Patient Profile for Martha Brownlove

General Information

ID:	mb01312009
Prescriber:	Davidson, Henry M.D.
Name:	Martha Brownlove
Address:	62 Main Street
City:	Bellfast
State:	CO
Zip:	40000
Country:	USA
Phone:	789.345.6789

Current Conditions

- allergic rhinitis
- allergy diagnosis
- atrial fibrillation
- chronic obstructive pulmonary disease (COPD)
- constipation
- cough
- females
- hypertension
- insomnia
- macular degeneration
- migraine
- nausea/vomiting
- nutritional supplementation
- osteoporosis
- pyrosis (heartburn)
- renal impairment
- stroke prophylaxis
- urinary tract infection (UTI)

Current Allergies

No allergies noted

Current Medications

- Medication
- Albuterol Dosage: with Atrovent Sig: in nebulizer at bedtime
- Atrovent® Dosage: with Xopenex in AM and Albuterol in PM Sig: in nebulizer AM and PM
- Bactrim™ DS Sig: BID when UTI
- Cafergot® Dosage: 1/100mg Sig: 2 at onset of HeadAche
- Calcium Magnesium Zinc Tablets Sig: tab 2 twice a day
- Codimal® DH Sig: 5cc every 4 hr. PRN cough
- Combivent® Dosage: Inhaler Sig: PRN shortness of breath
- Cyanocobalamin, Vitamin B12 Dosage: 100 mcg Sig: tab 2 daily
- Digitek™ Dosage: 0.25 mg Sig: daily
- Diphenhydramine Dosage: 50 mg Sig: at bedtime as needed for allergies and sleep
- Donnatal® Sig: every 4 to 6 hr PRN indigestion
- Fiorinal® with Codeine Sig: every 4 hours AS Needed headache
- Flunisolide Dosage: 0.25% Sig: Inhaler puffs 2 BID

- Foradil® Aerolizer Sig: in nebulizer twice a day
- Fosamax® Dosage: 70 mg Sig: weekly
- Histex™ I/E Dosage: 10 mg Sig: twice a day for allergy
- Klonopin® Dosage: 1mg Sig: tab 1/2 (0.5mg) at bedtime
- Melatonin Dosage: 3mg Sig: at bedtime as needed for sleep
- Metamucil® Sig: TBS in water each AM PRN constipation
- Norel®SR Sig: one in AM for allergy
- Norvasc® Dosage: 2.5 mg Sig: daily
- Percocet® Dosage: 5/325 mg Sig: every 4 hours PRN headache
- Plavix® Dosage: 75 mg Sig: tab 1 every other day
- Rythmol Dosage: 150 mg Sig: twice a day
- Sea Mist® Nasal Spray Sig: throughout the day PRN nasal congestion
- Theophylline Dosage: S.A. 300mg Sig: twice a day
- Tigan® Dosage: 300mg Sig: PRN nausea & vomiting
- Unisom® Sleeptabs™ Dosage: 50mg Sig: at bedtime PRN sleep
- Verapamil Dosage: 180 mg Sig: daily
- Vitamin D Dosage: 1000 U Sig: daily
- Xopenex® Dosage: with Atrovent Sig: nebulizer each AM
- Zantac 150™ Dosage: 150mg Sig: bid PRN heartburn

Dosing Parameters

Gender:	Female
Birthdate:	11/14/1932
Weight:	49.09 kgs
Height:	165.1 cm
Ideal Body Weight:	58.6 kgs
Body Surface Area:	1.5 m²
Serum Creatinine:	0.9 mg/dL
Creatinine Clearance:	42.5 mL/min

Notes

Title: Initial Interview & Assessment
Date: 01/31/2007

This 74 year old, very strong willed, white female presents with serious respiratory problems related to COPD and years of 2 packs a day smoking. She has problems with atrial fibrillation, probably due to some of the bronchodilator and anticholinergic medications she is currently using. She currently requires many of these bronchodilators daily which may also be a problem with the body rebound effects of constriction of the bronchial pathways. She has serious problems with constipation and severe insomnia,both of which are exacerbated by a multitude of anticholinergic drugs she is currently taking, and can be resolved with medication changes and time. To add to the problems, she has many allergies that she has been treating with both prescription medications and over-the-counter medications that have high anticholinergic activity, drastically adding to all of her other problems. I plan to separate out all the offending drugs in an effort to resolve many of the problems she is currently experiencing. I would be negligent in my professional duty if I didn't in some way try to discourage her continued smoking. I didn't do this throughout our interview because I wanted her complete attention and her freedom to share with me all the symptoms and problems she is currently experiencing. I do have a plan that I will

discuss with her on her return visit as to a possible practical approach to reducing or discontinuing this serious health issue that is literally killing her. She experiences multiple bruises on her extremities that are the result of capillary fragility precipitated by some of the medications she is currently taking and/or the Coumadin therapy that has been discontinued. The Coumadin therapy for the atrial fibrillation may not have been necessary and may have been a result of breathing medications she was and still is taking. As we remove many of the offenders, it may prove that the other atrial fibrillation drugs she is currently taking are not necessary. Of course, this will be accomplished through a very slow titration process to discontinue many of these drugs. She requires oxygen at various times and my goal is to stop the need for supplemental oxygen and reduce signs of atrial fibrillation as well as many other drug precipitated adverse events. She is very active and socially involved, but worries about macular degeneration, which she thinks she has, and future eye sight loss. She suffers from heartburn, again, due to some of the drugs she is currently taking. One drug for osteoporosis, Fosamax, probably contributes to this problem since her Creatinine Clearance is border line for its use at all. Serious problems with erosive esophagitis can result from the use of this drug and lead to Gastrointestinal bleeds that could be fatal. She is about 10 Kgs under ideal body weight which may be drug related. She suffers from Migraine type headaches a few times a week which may be due to some of the bronchodilator drugs or from anxiety exacerbated by these drugs, many offending anticholinergic drugs or from the slight depression she currently has (Geriatric Depression Scale value 5). Some treatment of this problem may result in the reduction of these episodes of headaches and insomnia. Although many of her health problems can be resolved, it will take a great deal of effort on her part as well as several months of time for her body systems to readjust to normal function. I will discuss each drug and problems consistent with that drug and the patient's response further in this report.

Title: Drug Therapy Evaluation & Recommendations
Date: 02/12/2007

Review of the drug therapy currently prescribed resulted in the following problem areas:

Albuterol / Xopenex - both drugs are the same, act exactly the same way, carry the same side effects profile and are not intended for maintenance use but for severe attacks. The Levalbuterol (Xopenex) offers no additional benefits over the less expensive racemic Albuterol. Serious adverse events are expected from the continuous use of these products. Many of the adverse events are experienced in this patient from the insomnia, anxiety, dyspepsia, cough, severe headaches and arrhythmia exacerbation. This is one of the probable offenders for the atrial fibrillation as well as the severe headaches. Slow titration of this drug to be used only on an "as necessary" basis for severe episodes will be our goal.

Atrovent - ipratropium a very good bronchodilator in treating COPD and many other respiratory diseases has one main fault in that the half-life is around four hours and as with

Albuterol/Levalbuterol allows for a rebound constriction of the bronchial system which can be more dramatic and alarming to the patient. A newer drug has been developed that is an improvement of ipratropium, tiotropium (Spiriva) which has a very long (24 hour+) half life and will not allow for the body bronchial system to rebound. Additionally, change to this will allow for once a day dosing and stop the need for the Albuterol/Levoalbuteral. This change will have to be gradual, as we have to taper away the offending drugs and in doing so may stop many of the above listed adverse events, especially the insomnia, atrial fibrillation and headaches. I have seen much success in this conversion therapy.

Bactrim DS - used when patient has problems with UTIs and not a continuous drug. If the UTIs are persistent, use of a prophylactic drug trimethorprim at bedtime daily may keep the UTI problem controlled. The patient contends this is not a problem at present.

Cafergot - use of ergotamine in this patient is very risky. Several factors make use of the Cafergot contraindicated and include renal clearance problems (creatinine clearance of 42cc/min), cardiac problems, heavy smoker, postmenopausal females and hypertension. I believe as we get away from many of the bronchodilators and anticholinergics currently used that the need for this drug will disappear. Serious caution should be used to ever consider another dose.

Calcium/Magnesium/Zinc - used as supplements daily is permissible but the use of Calcium Citrate instead of the carbonate salt will reduce the potential for constipation, from which the patient suffers, and is more readily absorbable in the geriatric's gut. The Magnesium and Zinc can be supplemented through a Centrum Silver (or store like brand) and allow for more control of the Calcium needs singularly.

Codimal DH - although the hydrocodone is a cough suppressant, the combination with the phenylephrine and pyrilamine are totally contraindicated in this patient due to the cardiac effects that could lead to heart failure. Almost all of the complaints expressed by this patient are symptoms consistent with the use of this drug. Also, opiates (Hydrocodone) are not considered appropriate in the treatment of cough in the COPD patient since they suppress respiration, enforce cholinergic effects by stimulating brain medullary vagal nuclei causing bradycardia and vasovagal syncope, enduce release of histamine leading to peripheral vasodilation and orthostatic hypotension. This drug should be stopped and alternative treatments considered as I will mention in the new drug therapy section.

Combivent - a combination of Albuterol and Atrovent are concomitant treatments with other respiratory treatments used and provide no benefits but increase the risk of adverse events currently described by the patient. This therapy should be stopped.

Vitamin B12 tablets - use of oral Vitamin B12 provides no benefit whatsoever due to the older patient's gut not producing intrinsic factor essential for B12 absorption. I do believe the patient needs supplemental B12 since other drugs she is currently taking deplete body stores. Also, the addition of Folic Acid is necessary which together with B12 improve muscle coordination and cognition. She was adamant that she was not going to take an injection so that leaves the intranasal use a recommendation. Spraying the controlled 500mcg dose in each nostril weekly for

60 days then monthly may improve body stores of B12, improving muscle tone and overall body condition.

Digitek - use of digoxin in this patient is a good choice. Consistent with the current age, weight and creatinine clearance of 42cc/min. the current 0.25mg dose is too high and should be reduced by 50%. Although I do not have a Serum Digoxin level in her laboratory work, it has been consistent with my findings that 0.25mg dosing in the geriatric setting is inappropriate. A reduction of Digoxin dosing to 0.125mg daily should be implemented at once. At a later date, after titration of all the respiratory drugs is complete, a reevaluation for the need of Digoxin for the Atrial Fibrillation can be done.

Diphenhydramine, Donnatal, Histex, Unisom Sleeptab, Norel SR, Tigan - All of these compounds are totally contraindicated in patients with cardiac disease, COPD and geriatric patients. All are highly anticholinergic and produce all the symptoms experienced in this patient. None of these should ever be used again. Serious cardiac failure, respiratory failure can occur. Other alternative drugs will be discussed later in the report.

Fiorinal/Codeine - although a favorite of the patient in treating headaches, the chemistry of the drugs is not compatible with COPD and respiratory disease. The potential loss of the body's ability to process CO2 makes serious adverse events for the COPD patient. Respiratory suppression due to the Phenobarbital portion also places the patient at very high risk. Phenobarbital is considered as an inappropriate drug for the geriatric patient due to the long half-life and prolonged adverse events. The codeine portion is contraindicated due to many serious problems seen with opiate therapy. Other drugs will be suggested.

Flunisolide - The need for this steroid inhalation therapy will eventually go away after some of the many offending drugs currently used are stopped. After we reach a certain point in the titration process of the offending drugs, we may try tapering the use down to possibly discontinuing. Even though steroid inhalation therapy is not as detrimental to bone loss, it does contribute to some degree. If we can work into the use of Spiriva with Albuterol as needed for support, many of the current problems you are being treated for will subside.

Foradil Aerolizer - a highly selective beta-2 antagonist similar to Salmeterol has been associated with respiratory failure, prolongation of QT wave and many serious adverse events in the geriatric patient. Elderly patients may be more sensitive to the side effects of beta=agonists, especially tremor, tachycardia; this risk is higher in patients with preexisting coronary artery disease. Other events currently present in the patient of insomnia, nausea and vomiting and rhinitis have a high incidence of events in the geriatric patient. My recommendation is to taper to discontinue this medication as we stabilize the use of Spiriva Handihaler in this patient.

Fosamax - this drug should not be considered in this patient. Based on a Creatinine Clearance of 42cc/min clearance of the drugs is inadequate and will lead to serious problems with the gastrointestinal tract to possible hemorrhage, with could be fatal. In the past year I have seen five cases of osteonecrosis of the jaw in the geriatric female patient. Risk from treatment with any of the bisphosphonate therapies are much greater than benefits received at the patient's

current age. Use of Calcium Citrate and Vitamin D should provide risk free bone enhancement alone.

