986-8999 (toll-free) Fax: 215-993-1220 Website: *http://www.merckpregnancyregistries.com/maxalt.html*
Meridia (sibutramine)	Weight loss management	Motherisk Pregnancy Registry Program	**Motherisk Program** Phone: 1-800-670-6126 Website: *http://www.motherisk.org/*
Myozyme (alglucosidase alfa)	Pompe's disease (GAA deficiency)	Pompe Disease Registry	**Genzyme Corporation** *In North America:* Phone: +617-591-5500 E-mail: *help@PompeRegistry.com*

Table 2: Specific Medical Products (generic drug name)—cont'd

Medical Products Studied	Medical Condition	Registry Name	Contact Information
			In Europe: Phone: +31-35-699-1232 E-mail: *europe@PompeRegistry.com*a *In Latin America:* Phone: +617-591-5500 E-mail: *help@PompeRegistry.com* *In Asia-Pacific:* Phone: +852 2810 1613 Website: *http://www.lsdregistry.net/pomperegistry/*
Naglazyme	Maroteaux-Lamy syndrome (also known as polydystrophic dwarfism or mucopolysaccharidosis VI)	MPS VI Clinical Surveillance Program (CSP)	**MPS VI Clinical Surveillance Program (CSP)** Website: *http://clinicaltrials.gov/ct/show/NCT00214773?order=2*
Neoral (cyclosporine, USP) MODIFIED	Psoriasis Rheumatoid arthritis	Neoral® Pregnancy Registry for Psoriasis and Rheumatoid Arthritis	**Thomas Jefferson University** Phone: 1-888-522-5581 (toll-free) Phone: 215-955-0129 Fax: 215-923-1420
Orencia (abatacept)	Severe rheumatoid arthritis	OTIS AutoImmune Diseases Study	**Organization of Teratology Information Specialists (OTIS)** Phone: 1-877-311-8972 (toll-free) Website: *http://otispregnancy.org/otis_study_ra.asp*
Raptiva (efalizumab)	Chronic moderate to severe plaque psoriasis	Raptiva Pregnancy Registry	**Raptiva Pregnancy Registry** Phone: 877-RAPTIVA (877-727-8482) Option 3 (toll-free) Website: *http://www.raptivapregnancyregistry.com/*
Rebif (interferon beta-1α)	Multiple sclerosis	Rebif Pregnancy Registry	**Serono, Inc.** MS Lifelines Phone: 877-44-REBIF (877-447-3243) Website: *http://www.rebifpregnancyregistry.com/*
Ribavirin (trade name: Copegus)	Hepatitis C	Ribavirin Pregnancy Registry	**Kendle International** Phone: (800) 593-2214 Phone: (910) 509-4991 (call collect) Website: *http://www.ribavirinpregnancyregistry.com/*
Singulair (montelukast)	Asthma	Merck Pregnancy Registry Program	**Merck & Company, Inc.** Merck National Service Center Phone: 1-800-986-8999 (toll-free) Fax: 215-993-1220 Website: *http://www.merckpregnancyregistries.com/singulair.html*

Table 2: Specific Medical Products (generic drug name)—cont'd

Medical Products Studied	Medical Condition	Registry Name	Contact Information
Singulair (montelukast)	Asthma **This is a different study than the one conducted by Merck**	Motherisk Singulair in Pregnancy	**Motherisk Program** Phone: 1-800-670-6126 Website: *http://www.motherisk.org/*
Twinrix (hepatitis A inactivated & hepatitis B recombinant vaccine): Exposure anytime from 1mo preceding LMP through the end of pregnancy	Prevention of hepatitis A and hepatitis B	Twinrix Pregnancy Registry	**Twinrix® Pregnancy Registry** GlaxoSmithKline Global Clinical Safety & Pharmacovigilance Phone:1-888-825-5249 (toll-free) Fax: 1-919-483-5404 Website: *http://pregnancyregistry.gsk.com/twinrix.html*
Tysabri (natalizumab)	Multiple sclerosis	Tysabri Pregnancy Registry	**Pregnancy Exposure Coordinating Center** 3168 Collins Ferry Road Morgantown, WV 26505-3352 Phone: 1-866-831-2358 Fax: 1-866-718-6927 E-mail: *LSKC.biogenidec.tysabri@unitedbiosource.com*
Varivax, Zostavax, and Proquad	Prevention of chickenpox; prevention of herpes zoster; prevention of measles, mumps, rubella, and chicken pox	The Pregnancy Registry for Varicella Zoster Virus (VZV)–containing Vaccines	**Merck & Company, Inc.** Merck National Service Center Phone: 1-800-986-8999 (toll-free) Fax: 215-993-1220 Website: *http://www.merckpregnancyregistries.com/varivax.html*
Wellbutrin, Wellbutrin SR, and Zyban (bupropion hydrochloride)	Depression	Bupropion Pregnancy Registry	**Kendle International** *North America:* Phone: 1-800-336-2176 (toll-free) Fax: 1-800-800-1052 *Outside North America:* Phone: 910-256-0549 (call collect) Fax: 910-256-0637 Website: *http://www.kendle.com/registries/*
Xolair (omalizumab)	Asthma	EXPECT Xolair Pregnancy Registry	**The Xolair Pregnancy Registry Center** Phone: 1-866-496-5247 Option 3 (toll-free) Website: *http://www.xolairpregnancyregistry.com/*