Klonopin - use of benzodiazepine drugs in the older adult is considered risky. Studies show an increase in the incidence of falls of 70%. This is due to the slow hepatic breakdown of the drug, causing the drug not to clear completely before the next dose. Since there is a degree of Depression shown in Geriatric Depression Scale (value 5), introduction of Effexor XR at bedtime with a gradual increase in dose titration may improve anxiety and especially the insomnia. Effexor XR is very geriatric friendly.

Plavix - Almost all studies in recent months show that there is no statistical difference in the platelet inhibition properties of Plavix over regular Aspirin. Therefore a daily dose of full strength Aspirin 325mg Enteric Coated will provide the prophylactic benefits to stroke more cost effectively. A change to Aspirin EC 325mg is recommended.

Norvasc - a dihydropyridine calcium channel blocker is an excellent drug but is not necessary, since you already have a calcium channel blocker Verapamil ordered as well. The benzothiazepine Calcium Channel blockers are more geriatric friendly and provide fewer adverse events. Exacerbation of GERD from which the patient suffers is an often seen adverse event with Norvasc.

Verapamil - a benzothiazepine Calcium Channel blocker currently dosed at 180mg (time release) daily may be adequate after removal of all the above offending drugs. It may in fact control the atril fibrillation with the digoxin without any other drug therapy needed. A close check on blood pressure values AM and PM for the following month or two will be necessary to make sure the dose is correct or adjustments are necessary. If greater dosing is required, I would like to divide the time release dose into two daily doses which will extend the AUC (activity under the curve) providing better control of cardiac problems including blood pressure.

Rythmol - Use of proparfenone has to be used with caution in the geriatric patient especially those with renal impairment (CrCl 42cc/min) since about 40% of the metabolites are renally excreated. This drug is considered contraindicated in patients with respiratory disease, Asthma and COPD. After the changes of many drugs listed above this drug may not be necessary and the problems with arrhythmias may all be controlled with the Verapamil and Digoxin. As we progress with the tapering and titration of the other drugs, a trial taper to discontinue of the Rythmol needs to be initiated.

Theophyllin - this drug is known to cause atrial fibrillation and should be tapered and discontinued. An old treatment for respiratory problems, newer studies indicate that its usefulness may not exist. The stress placed on the diaphragm may exacerbate more cardiac problems without being beneficial to the COPD patient. A taper to discontinue this drug is needed.

Zantac - an excellent H2 blocker has limitations in patients with renal impairment as seen in this patient. Dosing should be lowered to 75mg twice a day and only if necessary for heartburn and indigestion. Use of Buttermilk or Yogurt (Acitivia) throughout the day and always at bedtime should support any digestive problems and possibly improve constipation problems. I know the

patient does not like buttermilk or yogurt or milk products, but I believe I have convinced her to try the new Acitivia yogurt, and then let's just see.

Vitamin D - Since we are going to try Calcium Citrate with Vitamin D, additional doses of Vitamin D may not be necessary. Considering the Vitamin D she will receive in the Citracal Plus D three times a day and the Centrum Silver, all her Vitamin D requirements will be met.

Drug Therapy Management

Stop Albuterol (using tapering guidelines listed below with Spiriva)
Stop Xopenex (using tapering guidelines listed below with Spiriva)
Stop Bactrim DS
Stop Cafegot (additional analgesics will be used if headache persists)
Stop Calcium, Magnesium, Zinc
Stop Codimal DH
Stop Combivent
Stop Vitamin B12 tablets
Stop Digitek 0.25mg
Stop Diphenhydramine (Benadryl)
Stop Donnatal
Stop Fiorinal/Codeine
Stop Flunisolide Inhaler (following titration below)
Stop Foradil Aerolozer (following tapering and titration listed below)
Stop Fosamax
Stop Histex
Stop Norel SR
Stop Norvasc
Stop Plavix
Stop Rythmol (using tapering and titrations listed below)
Stop Theophyllin (use tapering listed below)
Stop Tigan
Stop Unisom Sleeptabs
Stop Vitamin D except for 1000U three times a week
Stop Zantac (see tapering listed below)

New Drug Therapy

Start Spiriva Handihaler - Inhale each AM (Wash out mouth well after each dose)
Start taper to Discontinue Albuterol/Atrovent at bedtime x 7 days then
Every other bedtime for 4 doses and discontinue
After 7 days of no Albuterol/Atrovent
Start taper to Discontinue Theophyllin 300mg at noon daily for 4 doses and then discontinue all Theophyllin.
After 7 days …
Start taper of Foradil Aerolizer at 6PM daily x 7 days then every other day for 4 doses then discontinue.
After 7 days
Taper to Discontinue Flunisolide Inhaler at noon daily x 14 days, then every other day For 8 doses and discontinue.
Start Ventolin Inhaler puffs 2 every 4 hours as needed for severe shortness of breath
Start Nascobal Actuation Nasal Spray (vitamin B12 spray)(Qol Medical) in each nostril metered dose weekly x 4 weeks then the first day of each month.
Start Folic Acid 1mg daily
Start Zyrtec 10mg daily for allergies (take every day)
Start Tramadol 50mg + Acetaminophen 500mg every 8 hours for headache or pain
Start Effexor XR 37.5mg at bedtime for 5 days then 75mg at bedtime
Then taper to discontinue Klonopin 0.5mg every other bedtime for 30 days
then 0.25mg every other bedtime for 30 days and discontinue.
(if you become uncomfortable or anxious, increase Effexor XR to 112.5mg at bedtime)
Start Verapamil ER 120mg AM and PM daily (monitor AM and PM blood pressures as we talked about upon arising and just before going to bed) Record on you record with pulse
Start Centrum Silver (or like store brand) daily
Start Citracal Caplets Plus D take one tablet with breakfast, lunch and dinner daily
Start Aspirin EC 325mg daily
Start Digitek 0.125mg daily
Start Zantac 75mg twice a day only as needed for heartburn or indigestion
Start Vicks (Delsym Suspension) 5cc every 4 to 6 hours as needed for cough.
Continue your Metamucil, Sea Mist Nasal Spray, Percocet for severe pain,
Keep your Cafegot and Fiorinal on hand for severe headaches but do not use unless it is absolutely necessary. After completion of all the tapers and titrations then discard these two drugs.

Wait 30 days after all these changes to continue:

Consistent with your blood pressure values you will have for me to evaluate, we will continue with:

Taper to discontinue Rythmol 150mg daily x 10 days, then 75mg daily x 10 days, then 75mg every other day x 5 doses and discontinue. (continue to keep your Blood pressure and pulse log)

Remember that it will take time to see all the changes that the new drug therapy will produce. After completing the titration and tapering processes that are required, we should see big improvements relating to the complaints recorded. The additional vitamin supplements should also make you feel better after 30 days or so. Further titration of the Verapamil dosing may be needed until we reach your dose. Continue to keep your blood pressure and pulse log. This is very important. Coming off all these bronchodilators is not going to be easy since your mental dependence to breathing therapy is worse than your physical dependence. You are on so many different short acting bronchodilators now that the rebound effects are overwhelming you and this must be stopped. In conjunction with all the anticholinergic drugs and bronchodilators there is no wonder that you have problems with atrial fibrillation that may be resolved once we have stabilized your breathing medications. The Zyrtec should meet your allergy needs alone. It is well tolerated and will work with your medications with no problems. The Effexor XR should make you feel less anxious and improve your sleep. It will take a few days for the Effexor XR to respond but by the time you reach your 75mg at bedtime dose you should be seeing a difference. Then start the Klonopin taper to discontinue. I feel that at the end of this drug removal process we can also taper and remove the Rythmol which is a serious offender drug in the COPD patient. I feel the Verapamil and digoxin free from all the other drugs will provide you with ample support for your atrial fibrillation, if it still exists, which it may not, and was just a result of all the other inappropriate drugs.

Smoking ???

I know you know that continuing smoking is a serious issue. I know all the reasons for not quitting as well as how hard it is to do. I have been there. I do know many physical problems you now have and will continue to worsen if you don't make some aggressive attempt to stop or reduce your current addition to nicotine. With that said I want you to consider a trial of the new Chantix tablets that have had wonderful results in many cases. Trial studies show in the initial 12 week period of treatment 42% of the heavy smokers remained smoke free. An additional 12 weeks of therapy for the failure patients resulted in an amazing additional 42% of the group of subjects remained smoke free. These are very dramatic results for any product produced so far. You

start the medication and continue to smoke for the first 7 to 10 days and, based on patients that have used this drug, the desire to smoke went away. Since you have some renal impairment, dosing would be 0.5mg daily for 10 days then 0.5mg twice a day for 12 weeks. I would seriously like for you to try this new treatment and see if you can beat this serious addiction. I want you to feel better and respond to the other therapy changes we have discussed and I know that all will work better for you if in some way we can stop the smoking addiction. There is a complete program with support groups you can phone if needed, everything we will discuss if you want to try. If you think you want to give it a try let me know and I will help you in any way.

Let me remind you that this drug therapy regimen is thoroughly thought out and should be followed in its entirety. Choosing only bits and pieces of it may keep us from reaching our mutual goal of improvement in your quality of life and health. I am as close as your phone, so if problems occur please call me. I look forward to seeing you for a follow-up visit around the end of April or the first of May, but would like a progress report weekly by phone until we have all your medication dosages adjusted for you.

Drug Interactions

Albuterol and Flunisolide

Severity: Moderate

Methylxanthine derivatives (e.g., theophylline, aminophylline [5277]) and corticosteroids [3085] may aggravate the hypokalemic effect that may be seen with beta-agonists.[5197] Consider checking potassium levels if clinically indicated. However, beta-agonists are commonly used in conjunction with aminophylline, theophylline, and corticosteroid therapy. In addition, concomitant use of beta-agonists with xanthines, such as theophylline, can cause additive CNS stimulation. Although theophylline (or aminophylline) may be used together with beta-agonists, some patients may experience sensations of tremor or nervousness with combined use. Concomitant use of drugs and herbals such as cocaine, caffeine, guarana, green tea, and other sympathomimetics (such as oral decongestants or ephedra, ma huang) with beta-agonists might result in additive CNS stimulation (e.g., tremor, insomnia) or cardiovascular effects (e.g., increased blood pressure and heart rate).

Albuterol and Phenylephrine (found in Codimal® DH)

Severity: High

If asthma symptoms occur between the use of long-acting beta-agonists (e.g., salmeterol or formoterol), short-acting beta$_2$-agonists (e.g., albuterol) may be used safely for the symptomatic relief of acute asthma symptoms.[5197] [5262] When beginning treatment with a long-acting beta-agonist, patients who have been taking inhaled, short-acting beta$_2$-agonists on a regular basis (e.g., four times a day) should be instructed to discontinue the regular, scheduled use of these drugs and use them only for the symptomatic relief of acute asthma symptoms. Patients should be cautioned that increasing short-acting inhaled beta$_2$-agonist use is a signal of deteriorating asthma. Due to the pharmacology of albuterol [5262], the concomitant use of albuterol with other short-acting beta-agonists or short-acting sympathomimetic aerosol bronchodilators is NOT recommended due to the increased risk of adverse cardiovascular effects (considered duplicate therapy). Caution and close observation should also be used when albuterol is used concurrently with other adrenergic sympathomimetics, administered by any route, to avoid potential for increased cardiovascular effects.[5262]

Albuterol and Albuterol; Ipratropium (Combivent®)

Severity: High

If asthma symptoms occur between the use of long-acting beta-agonists (e.g., salmeterol or formoterol), short-acting beta$_2$-agonists (e.g., albuterol) may be used safely for the symptomatic relief of acute asthma symptoms.[5197] [5262] When beginning treatment with a long-acting beta-agonist, patients who have been taking inhaled, short-acting beta$_2$-agonists on a regular basis (e.g., four times a day) should be instructed to discontinue the regular, scheduled use of these drugs and use them only for the symptomatic relief of acute asthma symptoms. Patients should be cautioned that increasing short-acting inhaled beta$_2$-agonist use is a signal of deteriorating asthma. Due to the pharmacology of albuterol [5262], the concomitant use of albuterol with other short-acting beta-agonists or short-acting sympathomimetic aerosol bronchodilators is NOT recommended due to the increased risk of adverse cardiovascular effects (considered duplicate therapy). Caution and close observation should also be used when albuterol is used concurrently with other adrenergic sympathomimetics, administered by any route, to avoid potential for increased cardiovascular effects.[5262]

Albuterol and Formoterol (Foradil® Aerolizer)

Severity: High

If asthma symptoms occur between the use of long-acting beta-agonists (e.g., salmeterol or formoterol), short-acting beta$_2$-agonists (e.g., albuterol) may be used safely for the symptomatic relief of acute asthma symptoms.[5197] [5262] When beginning treatment with a long-acting beta-agonist, patients who have been taking inhaled, short-acting beta$_2$-agonists on a regular basis (e.g., four times a day) should be instructed to discontinue the regular, scheduled use of these drugs and use them only for the symptomatic relief of acute asthma symptoms. Patients should be cautioned that increasing short-acting inhaled beta$_2$-agonist use is a signal of deteriorating asthma. Due to the pharmacology of albuterol [5262], the concomitant use of albuterol with other short-acting beta-agonists or short-acting sympathomimetic aerosol bronchodilators is NOT recommended due to the increased risk of adverse cardiovascular effects (considered duplicate therapy). Caution and close observation should also be used when albuterol is used concurrently with other adrenergic sympathomimetics, administered by any route, to avoid potential for increased cardiovascular effects.[5262]

If asthma symptoms occur between formoterol controller doses, short-acting beta-2 agonists (e.g., albuterol) may be used safely for the symptomatic relief of acute asthma symptoms.[5038] When beginning treatment with formoterol, patients who have been taking inhaled, short-acting beta-2 agonists on a regular basis (e.g., four times a day) should be instructed to discontinue the regular, scheduled use of these drugs and use them only for the symptomatic relief of acute asthma symptoms. Patients should be cautioned that increasing short-acting inhaled beta-2 agonist use is a signal of deteriorating asthma. Due to the pharmacology of formoterol [5038], the concomitant use of formoterol with other long-acting beta-agonists (e.g., salmeterol-containing products [5197]) is NOT recommended due to the increased risk of adverse cardiovascular effects (considered duplicate therapy). Caution and close observation should be used when formoterol is used concurrently with other adrenergic sympathomimetics, administered by any route, to avoid potential for increased cardiovascular effects based on the pharmacology of formoterol.[5038]

Albuterol and Levalbuterol (Xopenex®)

Severity: High

Mean decreases of 16% and 22% in serum digoxin levels were demonstrated after single-dose intravenous and oral administration of racemic albuterol, respectively, to normal volunteers who had received digoxin for 10 days.[5262] The clinical significance of these findings for patients with obstructive airway disease who are receiving albuterol or levalbuterol and digoxin on a chronic basis is unclear. Nevertheless, it would be prudent to carefully evaluate the serum digoxin levels in patients who are currently receiving digoxin and albuterol or levalbuterol therapy.[5262]

If asthma symptoms occur between the use of long-acting beta-agonists (e.g., salmeterol or formoterol), short-acting beta$_2$-agonists (e.g., levalbuterol) may be used safely for the symptomatic relief of acute asthma symptoms.[5047] [5197] When beginning treatment with a long-acting beta-agonist, patients who have been taking inhaled, short-acting beta$_2$-agonists on a regular basis (e.g., four times a day) should be instructed to discontinue the regular, scheduled use of these drugs and use them only for the symptomatic relief of acute asthma symptoms. Patients should be cautioned that increasing short-acting inhaled beta$_2$-agonist use is a signal of deteriorating asthma. Due to the pharmacology of levalbuterol [5047], the concomitant use of levalbuterol with other short-acting beta-agonists or short-acting sympathomimetic aerosol bronchodilators is NOT recommended due to the increased risk of adverse cardiovascular effects (considered duplicate therapy). Caution and close observation should also be used when levalbuterol is used concurrently with other adrenergic sympathomimetics, administered by any route, to avoid potential for increased cardiovascular effects.[5047]

If asthma symptoms occur between the use of long-acting beta-agonists (e.g., salmeterol or formoterol), short-acting beta$_2$-agonists (e.g., albuterol) may be used safely for the symptomatic relief of acute asthma symptoms.[5197] [5262] When beginning treatment with a long-acting beta-agonist, patients who have been taking inhaled, short-acting beta$_2$-agonists on a regular basis (e.g., four times a day) should be instructed to discontinue the regular, scheduled use of these drugs and use them only for the symptomatic relief of acute asthma symptoms. Patients should be cautioned that increasing short-acting inhaled beta$_2$-agonist use is a signal of deteriorating asthma. Due to the pharmacology of albuterol [5262], the concomitant use of albuterol with other short-acting beta-agonists or short-acting sympathomimetic aerosol bronchodilators is NOT recommended due to the increased risk of adverse cardiovascular effects (considered duplicate therapy). Caution and close observation should also be used when albuterol is used concurrently with other adrenergic sympathomimetics, administered by any route, to avoid potential for increased cardiovascular effects.[5262]

Albuterol and Acetaminophen; Chlorpheniramine; Phenylephrine; Phenyltoloxamine (Norel®SR)

Severity: High

If asthma symptoms occur between the use of long-acting beta-agonists (e.g., salmeterol or formoterol), short-acting beta$_2$-agonists (e.g., albuterol) may be used safely for the symptomatic relief of acute asthma symptoms.[5197] [5262] When beginning treatment with a long-acting beta-agonist, patients who have been taking inhaled, short-acting beta$_2$-agonists on a regular basis (e.g., four times a day) should be instructed to discontinue the regular, scheduled use of these drugs and use them only for the symptomatic relief of acute asthma symptoms. Patients should be cautioned that increasing short-acting inhaled beta$_2$-agonist use is a signal of deteriorating asthma. Due to the pharmacology of albuterol [5262], the concomitant use of albuterol with other short-acting beta-agonists or short-acting sympathomimetic aerosol bronchodilators is NOT recommended due to the increased risk of adverse cardiovascular effects (considered duplicate therapy). Caution and close observation should also be used when albuterol is used concurrently with other adrenergic sympathomimetics, administered by any route, to avoid potential for increased cardiovascular effects.[5262]

Albuterol and Digoxin (Digitek™)

Severity: Low

Mean decreases of 16% and 22% in serum digoxin levels were demonstrated after single-dose intravenous and oral administration of racemic albuterol, respectively, to normal volunteers who had received digoxin for 10 days.[5262] The clinical significance of these findings for patients with obstructive airway disease who are receiving albuterol or levalbuterol and digoxin on a chronic basis is unclear. Nevertheless, it would be prudent to carefully evaluate the serum digoxin levels in patients who are currently receiving digoxin and albuterol or levalbuterol therapy.[5262]

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Albuterol and Propafenone (Rythmol)

Severity: High

Drugs known to prolong the QTc interval have an increased risk of ventricular arrhythmias. Beta-agonists may be associated with adverse cardiovascular effects including QTc interval prolongation, usually at higher doses and/or when associated with hypokalemia.[5038] [5047] [5262] In addition, beta-agonists should be avoided in patients with congenital long QT syndrome.[4951] Beta-agonists should be administered with extreme caution to patients being treated with drugs known to prolong the QTc interval because the action of beta-agonists on the cardiovascular system may be potentiated.[5038] [5047] Drugs known to increase the QT interval include Class IA antiarrhythmics, Class III antiarrhythmics, flecainide, and propafenone. In addition to antiarrhythmic drugs, other drugs which may result in QT prolongation include: some antipsychotics (e.g., phenothiazines, pimozide, haloperidol, risperidone, sertindole, ziprasidone), amoxapine, arsenic trioxide, astemizole, bepridil, cisapride, chloroquine, clarithromycin, dasatinib [9211], dolasetron [5037], droperidol, halofantrine, halogenated anesthetics, erythromycin, levomethadyl, maprotiline, methadone, some quinolone antibiotics (e.g. ofloxacin, ciprofloxacin, gatifloxacin, gemifloxacin, grepafloxacin, levofloxacin, moxifloxacin, norfloxacin, sparfloxacin), ondansetron [8046], palonosetron [8716], pentamidine, probucol, terfenadine, tricyclic antidepressants, and vorinostat [8046]. This list is not inclusive of all agents that may prolong the QT interval. Tricyclic antidepressants (TCAs) can also potentiate the vascular effects of beta-agonists.

Propafenone is a Class IC antiarrhythmic which increases the QT interval, but largely due to prolongation of the QRS interval.[5014] The use of propafenone in conjunction with other drugs that prolong the QT interval has not been studied and is not recommended by the manufacturer due to potential risk for ventricular tachycardia, including torsade de pointes (TdP) and monomorphic ventricular tachycardia.[5014] According to the manufacturer, propafenone coadministration with tricyclic antidepressants is not recommended.[5014] In addition, drugs which directly prolong the QT interval are not recommended during propafenone therapy. Drugs which have been established to have a causal association with QT prolongation and TdP include: Class IA antiarrhythmics (disopyramide, procainamide, quinidine) [4951] [4952] [5187], Class III antiarrhythmics (amiodarone, bretylium, dofetilide, ibutilide, sotalol) [4951] [4952] [5187], astemizole [140], arsenic trioxide [4951] [4977], bepridil [4951] [4953], cisapride [4951], chloroquine [4951] [4955] [4956], clarithromycin [4951] [4964], droperidol [3610] [4951] [4963], erythromycin [228] [4951] [4978], grepafloxacin [5149], halofantrine [4951] [4968], haloperidol [42] [336] [4951] [5036], levomethadyl [4951] [5079] [5081] [5146], methadone [4951] [5048] [5049] [5050] [5051], pentamidine [168] [335] [4951] [5149], certain phenothiazines (chlorpromazine [4951], mesoridazine [4951] [5831], and thioridazine [4951] [5022]), pimozide [4951], probucol [5145], sparfloxacin [4951] [4958], and terfenadine [141] [231]. Other agents associated with a lower, but possible risk for QT prolongation and TdP based on varying levels of documentation (see separate drug monographs) include: abarelix [5392], alfuzosin [4988], amoxapine [5145], apomorphine [5136], beta-agonists [4951] [5038] [5047], ofloxacin [7501], ciprofloxacin [4951] [5149] [5496] [5507] [6579], clozapine [5146], cyclobenzaprine [5155] [5156], dasatinib [9211], dolasetron [5037], gatifloxacin [5149] [5150] [5152], gemifloxacin [5154], halogenated anesthetics [5187] [5188] [5486] [5487] [5488], levofloxacin [5149] [5150] [5151], local anesthetics, maprotiline [5145], mefloquine [6617] [7535], moxifloxacin [5149] [5150] [5153], olanzapine [9575] [9576], ondansetron [8046], norfloxacin [6564], octreotide [4951], palonosetron [5148], some phenothiazines (fluphenazine [5145], perphenazine [5145], prochlorperazine [5145], and trifluoperazine [5145]), propafenone [5014] [5146], ranolazine [8747], risperidone [4951] [5144], sertindole [5187], tacrolimus [4049] [4050] [4951], telithromycin [4880], tricyclic antidepressants when given in excessive doses or overdosage [5145] [5146], troleandomycin (based on interactions with macrolides) [5149], vardenafil [4942], vorinostat [9633], or ziprasidone [4959]. This list is not inclusive of all agents that can cause QT interval prolongation. In addition, some of the listed drugs are CYP2D6 inhibitors (e.g., amiodarone, chloroquine, chlorpromazine, haloperidol, perphenazine, quinidine, ranolazine, and thioridazine) with potential to inhibit the metabolism of propafenone. In addition to potential for additive QT prolongation, concomitant administration of propafenone with desipramine (tricyclic antidepressant) may result in elevated serum desipramine levels.[5014] In addition to avoiding concurrent drug interactions, the potential for TdP can be reduced by avoiding the use of QT prolonging drugs in patients at substantial risk for TdP.[5162] Examples of general risk factors for TdP include congenital long QT syndrome, female sex, elderly patients, significant bradycardia, hypokalemia, hypomagnesemia, and underlying cardiac disease (e.g., arrhythmias, cardiomyopathy, acute myocardial ischemia).

Albuterol and Theophylline, Aminophylline (Theophylline)

Severity: Moderate

Methylxanthine derivatives (e.g., theophylline, aminophylline [5277]) and corticosteroids [3085] may aggravate the hypokalemic effect that may be seen with beta-agonists.[5197] Consider checking potassium levels if clinically indicated. However, beta-agonists are commonly used in conjunction with aminophylline, theophylline, and corticosteroid therapy. In addition, concomitant use of beta-agonists with xanthines, such as theophylline, can cause additive CNS stimulation. Although theophylline (or aminophylline) may be used together with beta-agonists, some patients may experience sensations of tremor or nervousness with combined use. Concomitant use of drugs and herbals such as cocaine, caffeine, guarana, green tea, and other sympathomimetics (such as oral decongestants or ephedra, ma huang) with beta-agonists might result in additive CNS stimulation (e.g., tremor, insomnia) or cardiovascular effects (e.g., increased blood pressure and heart rate).