Adapted from Food and Drug Administration. List of Pregnancy Exposure Registries. Available at: *http://www.fda.gov/womens/registries/registries.html.*

Appendix II FDA Pregnancy Risk Categories and Percentage of Drugs in Each

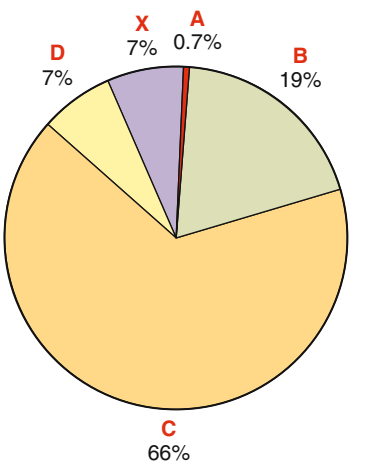
Category A Controlled studies in women fail to demonstrate a risk to the fetus in the first trimester (and there is no evidence of a risk in later trimesters), and the possibility of fetal harm appears remote.

Category B Either animal-reproduction studies have not demonstrated a fetal risk but there are no controlled studies in pregnant women, or animal-reproduction studies have shown an adverse effect (other than a decrease in fertility) that was not confirmed in controlled studies in women in the first trimester (and there is no evidence of a risk in later trimesters).

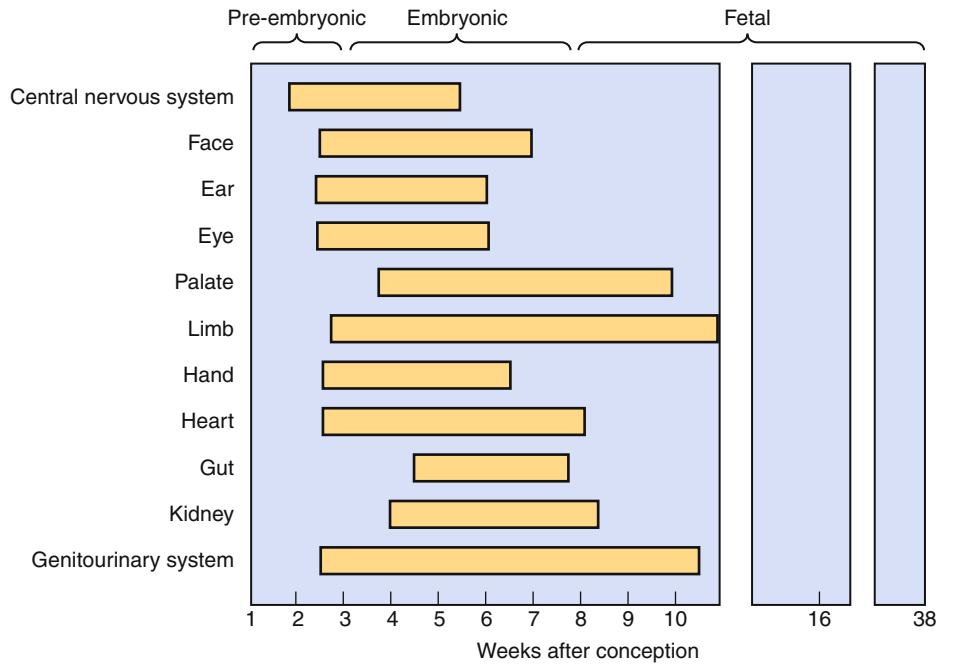
Category C Either study in animals has revealed adverse effects on the fetus (teratogenic or embryocidal or other) and there are no controlled studies in women, or studies in women and animals are not available. Drugs should be given only if the potential benefit justifies the potential risk to the fetus.

Category D There is positive evidence of human fetal risk, but the benefits from use in pregnant women may be acceptable despite the risk (e.g., if the drug is needed in a life-threatening situation or for a serious disease for which safer drugs cannot be used or are ineffective).

Category X Studies in animals or human beings have demonstrated fetal abnormalities, or there is evidence of fetal risk based on human experience or both, and the risk of the use of the drug in pregnant women clearly outweighs any possible benefit. The drug is contraindicated in women who are or may become pregnant.