Methylxanthine derivatives, (such as theophylline [5277] and aminophylline) and corticosteroids [3085] may aggravate the hypokalemic effect that may be seen with beta-agonists.[5197] Consider checking potassium levels if clinically indicated. However, beta-agonists are commonly used in conjunction with aminophylline, theophylline, and corticosteroid therapy.[5197]

Ipratropium (Atrovent®) **and Atropine; Hyoscyamine; Phenobarbital; Scopolamine** (Donnatal®)

Severity: Moderate

Although ipratropium is minimally absorbed into the systemic circulation after inhalation, there is a potential for ipratropium to have additive anticholinergic effects when administered with other antimuscarinics.[6422] Caution is advised when administering ipratropium to individuals receiving other antimuscarinics [6338]. Other common medications with anticholinergic activity are not as likely to interact with ipratropium as other antimuscarinics.

Additive anticholinergic effects may be seen when combinations of atropine; hyoscyamine; phenobarbital; scopolamine are used concomitantly with other antimuscarinics.[6338] [7179] Other commonly used drugs with moderate to significant anticholinergic effects include amantadine, amoxapine, bupropion, clozapine, cyclobenzaprine, maprotiline [5491], olanzapine, orphenadrine, the sedating H_1-blockers, most phenothiazines, and most tricyclic antidepressants. Clinicians should note that antimuscarinic effects might be seen not only on GI smooth muscle, but also on bladder function, the eye, and temperature regulation. Many of the agents with anticholinergic properties listed can increase the risk of CNS depression when combined with phenobarbital or scopolamine as well. Phenobarbital may also increase the metabolism of many antidepressants and antipsychotics listed.

Ipratropium (Atrovent®) **and Albuterol; Ipratropium** (Combivent®)

Severity: Moderate

Albuterol and beta-blockers are pharmacologic opposites, and will counteract each other when given concomitantly. Beta-blockers will not only block the pulmonary effects of inhaled beta-agonists, but in some cases may exacerbate bronchospasm in patients with reactive airways. If beta-blocking agents cannot be avoided during the use of albuterol; ipratropium, then a $beta_1$-selective (cardioselective) agonist should be chosen, and the patient should be carefully monitored for decreased effects of either medication.

Although ipratropium is minimally absorbed into the systemic circulation after inhalation, there is a potential for ipratropium to have additive anticholinergic effects when administered with other antimuscarinics.[6422] Caution is advised when administering ipratropium to individuals receiving other antimuscarinics [6338]. Other common medications with anticholinergic activity are not as likely to interact with ipratropium as other antimuscarinics.

Although ipratropium is minimally absorbed into the systemic circulation after inhalation, there is a potential for ipratropium to have additive anticholinergic effects when administered with other antimuscarinics. Caution is advised when administering albuterol; ipratropium in individuals taking other antimuscarinic medications. Other common medications with anticholinergic activity are not as likely to interact with ipratropium as other antimuscarinics.

Sulfamethoxazole; Trimethoprim, SMX-TMP (Bactrim™ DS) **and Digoxin** (Digitek™)

Severity: Moderate

Because both trimethoprim and digoxin undergo tubular secretion,[5981] [6110] trimethoprim can interfere with the renal tubular secretion of digoxin when administered concomitantly. The renal clearance of digoxin decreased significantly in elderly subjects receiving trimethoprim for 14 days, resulting in a 22% increase in digoxin concentrations. Similar changes were not noted in a single-dose study of young healthy volunteers.[6111] Patients receiving digoxin, especially the elderly, should be monitored carefully for digoxin toxicity if trimethoprim is added.

Caffeine; Ergotamine (Cafergot®) **and Amlodipine** (Norvasc®)

Severity: High

Because of the potential to cause coronary vasospasm [5585], ergotamine theoretically could antagonize the therapeutic effects of anti-anginal agents including nitrates and nitrites, beta-blockers, and calcium-channel blockers. Caffeine-ergotamine is contraindicated for use in patients with coronary heart disease or hypertension.[5585] Clinicians should also note that calcium-channel blockers with CYP3A4 inhibitory properties (e.g., diltiazem, nicardipine, verapamil) may also reduce the hepatic metabolism of ergotamine and increase the risk of ergot toxicity.[5585]

Caffeine; Ergotamine (Cafergot®) **and Verapamil**

Severity: High

Because of the potential to cause coronary vasospasm [5585], ergotamine theoretically could antagonize the therapeutic effects of anti-anginal agents including nitrates and nitrites, beta-blockers, and calcium-channel blockers. Caffeine-ergotamine is contraindicated for use in patients with coronary heart disease or hypertension.[5585] Clinicians should also note that calcium-channel blockers with CYP3A4 inhibitory properties (e.g., diltiazem, nicardipine, verapamil) may also reduce the hepatic metabolism of ergotamine and increase the risk of ergot toxicity.[5585]

Verapamil is an inhibitor of CYP3A4 isoenzymes. Co-administration with verapamil may lead to an increase in serum levels of drugs that are CYP3A4 substrates. Examples of CYP3A4 substrates include: alfentanil [4718], astemizole [4718], benzodiazepines metabolized by oxidation, buprenorphine [4718], buspirone, certain HMG-CoA reductase inhibitors, certain opiates, cilostazol [4718], cisapride [4718], cyclosporine [4718], darifenacin [7474], disopyramide [4718], dofetilide [4947], ergot alkaloids [5585], ethosuximide [4611], fentanyl [4718], halofantrine [4968], pimozide [4718], sildenafil [4718], sirolimus [4718], sufentanil [4718], tacrolimus [4718], terfenadine [4718], vinca alkaloids, ziprasidone [4718], zolpidem [4718], zonisamide, and others. This list is not inclusive of all agents metabolized by CYP3A4. CYP3A4 inhibitors such as verapamil are considered contraindicated during astemizole [5130], pimozide [5250], and terfenadine [141] therapy due to the potential for drug toxicity (e.g., QT prolongation).

Caffeine; Ergotamine (Cafergot®) **and Phenylephrine** (found in Codimal® DH)

Severity: Very High. This drug combination should be avoided.

Ergotamine should not be administered with other vasoconstrictors (e.g., sympathomimetics).[5585] Ergotamine inhibits the uptake of norepinephrine and stimulates alpha-adrenergic receptors, causing prolonged vasoconstriction. The effects may be additive to other vasoconstrictors. Some sympathomimetics (e.g., cocaine, dopamine, epinephrine, isoproterenol, midodrine[4895], norepinephrine, phenylephrine, phenylpropanolamine and possibly other drugs, like ephedrine, ephedra, ma huang, or pseudoephedrine) may combine with ergotamine to produce dangerous hypertension.[5585] There is also an additive risk of developing peripheral ischemia and gangrene.

Some ergot alkaloids [5066], notably ergotamine and, to a lesser extent, ergonovine, may produce peripheral vasoconstriction due to alpha-receptor agonism in the peripheral circulation. Although no data are available, it is possible that concomitant use of phenylephrine with ergotamine could cause additive and possibly severe peripheral vasoconstriction. Similar problems have been observed when ergot alkaloids were used in combination with other drugs known to cause peripheral vasoconstriction (e.g., ergonovine with dopamine; ergotamine with propranolol). Hypertension, headache, myocardial ectopy, and seizures have occurred when bromocriptine, an ergot derivative, was combined with various sympathomimetics. Phenylephrine use should be avoided in patients on ergot alkaloids or bromocriptine whenever possible.[5066]

Calcium Salts (found in Calcium Magnesium Zinc Tablets) **and Alendronate** (Fosamax®)

Severity: Moderate

Antacids are likely to interfere with the absorption of alendronate. At least 30 minutes should elapse after an alendronate dose before taking antacids or any other drugs.[5375] Concomitant administration of oral alendronate with vitamin supplements; mineral supplements; or other medications that contain calcium salts (e.g., calcium carbonate), iron salts such as ferrous sulfate or polysaccharide-iron complex, aluminum salts (i.e., aluminum hydroxide), or magnesium salts may interfere with the absorption of alendronate.[5375] Even though calcium salts are not to be administered with alendronate, patients need to maintain an adequate intake of calcium and vitamin D to avoid hypocalcemia. Due to the action of alendronate on bone, hypocalcemia and associated adverse effects can develop. The ingestion of high-calcium foods can interfere with the absorption of alendronate, and should not be eaten before, or for at least 30 minutes after, administration of alendronate.

Coadministration of bisphosphonates with oral medications containing divalent cations will interfere with the oral absorption of bisphosphonates.[6090] Thus antacids, vitamins with mineral supplements, or medications that contain aluminum salts (e.g., aluminum hydroxide), calcium salts (e.g., calcium carbonate), iron, or magnesium will interfere with the bioavailability of bisphosphonates.[6090] These agents should not be administered within 2 hours of bisphosphonates.

Calcium Salts (found in Calcium Magnesium Zinc Tablets) **and Digoxin** (Digitek™)

Severity: High

Intravenous administration of calcium should particularly be avoided in patients taking cardiac glycosides [4999] due to an increased risk of developing arrhythmias. Calcium and cardiac glycosides are synergistic in their inotropic and chronotropic effects and hypocalcemia can compromise the therapeutic actions of digitalis.[227] Cardiac glycoside therapy, however, does not preclude the use of calcium salts. Nevertheless, arrhythmias can occur if the calcium salts are given IV to patients on cardiac glycosides. The manufacturer recommends that PhosLo® (calcium acetate), indicated for treating hyperphosphatemia, should not be coadministered to patients receiving digoxin to avoid the risk of hypercalcemia and associated cardiac arrhythmias.

Since electrolyte disorders modify the actions of digoxin, drugs that can affect electrolyte balance potentially can affect the response to digoxin. Hypokalemia, hypomagnesemia, or hypercalcemia increase digoxin's effect.[4999] The following drugs can precipitate digoxin toxicity via their effect on electrolyte balance: amphotericin B [5062], corticosteroids [6115], corticotropin, ACTH, potassium-depleting diuretics (e.g., acetazolamide [4994], loop diuretics [3085], methazolamide [5023], and thiazide diuretics [3085] [5219]), and sodium polystyrene sulfonate [6116]. Calcium salts augment the actions of digoxin. In addition, when calcium is administered via rapid intravenous injection, the risk of serious arrhythmias in digitalized patients is increased.[4999] It is recommended that serum potassium, magnesium, and calcium be monitored regularly in patients receiving digoxin.

Calcium Salts (found in Calcium Magnesium Zinc Tablets) **and Ergocalciferol, Vitamin D2** (Vitamin D)

Severity: Moderate

Calcium is often combined with vitamin D in nutritional supplementation products to supply the recommended RDA/RDI in the general population and to promote optimum bone health. The concurrent use of vitamin D with calcium carbonate or other calcium salts is generally beneficial; in some patients, however, because ergocalciferol can increase serum calcium concentrations,[6916] this combination may result in hypercalcemia.

The concurrent use of vitamin D analogs with calcium-containing antacids or other calcium salts may contribute to vitamin D-induced hypercalcemia.[4686] Calcium replacement or use of calcium-based phosphate binders may be required in patients receiving doxercalciferol, but careful monitoring of serum calcium and phosphorus levels is needed.

Calcium Salts (found in Calcium Magnesium Zinc Tablets) **and Flunisolide**

Severity: Moderate

Calcium absorption is reduced when calcium salts are taken concomitantly with systemic corticosteroids. Systemic corticosteroids induce a negative calcium balance by inhibiting intestinal calcium absorption as well as by increasing renal calcium losses. The mechanism by which these drugs inhibit calcium absorption in the intestine is likely to involve a direct inhibition of absorptive cell function.[8256] [8255]

Calcium Salts (found in Calcium Magnesium Zinc Tablets) **and Verapamil**

Severity: Low

Intravenous administration of calcium salts may be used therapeutically to reverse some of the toxic effects of calcium-channel blockers (e.g., diltiazem, verapamil) in the setting of drug overdose or excessive dosage.[228] [5801] Although the vascular effects (e.g., hypotension) can be reversed, AV nodal effects do not seem to be affected by exogenously administered calcium salts.[5801] This interaction is an expected and therapeutic one under such circumstances of use. While theoretically, the administration any calcium salt would be expected to attenuate the activity of calcium-channel blockers, this interaction is not expected to be of concern when calcium is used orally or intravenously for nutritional supplementation to maintain calcium hemostasis.

Magnesium Salts (found in Calcium Magnesium Zinc Tablets) **and Clonazepam** (Klonopin®)

Severity: Low

Because of the CNS-depressant effects of magnesium sulfate [7197], additive central-depressant effects can occur following concurrent administration with barbiturates, opiate agonists, sedating H_1-blockers, antidepressants, benzodiazepines, general anesthetics, local anesthetics, and phenothiazines.

Magnesium Salts (found in Calcium Magnesium Zinc Tablets) **and Digoxin** (Digitek™)

Severity: High

Magnesium salts, such as magnesium sulfate, can antagonize the electrophysiologic effects of digoxin or other cardiac glycosides. Nevertheless, it is acceptable to administer magnesium salts to patients in order to achieve appropriate serum magnesium concentrations.[6127] Magnesium has also been shown to be an effective adjunct in the treatment of digoxin-induced arrhythmias.[251] [252] [6128] [7197] [7207] However, concurrent use of digoxin or other cardiac glycosides with oral magnesium

citrate may inhibit absorption and possibly decrease plasma concentrations of the glycoside.[4999] Saline laxatives such as magnesium citrate must be administered with caution to patients receiving cardiac glycoside therapy as electrolyte disturbances, particularly hypokalemia, are possible with their use. Cardiac conduction changes and heart block may occur in patients with electrolyte imbalances.[6115]

Magnesium salts, such as magnesium sulfate, can antagonize the electrophysiologic effects of digoxin. Nevertheless, it is acceptable to administer magnesium salts to patients in order to achieve appropriate serum magnesium concentrations.[6127] Magnesium has also been shown to be an effective adjunct in the treatment of digoxin-induced arrhythmias.[6128]

Magnesium Salts (found in Calcium Magnesium Zinc Tablets) **and Diphenhydramine**

Severity: Low

Because of the CNS-depressant effects of magnesium sulfate [7197], additive central-depressant effects can occur following concurrent administration with barbiturates, opiate agonists, sedating H_1-blockers, antidepressants, benzodiazepines, general anesthetics, local anesthetics, and phenothiazines.

Magnesium Salts (found in Calcium Magnesium Zinc Tablets) **and Ergocalciferol, Vitamin D2** (Vitamin D)

Severity: High

Magnesium is often combined with vitamin D and calcium in nutritional supplementation products to supply the recommended RDA/RDI in the general population. As is recommended with other vitamin D analogs,[6902] [6904] however, antacids and magnesium-containing drug products (e.g., magaldrate, magnesium hydroxide, magnesium citrate) or supplemental magnesium salts should be used cautiously in selected patients receiving ergocalciferol. Because vitamin D analogs such as ergocalciferol can increase serum magnesium concentrations, particularly in the presence of renal impairment, the combined use of ergocalciferol and magnesium-containing products should be avoided, if possible, in patients with chronic renal failure.

Supplemental magnesium salts should not be used in patients receiving vitamin D analogs. Vitamin D analogs can increase serum magnesium concentrations in patients with chronic renal failure.

Magnesium Salts (found in Calcium Magnesium Zinc Tablets) **and Hydrocodone** (found in Codimal® DH)

Severity: Low

Because of the CNS-depressant effects of magnesium sulfate [7197], additive central-depressant effects can occur following concurrent administration with barbiturates, opiate agonists, sedating H_1-blockers, antidepressants, benzodiazepines, general anesthetics, local anesthetics, and phenothiazines.

Magnesium Salts (found in Calcium Magnesium Zinc Tablets) **and Acetaminophen; Oxycodone** (Percocet®)

Severity: Low

Because of the CNS-depressant effects of magnesium sulfate [7197], additive central-depressant effects can occur following concurrent administration with barbiturates, opiate agonists, sedating H_1-blockers, antidepressants, benzodiazepines, general anesthetics, local anesthetics, and phenothiazines.

Magnesium Salts (found in Calcium Magnesium Zinc Tablets) **and Aspirin, ASA; Butalbital; Caffeine; Codeine** (Fiorinal® with Codeine)

Severity: Low

Because of the CNS-depressant effects of magnesium sulfate [7197], additive central-depressant effects can occur following concurrent administration with barbiturates, opiate agonists, sedating H_1-blockers, antidepressants, benzodiazepines, general anesthetics, local anesthetics, and phenothiazines.

Magnesium Salts (found in Calcium Magnesium Zinc Tablets) **and Atropine; Hyoscyamine; Phenobarbital; Scopolamine** (Donnatal®)

Severity: Low

Because of the CNS-depressant effects of magnesium sulfate [7197], additive central-depressant effects can occur following concurrent administration with barbiturates, opiate agonists, sedating H_1-blockers, antidepressants, benzodiazepines, general anesthetics, local anesthetics, and phenothiazines.

Magnesium Salts (found in Calcium Magnesium Zinc Tablets) **and Doxylamine** (Unisom® Sleeptabs™)

Severity: Low

Because of the CNS-depressant effects of magnesium sulfate [7197], additive central-depressant effects can occur following concurrent administration with barbiturates, opiate agonists, sedating H_1-blockers, antidepressants, benzodiazepines, general anesthetics, local anesthetics, and phenothiazines.

Magnesium Salts (found in Calcium Magnesium Zinc Tablets) **and Carbinoxamine** (Histex™ I/E)

Severity: Low

Because of the CNS-depressant effects of magnesium sulfate [7197], additive central-depressant effects can occur following concurrent administration with barbiturates, opiate agonists, sedating H_1-blockers, antidepressants, benzodiazepines, general anesthetics, local anesthetics, and phenothiazines.

Magnesium Salts (found in Calcium Magnesium Zinc Tablets) **and Acetaminophen; Chlorpheniramine; Phenylephrine; Phenyltoloxamine** (Norel®SR)

Severity: Low

Because of the CNS-depressant effects of magnesium sulfate [7197], additive central-depressant effects can occur following concurrent administration with barbiturates, opiate agonists, sedating H_1-blockers, antidepressants, benzodiazepines, general anesthetics, local anesthetics, and phenothiazines.

Hydrocodone (found in Codimal® DH) **and Clonazepam** (Klonopin®)

Severity: Moderate

Concomitant use of hydrocodone with other central nervous system (CNS) depressants can potentiate the effects of hydrocodone and may lead to additive CNS or respiratory depression.[7132] Also, the use of monoamine oxidase inhibitors (MAOIs) or tricyclic antidepressants with hydrocodone may increase the effect of either the antidepressant or hydrocodone. Examples of drugs associated with CNS depression include amoxapine; anxiolytics, sedatives, and hypnotics; clozapine; dronabinol, THC; droperidol; entacapone; ethanol [6341]; general anesthetics; sedating H_1-blockers; MAOIs; maprotiline; mirtazapine; molindone; nabilone [9044]; nefazodone; olanzapine; other opiate agonists; phenothiazines; pimozide; pramipexole; pregabalin [7523], quetiapine; risperidone; ropinirole; skeletal muscle relaxants; tolcapone; tricyclic antidepressants; and trazodone. If hydrocodone is used with a CNS depressant, the dose of one or both drugs should be reduced.[7132]

Concomitant administration of clonazepam with other CNS-depressant drugs [7168], including barbiturates, buprenorphine, butorphanol, dronabinol, THC [7185], entacapone [5769], ethanol [7198], sedating H_1-blockers, general anesthetics [6892], nabilone [9044], nalbuphine [6778], opiate agonists, pentazocine, phenothiazines, pregabalin [7523], tolcapone, tramadol, tricyclic antidepressants, or other anxiolytics, sedatives, and hypnotics, can potentiate the CNS effects (i.e., increased sedation or respiratory depression) of either agent.[5174]

Hydrocodone (found in Codimal® DH) **and Diphenhydramine**

Severity: Moderate

Concomitant use of hydrocodone with sedating H_1-blockers can potentiate respiratory depression and/or sedation.[7132] In addition, chlorpheniramine and diphenhydramine inhibit CYP2D6, an enzyme responsible for the metabolism of hydrocodone [4718]; the dose of the antihistamine and/or hydrocodone should be reduced. Close monitoring for central nervous system depression is recommended.

Concomitant use of hydrocodone with other central nervous system (CNS) depressants can potentiate the effects of hydrocodone and may lead to additive CNS or respiratory depression.[7132] Also, the use of monoamine oxidase inhibitors (MAOIs) or tricyclic antidepressants with hydrocodone may increase the effect of either the antidepressant or hydrocodone. Examples of drugs associated with CNS depression include amoxapine; anxiolytics, sedatives, and hypnotics; clozapine; dronabinol, THC; droperidol; entacapone; ethanol [6341]; general anesthetics; sedating H_1-blockers; MAOIs; maprotiline; mirtazapine; molindone; nabilone [9044]; nefazodone; olanzapine; other opiate agonists; phenothiazines; pimozide; pramipexole; pregabalin [7523], quetiapine; risperidone; ropinirole; skeletal muscle relaxants; tolcapone; tricyclic antidepressants; and trazodone. If hydrocodone is used with a CNS depressant, the dose of one or both drugs should be reduced.[7132]

Because diphenhydramine can cause pronounced sedation,[6568] an enhanced CNS depressant effect may occur when it is combined with other CNS depressants [6568] including anxiolytics, sedatives, and hypnotics (such as barbiturates and

benzodiazepines) [6946] [6948], buprenorphine [5278], butorphanol [5912], carisoprodol, clozapine [4989], dronabinol, THC, droperidol [5468], entacapone [5769], ethanol [6341] [6948], general anesthetics [6892], haloperidol [5036], methocarbamol, mirtazapine [5366], molindone [5553], nabilone [9044], nalbuphine [6778], nefazodone [5414], olanzapine [5517], opiate agonists, pentazocine [6777], phenothiazines [6946], pimozide [5250], pramipexole [7757], pregabalin [7523], procarbazine [5356], quetiapine [5855], risperidone [5144], ropinirole [8018], tolcapone [5578], tramadol [5043], trazodone [5450], tricyclic antidepressants [6947], or with other sedating H_1-blockers [6568]. In addition, concurrent use of cannabinoids with sedating H_1-blockers may result in additive tachycardia, which may be pronounced.

Hydrocodone (found in Codimal® DH) **and Ipratropium** (Atrovent®)

Severity: Moderate

Hydrocodone is an opiate agonist [7132] and therefore may increase the tone and decrease the propulsive contractions of the smooth muscle of the gastrointestinal tract. Prolongation of the gastrointestinal transit time may be the mechanism of the constipating effect.[6365] Opiate analgesics combined with antimuscarinics can cause severe constipation or paralytic ileus, especially with chronic use.

Hydrocodone (found in Codimal® DH) **and Acetaminophen; Oxycodone** (Percocet®)

Severity: High

Hydrocodone is an opiate agonist [7132]; concomitant use of hydrocodone-containing products with other opiate agonists may lead to additive respiratory depression and/or sedation. Propoxyphene should be especially avoided in combination with hydrocodone due propoxyphene-induced inhibition of CYP2D6, an enzyme responsible for the metabolism of hydrocodone.[4718] Also, propoxyphene will only partially suppress the withdrawal syndrome in patients physically dependent on morphine or other opiate agonists.[7070]

Concomitant use of oxycodone with other opiate agonists may lead to additive respiratory depression and/or sedation. Propoxyphene should be especially avoided in combination with oxycodone due propoxyphene-induced inhibition of CYP2D6, an enzyme responsible for the metabolism of oxycodone.[4718] Also, propoxyphene will only partially suppress the withdrawal syndrome in patients physically dependent on morphine or other opiate agonists.[7070]

Hydrocodone (found in Codimal® DH) **and Aspirin, ASA; Butalbital; Caffeine; Codeine** (Fiorinal® with Codeine)

Severity: High

Hydrocodone is an opiate agonist [7132]; concomitant use of hydrocodone-containing products with other opiate agonists may lead to additive respiratory depression and/or sedation. Propoxyphene should be especially avoided in combination with hydrocodone due propoxyphene-induced inhibition of CYP2D6, an enzyme responsible for the metabolism of hydrocodone.[4718] Also, propoxyphene will only partially suppress the withdrawal syndrome in patients physically dependent on morphine or other opiate agonists.[7070]

Concomitant use of hydrocodone with other central nervous system (CNS) depressants can potentiate the effects of hydrocodone and may lead to additive CNS or respiratory depression.[7132] Also, the use of monoamine oxidase inhibitors (MAOIs) or tricyclic antidepressants with hydrocodone may increase the effect of either the antidepressant or hydrocodone. Examples of drugs associated with CNS depression include amoxapine; anxiolytics, sedatives, and hypnotics; clozapine; dronabinol, THC; droperidol; entacapone; ethanol [6341]; general anesthetics; sedating H_1-blockers; MAOIs; maprotiline; mirtazapine; molindone; nabilone [9044]; nefazodone; olanzapine; other opiate agonists; phenothiazines; pimozide; pramipexole; pregabalin [7523], quetiapine; risperidone; ropinirole; skeletal muscle relaxants; tolcapone; tricyclic antidepressants; and trazodone. If hydrocodone is used with a CNS depressant, the dose of one or both drugs should be reduced.[7132]

Hydromorphone, a metabolite, contributes to the analgesic effects of the parent drug, hydrocodone. To date, the relative contributions of each compound to analgesia are unknown. Hydrocodone is metabolized to hydromorphone via the cytochrome P450 (CYP) 2D6 hepatic isoenzyme. Some of hydromorphone is also metabolized by CYP3A4 and by non-CYP routes. The analgesic effect of hydrocodone may vary greatly when it is combined with drugs that induce hepatic isoenzymes such as rifampin [4718], rifabutin [5948], rifapentine [5213], carbamazepine [4718], phenytoin (fosphenytoin) [4718], ethotoin, or barbiturates [4718]. Induction of hydrocodone metabolism may take several days.