Appendix III Timing of Development of Major Body Structures in the Embryo and Fetus



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Reproduced with permission from Moore KL, Persaud TVN. The Developing Human: Clinically Oriented Embryology, 6th ed. Philadelphia: WB Saunders Company, 1998:548.

Appendix V Examples of Known or Likely Teratogens or Fetal Toxins

Known Teratogens or Fetal Toxins

Radiation
Radioiodine
Infections
- Cytomegalovirus
- Herpes simplex virus I and II
- Parvovirus B19 (erythema infectiosum)
- Rubella virus
- Syphilis
- Toxoplasmosis
- Varicella virus
- Venezuelan equine encephalitis virus

Maternal & Metabolic Imbalance
- Alcoholism
- Amniocentesis, early (before day 70 postconception)
- Chorionic villus sampling (before day 60 postconception)
- Cretinism, endemic
- Diabetes mellitus
- Folic acid deficiency
- Hyperthermia
- Phenylketonuria
- Rheumatic disease
- Sjögren's syndrome
- Virilizing tumors

Drugs and Environmental Chemicals
- ACEIs (benazepril, captopril, enalapril, fosinopril, lisinopril, moexipril, quinapril, ramipril, trandolapril)
- Aminopterin
- Androgenic hormones
- Busulfan
- Chlorobiphenyls
- Cocaine
- Coumarin anticoagulants
- Cyclophosphamide
- Diethylstilbestrol
- Etretinate
- Fluconazole (high doses)
- Indomethacin and related NSAIDs
- Iodides
- Isotretinoin
- Lithium
- Mercury, organic
- Methimazole
- Methotrexate
- Methylene blue (after intra-amniotic injection)
- Misoprostol
- Penicillamine
- Phenobarbital
- Phenytoin
- Tetracyclines and its derivatives
- Thalidomide
- Toluene (abuse)
- Trimethadione
- Valproic acid

Possible Teratogens or Fetal Toxins

Binge drinking
Carbamazepine
Cigarette smoking
Colchicine
Disulfiram
Ergotamine
Lead
Primidone
Quinine (suicidal doses)
Streptomycin
Vitamin A (high doses)
Zinc deficiency

Unlikely Teratogens

Agent Orange
Anesthetics
Aspartame
Aspirin
Bendectin® (antinauseant)
Hydroxyprogesterone
Lysergic acid diethylamide (LSD)
Marijuana
Medroxyprogesterone
Metronidazole
Oral contraceptives
Progesterone
Rubella vaccine
Spermicides
Video display terminals and electromagnetic waves
Ultrasound

Appendix VI Injectable Hypoglycemic Agents

Insulin Group	Preparation	Onset (h)	Peak (h)	Duration (h)
Rapid-acting	Insulin aspart (Novolog)	<0.2	1-3	3-5
	Insulin lispro (Humalog)	0.25-0.5	0.5-2.5	≤5
	Regular	0.5-1	2-3	3-6
Intermediate-acting	NPH	2-4	4-10	10-16
	Lente	3-4	4-12	12-18
Long-acting	Ultralente	6-10	10-16	18-20
	Insulin glargine (Lantus)	2-4	Peakless	24
Mixtures (intermediate- + rapid-acting)	NPH/Lispro (75/25)	<0.25	Dual	10-16
	NPH/Reg (70/30)	0.5-1	Dual	10-16
	NPH/Aspart (70/30)	0.25	2-4	10-16
	NPH/Reg (50/50)	0.5-1	Dual	10-16

Appendix VII Effect of Pregnancy on Cytochrome P450 Isoenzymes

Enzyme	Effect of Pregnancy	Example of Substrates
CYP1A2	Inhibited, especially in the 3rd trimester	Amitryptiline, caffeine, haloperidol, olanzapine, ondansetron, theophylline
CYP2C19	Probably inhibited	Citalopram, propranolol, proton pump inhibitors, thalidomide
CYP2C9	Induced	NSAIDs
CYP2D6	Induced	Amitryptiline, clomipramine, chlorpheniramine, codeine, fluoxetine, haloperidol, metoclopramide, propranolol
CYP3A4	Induced	Calcium channel blockers, carbamazepine, chlorpheniramine, erythromycin, HIV protease inhibitors, midazolam, tacrolimus

NSAIDs, nonsteroidal anti-inflammatory drugs.

INDEX

Drug names printed in lightface type indicate generic names. Those in **boldface** roman type indicate United States brand names. Those in ***boldface italic*** type indicate international brand names.

B

C

D

E

F

G

H

I

J

K

L

M

N

O

P

Q

R

S

T

U

V

W

X

Y

Z