Caution should be exercised during concomitant use of any CNS-depressant drugs and aspirin; butalbital; caffeine; codeine. Dosage reduction of aspirin; butalbital; caffeine; codeine may be necessary.[5232] Additive CNS depression may occur if aspirin; butalbital; caffeine; codeine combination products are used concomitantly with opiate agonists, mixed opiate agonists/antagonists, dronabinol, THC, sedating H_1-blockers, tramadol, phenothiazines, general anesthetics, amoxapine, carisoprodol, droperidol, entacapone, haloperidol, maprotiline, methocarbamol, mirtazapine, molindone, nabilone [9044], nefazodone, olanzapine, pramipexole, pregabalin [7523], quetiapine, pimozide, risperidone, ropinirole, tolcapone, trazodone, skeletal muscle relaxants, or anxiolytics, sedatives, and hypnotics (including benzodiazepines). Concomitant use of haloperidol with codeine-containing products may decrease the

metabolism of codeine to morphine by inhibiting cytochrome CYP2D6.[4718] Additionally, barbiturates are known hepatic enzyme inducers and may increase metabolism of ramelteon (primarily metabolized by CYP1A2) over a longer period of time. Ramelteon efficacy may be reduced, although additive CNS depressant effects might overrule.[8143] [4718]

Hydrocodone (found in Codimal® DH) **and Atropine; Hyoscyamine; Phenobarbital; Scopolamine** (Donnatal®)

Severity: Moderate

Hydrocodone is an opiate agonist [7132] and therefore may increase the tone and decrease the propulsive contractions of the smooth muscle of the gastrointestinal tract. Prolongation of the gastrointestinal transit time may be the mechanism of the constipating effect.[6365] Opiate analgesics combined with antimuscarinics can cause severe constipation or paralytic ileus, especially with chronic use.

Concomitant use of hydrocodone with other central nervous system (CNS) depressants can potentiate the effects of hydrocodone and may lead to additive CNS or respiratory depression.[7132] Also, the use of monoamine oxidase inhibitors (MAOIs) or tricyclic antidepressants with hydrocodone may increase the effect of either the antidepressant or hydrocodone. Examples of drugs associated with CNS depression include amoxapine; anxiolytics, sedatives, and hypnotics; clozapine; dronabinol, THC; droperidol; entacapone; ethanol [6341]; general anesthetics; sedating H_1-blockers; MAOIs; maprotiline; mirtazapine; molindone; nabilone [9044]; nefazodone; olanzapine; other opiate agonists; phenothiazines; pimozide; pramipexole; pregabalin [7523], quetiapine; risperidone; ropinirole; skeletal muscle relaxants; tolcapone; tricyclic antidepressants; and trazodone. If hydrocodone is used with a CNS depressant, the dose of one or both drugs should be reduced.[7132]

Hydromorphone, a metabolite, contributes to the analgesic effects of the parent drug, hydrocodone. To date, the relative contributions of each compound to analgesia are unknown. Hydrocodone is metabolized to hydromorphone via the cytochrome P450 (CYP) 2D6 hepatic isoenzyme. Some of hydromorphone is also metabolized by CYP3A4 and by non-CYP routes. The analgesic effect of hydrocodone may vary greatly when it is combined with drugs that induce hepatic isoenzymes such as rifampin [4718], rifabutin [5948], rifapentine [5213], carbamazepine [4718], phenytoin (fosphenytoin) [4718], ethotoin, or barbiturates [4718]. Induction of hydrocodone metabolism may take several days.

Opiate agonists should be used cautiously with antimuscarinics since additive depressive effects on GI motility or bladder function may been seen.[5986] Opioids increase the tone and decrease the propulsive contractions of the smooth muscle of the gastrointestinal tract. Prolongation of the gastrointestinal transit time may be the mechanism of the constipating effect.[6365] Opiate analgesics combined with antimuscarinics can cause severe constipation or paralytic ileus, especially with chronic use. Additionally, additive sedative effects may occur with the addition of opiate agonists to phenobarbital. Some opiate agonists may become less effective with the addition of phenobarbital due to hepatic enzyme induction; for example, symptoms of opiate withdrawal have been noted when methadone-stabilized patients were administered phenobarbital.

Hydrocodone (found in Codimal® DH) **and Albuterol; Ipratropium** (Combivent®)

Severity: Moderate

Hydrocodone is an opiate agonist [7132] and therefore may increase the tone and decrease the propulsive contractions of the smooth muscle of the gastrointestinal tract. Prolongation of the gastrointestinal transit time may be the mechanism of the constipating effect.[6365] Opiate analgesics combined with antimuscarinics can cause severe constipation or paralytic ileus, especially with chronic use.

Hydrocodone (found in Codimal® DH) **and Doxylamine** (Unisom® Sleeptabs™)

Severity: Moderate

Concomitant use of hydrocodone with other central nervous system (CNS) depressants can potentiate the effects of hydrocodone and may lead to additive CNS or respiratory depression.[7132] Also, the use of monoamine oxidase inhibitors (MAOIs) or tricyclic antidepressants with hydrocodone may increase the effect of either the antidepressant or hydrocodone. Examples of drugs associated with CNS depression include amoxapine; anxiolytics, sedatives, and hypnotics; clozapine; dronabinol, THC; droperidol; entacapone; ethanol [6341]; general anesthetics; sedating H_1-blockers; MAOIs; maprotiline; mirtazapine; molindone; nabilone [9044]; nefazodone; olanzapine; other opiate agonists; phenothiazines; pimozide; pramipexole; pregabalin [7523], quetiapine; risperidone; ropinirole; skeletal muscle relaxants; tolcapone; tricyclic antidepressants; and trazodone. If hydrocodone is used with a CNS depressant, the dose of one or both drugs should be reduced.[7132]

Concomitant use of hydrocodone with sedating H_1-blockers can potentiate respiratory depression and/or sedation.[7132] In addition, chlorpheniramine and diphenhydramine inhibit CYP2D6, an enzyme responsible for the metabolism of hydrocodone [4718]; the dose of the antihistamine and/or hydrocodone should be reduced. Close monitoring for central nervous system depression is recommended.

Because doxylamine can cause pronounced sedation,[7801] an enhanced CNS depressant effect may occur when it is combined with other CNS depressants [6568] including anxiolytics, sedatives, and hypnotics (such as barbiturates and benzodiazepines) [6946] [6948], buprenorphine [5278], butorphanol [5912], carisoprodol, clozapine [4989], dronabinol, THC, droperidol [5468], entacapone [5769], ethanol [6341] [6948], general anesthetics [6892], haloperidol [5036], methocarbamol, mirtazapine [5366], molindone [5553], nabilone [9044], nalbuphine [6778], nefazodone [5414], olanzapine [5517], opiate agonists, pentazocine [6777], phenothiazines [6946], pimozide [5250], pramipexole [7757], pregabalin [7523], procarbazine [5356], quetiapine [5855], risperidone [5144], ropinirole [8018], tolcapone [5578], tramadol [5043], trazodone [5450], tricyclic antidepressants [6947], or with other sedating H_1-blockers [6568]. In addition, concurrent use of cannabinoids with sedating H_1-blockers may result in additive tachycardia, which may be pronounced.

Hydrocodone (found in Codimal® DH) **and Carbinoxamine** (Histex™ I/E)

Severity: Moderate

Concomitant use of hydrocodone with sedating H_1-blockers can potentiate respiratory depression and/or sedation.[7132] In addition, chlorpheniramine and diphenhydramine inhibit CYP2D6, an enzyme responsible for the metabolism of hydrocodone [4718]; the dose of the antihistamine and/or hydrocodone should be reduced. Close monitoring for central nervous system depression is recommended.

Carbinoxamine has potential for CNS depressant effects.[7585] An enhanced CNS depressant effect may occur when carbinoxamine is combined with other CNS depressants including anxiolytics, sedatives, and hypnotics (including barbiturates and benzodiazepines), butorphanol, entacapone, ethanol [6341], haloperidol, general anesthetics, nalbuphine, opiate agonists, pentazocine, pramipexole, pregabalin [7523], risperidone, ropinirole, tolcapone, trazodone, tramadol, or other sedating H_1-blockers [6568].

Hydrocodone (found in Codimal® DH) **and Acetaminophen; Chlorpheniramine; Phenylephrine; Phenyltoloxamine** (Norel®SR)

Severity: Moderate

Concomitant use of hydrocodone with sedating H_1-blockers can potentiate respiratory depression and/or sedation.[7132] In addition, chlorpheniramine and diphenhydramine inhibit CYP2D6, an enzyme responsible for the metabolism of hydrocodone [4718]; the dose of the antihistamine and/or hydrocodone should be reduced. Close monitoring for central nervous system depression is recommended.

Acetaminophen; chlorpheniramine; phenylephrine; phenyltoloxamine may cause CNS depression. An enhanced CNS depressant effect may occur when this product is combined with other CNS depressants [9107] including anxiolytics, sedatives, and hypnotics, barbiturates, buprenorphine, butorphanol, dronabinol, THC, droperidol, entacapone, ethanol, haloperidol, general anesthetics, mirtazapine, molindone, nalbuphine, nefazodone, opiate agonists, pentazocine, pimozide, pramipexole, pregabalin [7523], quetiapine, risperidone, ropinirole, skeletal muscle relaxants, tolcapone, trazodone, tramadol, or with other products containing sedating H_1-blockers. Additionally, concurrent use of dronabinol, THC with sympathomimetics such as phenylephrine may result in additive hypertension, tachycardia, and possibly cardiotoxicity.[3868] The risk of developing hepatotoxicity from acetaminophen appears to be increased in patients who regularly consume ethanol. In these patients, hepatotoxicity is possible even at normal, therapeutic dosages of acetaminophen.[1654] Acute or chronic ethanol use increases acetaminophen-induced hepatotoxicity by inducing CYP2E, leading to increased formation of the hepatotoxic metabolite of acetaminophen.[583] Administration of acetaminophen should be limited or avoided altogether in patients with alcoholism or patients who consume ethanol regularly.[4934]

Hydrocodone (found in Codimal® DH) **and Propafenone** (Rythmol)

Severity: Moderate

Concomitant use of a CYP2D6 inhibitor (e.g., amiodarone, bupropion, quinidine, cimetidine, chloroquine, fluoxetine, haloperidol, delavirdine, imatinib, STI-571, ritonavir, terbinafine, mibefradil, paroxetine, propafenone, quinacrine, quinine, citalopram, escitalopram, sertraline, and thioridazine) [4718] [4779] with hydrocodone will decrease the metabolism of hydrocodone to hydromorphone (see Hydrocodone Pharmacokinetics).[7145] The list is not inclusive of all inhibitors of CYP2D6. Although theoretical, patients may experience varying degrees of analgesia if they take hydrocodone with a CYP2D6 inhibitor. Also, additive CNS depression may occur if hydrocodone is used with haloperidol, chlorpheniramine, diphenhydramine, paroxetine, or thioridazine. A dose reduction of hydrocodone may be warranted if used concurrently with a CYP2D6 inhibitor. The patient should be monitored for enhanced sedation, respiratory depression or other effects that would be seen with excessive doses of opioids.

In vitro studies support that propafenone inhibits CYP2D6.[4718] Therefore, propafenone may theoretically increase concentrations of other drugs metabolized by the CYP2D6 isoenzyme. Caution is recommended when administering propafenone with other CYP2D6 substrates that have a narrow therapeutic range or where large increases in serum concentrations may be associated with severe adverse reactions. Examples of CYP2D6 substrates include amoxapine, atomoxetine, certain beta-blockers (e.g., carvedilol,

metoprolol, propranolol, and timolol), certain antiarrhythmics (e.g., encainide, flecainide, mexiletine, and propafenone), clozapine, codeine, cyclobenzaprine, fenfluramine, desipramine, dexfenfluramine, dextromethorphan, donepezil, fluoxetine, haloperidol, hydrocodone, imipramine, maprotiline, methadone, methamphetamine, morphine, oxycodone, paroxetine, perphenazine, risperidone, thioridazine, tramadol, trazodone, tricyclic antidepressants, or venlafaxine. This list is not inclusive of all agents substrates for CYP2D6.[4718]

Phenylephrine (found in Codimal® DH) **and Digoxin** (Digitek™)

Severity: High

Concomitant use of digoxin or cardiac glycosides with sympathomimetics can cause arrhythmias [4999] because sympathomimetics enhance ectopic pacemaker activity.

Concomitant use of digoxin with sympathomimetics can cause arrhythmias [4999] because sympathomimetics enhance ectopic pacemaker activity. Digoxin can also induce arrhythmias in patients receiving succinylcholine; succinylcholine causes extrusion of potassium from the muscle cells.[4999]

Phenylephrine (found in Codimal® DH) **and Acetaminophen; Chlorpheniramine; Phenylephrine; Phenyltoloxamine** (Norel®SR)

Severity: Very High. This drug combination should be avoided.

Avoid concurrent use of other products that contain acetaminophen with acetaminophen; chlorpheniramine; phenylephrine; phenyltoloxamine.[9107] Exceeding the maximum daily dose of acetaminophen may lead to an increased risk of hepatotoxicity. Also, high dosages of acetaminophen on a chronic basis can cause depletion of glutathione stores, which can lead to a greater production of the hepatotoxic metabolite, N-acetyl-para-benzoquinoneimine (NAPQI).[4925] Acetaminophen is in many prescription and nonprescription products. Advise patients to carefully read the ingredients of any other products they are taking in conjunction with acetaminophen; chlorpheniramine; phenylephrine; phenyltoloxamine to avoid duplication of therapy.

Phenylephrine can potentiate the effects and increase the toxicity of other sympathomimetics including cocaine by adding to their sympathomimetic activity.[6289] Although no data are available, phenylephrine should be used cautiously in patients using significant quantities of amphetamines, cocaine, or other sympathomimetic-containing products. Concurrent use of dronabinol, THC or nabilone [9044] with sympathomimetics may result in additive hypertension, tachycardia, and possibly cardiotoxicity.[3868]

Phenylephrine can potentiate the effects and increase the toxicity of other sympathomimetics, including cocaine [5275], by adding to their sympathomimetic activity. Concurrent use of amphetamines with other sympathomimetics can result in excessive CNS or cardiovascular stimulation. Amphetamines can sensitize the myocardium to the effects of other sympathomimetics.[5218] Acetaminophen; chlorpheniramine; phenylephrine; phenyltoloxamine should be used cautiously in patients using significant quantities of amphetamines, cocaine, or other sympathomimetics.

Phenylephrine (found in Codimal® DH) **and Theophylline, Aminophylline** (Theophylline)

Severity: High

Caffeine is a CNS-stimulant [4666], and, although data are lacking with phenylephrine, concurrent administration may produce excessive stimulatory effects such as nervousness, irritability, insomnia, or tremor. Other xanthines, such as theophylline, aminophylline or dyphylline can interact in a similar way.[5241] Excessive caffeine ingestion should be avoided while taking phenylephrine concurrently. This includes ingestion of foods and beverages that contain high amounts of caffeine such as coffee, teas, green tea, colas, and chocolate and dietary supplements such as guarana [4679].

Concurrent administration of theophylline or aminophylline with some sympathomimetics can produce excessive stimulation and effects such as nervousness, irritability, or insomnia. Seizures or cardiac arrhythmias are also possible. The herbal sympathomimetic ephedra, Ma huang may potentially increase the risk of developing cardiac arrhythmias if this herb is taken with theophylline.[5241]

Albuterol; Ipratropium (Combivent®) **and Flunisolide**

Severity: Moderate

Methylxanthine derivatives (e.g., theophylline, aminophylline) and corticosteroids may aggravate the hypokalemic effect that may be seen with beta-agonists. Consider checking potassium levels if clinically indicated. However, beta-agonists are commonly used in conjunction with aminophylline, theophylline, and corticosteroid therapy.

Albuterol; Ipratropium (Combivent®) **and Phenylephrine** (found in Codimal® DH)

Severity: Moderate

If asthma symptoms occur between the use of long-acting beta-agonists (e.g., salmeterol or formoterol), short-acting beta$_2$-agonists (e.g., albuterol) may be used safely for the symptomatic relief of acute asthma symptoms.[5197] [5262] When beginning treatment with a long-acting beta-agonist, patients who have been taking inhaled, short-acting beta$_2$-agonists on a regular basis (e.g., four times a day) should be instructed to discontinue the regular, scheduled use of these drugs and use them only for the symptomatic relief of acute asthma symptoms. Patients should be cautioned that increasing short-acting inhaled beta$_2$-agonist use is a signal of deteriorating asthma. Due to the pharmacology of albuterol [5262], the concomitant use of albuterol with other short-acting beta-agonists or short-acting sympathomimetic aerosol bronchodilators is NOT recommended due to the increased risk of adverse cardiovascular effects (considered duplicate therapy). Caution and close observation should also be used when albuterol is used concurrently with other adrenergic sympathomimetics, administered by any route, to avoid potential for increased cardiovascular effects.[5262]

Albuterol; Ipratropium (Combivent®) **and Atropine; Hyoscyamine; Phenobarbital; Scopolamine** (Donnatal®)

Severity: Moderate

Although ipratropium is minimally absorbed into the systemic circulation after inhalation, there is a potential for ipratropium to have additive anticholinergic effects when administered with other antimuscarinics. Caution is advised when administering albuterol; ipratropium in individuals taking other antimuscarinic medications. Other common medications with anticholinergic activity are not as likely to interact with ipratropium as other antimuscarinics.

Additive anticholinergic effects may be seen when combinations of atropine; hyoscyamine; phenobarbital; scopolamine are used concomitantly with other antimuscarinics.[6338] [7179] Other commonly used drugs with moderate to significant anticholinergic effects include amantadine, amoxapine, bupropion, clozapine, cyclobenzaprine, maprotiline [5491], olanzapine, orphenadrine, the sedating H_1-blockers, most phenothiazines, and most tricyclic antidepressants. Clinicians should note that antimuscarinic effects might be seen not only on GI smooth muscle, but also on bladder function, the eye, and temperature regulation. Many of the agents with anticholinergic properties listed can increase the risk of CNS depression when combined with phenobarbital or scopolamine as well. Phenobarbital may also increase the metabolism of many antidepressants and antipsychotics listed.

Albuterol; Ipratropium (Combivent®) **and Formoterol** (Foradil® Aerolizer)

Severity: High

If asthma symptoms occur between the use of long-acting beta-agonists (e.g., salmeterol or formoterol), short-acting beta$_2$-agonists (e.g., albuterol) may be used safely for the symptomatic relief of acute asthma symptoms.[5197] [5262] When beginning treatment with a long-acting beta-agonist, patients who have been taking inhaled, short-acting beta$_2$-agonists on a regular basis (e.g., four times a day) should be instructed to discontinue the regular, scheduled use of these drugs and use them only for the symptomatic relief of acute asthma symptoms. Patients should be cautioned that increasing short-acting inhaled beta$_2$-agonist use is a signal of deteriorating asthma. Due to the pharmacology of albuterol [5262], the concomitant use of albuterol with other short-acting beta-agonists or short-acting sympathomimetic aerosol bronchodilators is NOT recommended due to the increased risk of adverse cardiovascular effects (considered duplicate therapy). Caution and close observation should also be used when albuterol is used concurrently with other adrenergic sympathomimetics, administered by any route, to avoid potential for increased cardiovascular effects.[5262]

If asthma symptoms occur between formoterol controller doses, short-acting beta-2 agonists (e.g., albuterol) may be used safely for the symptomatic relief of acute asthma symptoms.[5038] When beginning treatment with formoterol, patients who have been taking inhaled, short-acting beta-2 agonists on a regular basis (e.g., four times a day) should be instructed to discontinue the regular, scheduled use of these drugs and use them only for the symptomatic relief of acute asthma symptoms. Patients should be cautioned that increasing short-acting inhaled beta-2 agonist use is a signal of deteriorating asthma. Due to the pharmacology of formoterol [5038], the concomitant use of formoterol with other long-acting beta-agonists (e.g., salmeterol-containing products [5197]) is NOT recommended due to the increased risk of adverse cardiovascular effects (considered duplicate therapy). Caution and close observation should be used when formoterol is used concurrently with other adrenergic sympathomimetics, administered by any route, to avoid potential for increased cardiovascular effects based on the pharmacology of formoterol.[5038]

Albuterol; Ipratropium (Combivent®) **and Levalbuterol** (Xopenex®)

Severity: High

Mean decreases of 16% and 22% in serum digoxin levels were demonstrated after single-dose intravenous and oral administration of racemic albuterol, respectively, to normal volunteers who had received digoxin for 10 days.[5047] The clinical significance of these findings for patients with obstructive airway disease who are receiving levalbuterol and digoxin on a chronic basis is unclear. Nevertheless, it would be prudent to carefully evaluate the serum digoxin levels in patients who are currently receiving digoxin and albuterol or levalbuterol therapy.[5047]

If asthma symptoms occur between the use of long-acting beta-agonists (e.g., salmeterol or formoterol), short-acting beta$_2$-agonists (e.g., albuterol) may be used safely for the symptomatic relief of acute asthma symptoms.[5197] [5262] When beginning treatment with a long-acting beta-agonist, patients who have been taking inhaled, short-acting beta$_2$-agonists on a regular basis (e.g., four times a day) should be instructed to discontinue the regular, scheduled use of these drugs and use them only for the symptomatic relief of acute asthma symptoms. Patients should be cautioned that increasing short-acting inhaled beta$_2$-agonist use is a signal of deteriorating asthma. Due to the pharmacology of albuterol [5262], the concomitant use of albuterol with other short-acting beta-agonists or short-acting sympathomimetic aerosol bronchodilators is NOT recommended due to the increased risk of adverse cardiovascular effects (considered duplicate therapy). Caution and close observation should also be used when albuterol is used concurrently with other adrenergic sympathomimetics, administered by any route, to avoid potential for increased cardiovascular effects.[5262]

If asthma symptoms occur between the use of long-acting beta-agonists (e.g., salmeterol or formoterol), short-acting beta$_2$-agonists (e.g., levalbuterol) may be used safely for the symptomatic relief of acute asthma symptoms.[5047] [5197] When beginning treatment with a long-acting beta-agonist, patients who have been taking inhaled, short-acting beta$_2$-agonists on a regular basis (e.g., four times a day) should be instructed to discontinue the regular, scheduled use of these drugs and use them only for the symptomatic relief of acute asthma symptoms. Patients should be cautioned that increasing short-acting inhaled beta$_2$-agonist use is a signal of deteriorating asthma. Due to the pharmacology of levalbuterol [5047], the concomitant use of levalbuterol with other short-acting beta-agonists or short-acting sympathomimetic aerosol bronchodilators is NOT recommended due to the increased risk of adverse cardiovascular effects (considered duplicate therapy). Caution and close observation should also be used when levalbuterol is used concurrently with other adrenergic sympathomimetics, administered by any route, to avoid potential for increased cardiovascular effects.[5047]

Albuterol; Ipratropium (Combivent®) **and Acetaminophen; Chlorpheniramine; Phenylephrine; Phenyltoloxamine** (Norel®SR)

Severity: Moderate

If asthma symptoms occur between the use of long-acting beta-agonists (e.g., salmeterol or formoterol), short-acting beta$_2$-agonists (e.g., albuterol) may be used safely for the symptomatic relief of acute asthma symptoms.[5197] [5262] When beginning treatment with a long-acting beta-agonist, patients who have been taking inhaled, short-acting beta$_2$-agonists on a regular basis (e.g., four times a day) should be instructed to discontinue the regular, scheduled use of these drugs and use them only for the symptomatic relief of acute asthma symptoms. Patients should be cautioned that increasing short-acting inhaled beta$_2$-agonist use is a signal of deteriorating asthma. Due to the pharmacology of albuterol [5262], the concomitant use of albuterol with other short-acting beta-agonists or short-acting sympathomimetic aerosol bronchodilators is NOT recommended due to the increased risk of adverse cardiovascular effects (considered duplicate therapy). Caution and close observation should also be used when albuterol is used concurrently with other adrenergic sympathomimetics, administered by any route, to avoid potential for increased cardiovascular effects.[5262]

Acetaminophen; chlorpheniramine; phenylephrine; phenyltoloxamine may interact with medications from a variety of classes due to the anticholinergic effects of chlorpheniramine or phenyltoloxamine and the sympathomimetic effects of phenylephrine.[9107] An interaction may occur when this product is combined with other drugs with anticholinergic activity, like the antimuscarinics.[6338] Commonly used drugs with moderate to significant anticholinergic effects include amantadine, amoxapine, clozapine, cyclobenzaprine, disopyramide, maprotiline, olanzapine, orphenadrine, most phenothiazines, and most tricyclic antidepressants. Clinicians should note that antimuscarinic effects might be seen not only on GI smooth muscle, but also on bladder function, the eye, and temperature regulation. With many of the listed agents, additive drowsiness may also occur when combined with chlorpheniramine and phenyltoloxamine. Additionally, the sympathomimetic effects of phenylephrine may interact with tricyclic antidepressants [5287] and maprotiline [5491], resulting in severe cardiovascular effects including arrhythmias, severe hypertension, hyperpyrexia, and/or severe headaches.

Albuterol; Ipratropium (Combivent®) **and Digoxin** (Digitek™)

Severity: Moderate

Mean decreases of 16% and 22% in serum digoxin levels were demonstrated after single-dose intravenous and oral administration of racemic albuterol, respectively, to normal volunteers who had received digoxin for 10 days.[5047] The clinical significance of these findings for patients with obstructive airway disease who are receiving levalbuterol and digoxin on a chronic basis is unclear. Nevertheless, it would be prudent to carefully evaluate the serum digoxin levels in patients who are currently receiving digoxin and albuterol or levalbuterol therapy.[5047]

Oral formulations of digoxin can produce higher serum concentrations when administered concurrently with antimuscarinics (e.g., propantheline) because of decreased GI motility induced by the antimuscarinic agent.[4999] [7704] This interaction has mostly

occurred in the literature with slowly-dissolving, large-particle formulations of digoxin tablets; the manufacture of oral digoxin products today, utilizing liquid formulations and/or smaller particle sizes, theoretically reduces the potential for absorption interactions. However, there is wide variability expected in individual responses to many digoxin-drug interactions.[4999] [7704] Other pharmacodynamic and pharmacokinetic systemic interactions are possible between digoxin and select antimuscarinic agents. Both trospium (a selective antimuscarinic) and digoxin are eliminated by active renal tubular secretion;[4999] [5974] coadministration has the potential to increase serum concentrations of trospium or digoxin due to competition for the drug elimination pathway. Darifenacin (30 mg daily) coadministered with digoxin (0.25 mg daily) resulted in a 16% increase in digoxin exposure.[7474] Anticholinergics, because of their ability to cause tachycardia [6824], can also antagonize the beneficial actions of digoxin in atrial fibrillation/flutter. Routine therapeutic monitoring should be continued when an antimuscarinic agent is prescribed with digoxin until the effects of combined use are known.

Albuterol; Ipratropium (Combivent®) **and Propafenone** (Rythmol)

Severity: High

Drugs known to prolong the QTc interval have an increased risk of ventricular arrhythmias. Beta-agonists may be associated with adverse cardiovascular effects, usually at higher doses and/or when associated with hypokalemia.[5038] [5047] [5262] In addition, beta-agonists should be avoided in patients with congenital long QT syndrome.[4951] Beta-agonists may rarely potentiate the cardiovascular adverse effects of drugs known to prolong the QT interval.[5038] [5047] These agents may include some antiarrhythmic agents including class IA antiarrhythmics, class III antiarrhythmics, flecainide, and propafenone. In addition to antiarrhythmic drugs, other drugs which can result in QT prolongation include: some antipsychotics (e.g., phenothiazines, pimozide, haloperidol, risperidone, sertindole, ziprasidone), amoxapine, arsenic trioxide, astemizole, bepridil, cisapride, chloroquine, clarithromycin, dasatinib [9211], dolasetron [5037], droperidol, halofantrine, halogenated anesthetics, erythromycin, levomethadyl, maprotiline, methadone, ondansetron [8046], palonosetron [8716], some quinolone antibiotics (e.g. gatifloxacin, gemifloxacin, grepafloxacin, levofloxacin, moxifloxacin, sparfloxacin), pentamidine, probucol, ranolazine, terfenadine, tricyclic antidepressants, and vorinostat [9633]. This list is not inclusive of all agents that may prolong the QT interval. Tricyclic antidepressants (TCAs) can also potentiate the vascular effects of beta-agonists. The antimuscarinic effects of the TCAs, amoxapine or maprotiline can be additive to those of other anticholinergics (e.g. ipratropium).

Propafenone is a Class IC antiarrhythmic which increases the QT interval, but largely due to prolongation of the QRS interval.[5014] The use of propafenone in conjunction with other drugs that prolong the QT interval has not been studied and is not recommended by the manufacturer due to potential risk for ventricular tachycardia, including torsade de pointes (TdP) and monomorphic ventricular tachycardia.[5014] According to the manufacturer, propafenone coadministration with tricyclic antidepressants is not recommended.[5014] In addition, drugs which directly prolong the QT interval are not recommended during propafenone therapy. Drugs which have been established to have a causal association with QT prolongation and TdP include: Class IA antiarrhythmics (disopyramide, procainamide, quinidine) [4951] [4952] [5187], Class III antiarrhythmics (amiodarone, bretylium, dofetilide, ibutilide, sotalol) [4951] [4952] [5187], astemizole [140], arsenic trioxide [4951] [4977], bepridil [4951] [4953], cisapride [4951], chloroquine [4951] [4955] [4956], clarithromycin [4951] [4964], droperidol [3610] [4951] [4963], erythromycin [228] [4951] [4978], grepafloxacin [5149], halofantrine [4951] [4968], haloperidol [42] [336] [4951] [5036], levomethadyl [4951] [5079] [5081] [5146], methadone [4951] [5048] [5049] [5050] [5051], pentamidine [168] [335] [4951] [5149], certain phenothiazines (chlorpromazine [4951], mesoridazine [4951] [5831], and thioridazine [4951] [5022]), pimozide [4951], probucol [5145], sparfloxacin [4951] [4958], and terfenadine [141] [231]. Other agents associated with a lower, but possible risk for QT prolongation and TdP based on varying levels of documentation (see separate drug monographs) include: abarelix [5392], alfuzosin [4988], amoxapine [5145], apomorphine [5136], beta-agonists [4951] [5038] [5047], ofloxacin [7501], ciprofloxacin [4951] [5149] [5496] [5507] [6579], clozapine [5146], cyclobenzaprine [5155] [5156], dasatinib [9211], dolasetron [5037], gatifloxacin [5149] [5150] [5152], gemifloxacin [5154], halogenated anesthetics [5187] [5188] [5486] [5487] [5488], levofloxacin [5149] [5150] [5151], local anesthetics, maprotiline [5145], mefloquine [6617] [7535], moxifloxacin [5149] [5150] [5153], olanzapine [9575] [9576], ondansetron [8046], norfloxacin [6564], octreotide [4951], palonosetron [5148], some phenothiazines (fluphenazine [5145], perphenazine [5145], prochlorperazine [5145], and trifluoperazine [5145]), propafenone [5014] [5146], ranolazine [8747], risperidone [4951] [5144], sertindole [5187], tacrolimus [4049] [4050] [4951], telithromycin [4880], tricyclic antidepressants when given in excessive doses or overdosage [5145] [5146], troleandomycin (based on interactions with macrolides) [5149], vardenafil [4942], vorinostat [9633], or ziprasidone [4959]. This list is not inclusive of all agents that can cause QT interval prolongation. In addition, some of the listed drugs are CYP2D6 inhibitors (e.g., amiodarone, chloroquine, chlorpromazine, haloperidol, perphenazine, quinidine, ranolazine, and thioridazine) with potential to inhibit the metabolism of propafenone. In addition to potential for additive QT prolongation, concomitant administration of propafenone with desipramine (tricyclic antidepressant) may result in elevated serum desipramine levels.[5014] In addition to avoiding concurrent drug interactions, the potential for TdP can be reduced by avoiding the use of QT prolonging drugs in patients at substantial risk for TdP.[5162] Examples of general risk factors for TdP include congenital long QT syndrome, female sex, elderly patients, significant bradycardia, hypokalemia, hypomagnesemia, and underlying cardiac disease (e.g., arrhythmias, cardiomyopathy, acute myocardial ischemia).

Albuterol; Ipratropium (Combivent®) **and Theophylline, Aminophylline** (Theophylline)

Severity: Moderate

Methylxanthine derivatives (e.g., theophylline, aminophylline) and corticosteroids may aggravate the hypokalemic effect that may be seen with beta-agonists. Consider checking potassium levels if clinically indicated. However, beta-agonists are commonly used in conjunction with aminophylline, theophylline, and corticosteroid therapy.

Methylxanthine derivatives, (such as theophylline [5277] and aminophylline) and corticosteroids [3085] may aggravate the hypokalemic effect that may be seen with beta-agonists.[5197] Consider checking potassium levels if clinically indicated. However, beta-agonists are commonly used in conjunction with aminophylline, theophylline, and corticosteroid therapy.[5197]

Digoxin (Digitek™) **and Flunisolide**

Severity: Moderate

Since electrolyte disorders modify the actions of digoxin, drugs that can affect electrolyte balance potentially can affect the response to digoxin. Hypokalemia, hypomagnesemia, or hypercalcemia increase digoxin's effect.[4999] The following drugs can precipitate digoxin toxicity via their effect on electrolyte balance: amphotericin B [5062], corticosteroids [6115], corticotropin, ACTH, potassium-depleting diuretics (e.g., acetazolamide [4994], loop diuretics [3085], methazolamide [5023], and thiazide diuretics [3085] [5219]), and sodium polystyrene sulfonate [6116]. Calcium salts augment the actions of digoxin. In addition, when calcium is administered via rapid intravenous injection, the risk of serious arrhythmias in digitalized patients is increased.[4999] It is recommended that serum potassium, magnesium, and calcium be monitored regularly in patients receiving digoxin.

Digoxin (Digitek™) **and Ipratropium** (Atrovent®)

Severity: Moderate

Oral formulations of digoxin can produce higher serum concentrations when administered concurrently with antimuscarinics (e.g., propantheline) because of decreased GI motility induced by the antimuscarinic agent.[4999] [7704] This interaction has mostly occurred in the literature with slowly-dissolving, large-particle formulations of digoxin tablets; the manufacture of oral digoxin products today, utilizing liquid formulations and/or smaller particle sizes, theoretically reduces the potential for absorption interactions. However, there is wide variability expected in individual responses to many digoxin-drug interactions.[4999] [7704] Other pharmacodynamic and pharmacokinetic systemic interactions are possible between digoxin and select antimuscarinic agents. Both trospium (a selective antimuscarinic) and digoxin are eliminated by active renal tubular secretion;[4999] [5974] coadministration has the potential to increase serum concentrations of trospium or digoxin due to competition for the drug elimination pathway. Darifenacin (30 mg daily) coadministered with digoxin (0.25 mg daily) resulted in a 16% increase in digoxin exposure.[7474] Anticholinergics, because of their ability to cause tachycardia [6824], can also antagonize the beneficial actions of digoxin in atrial fibrillation/flutter. Routine therapeutic monitoring should be continued when an antimuscarinic agent is prescribed with digoxin until the effects of combined use are known.

Digoxin (Digitek™) **and Aspirin, ASA; Butalbital; Caffeine; Codeine** (Fiorinal® with Codeine)

Severity: Moderate

Hepatic enzyme-inducing drugs, such as barbiturates and phenytoin, can accelerate the metabolism of digoxin, decreasing its serum concentrations.[6126] In addition, it appears that rifampin may decrease the metabolism of digoxin by inducing intestinal glycoprotein-P and decreasing the oral bioavailability of digoxin by 30.1%. The Cmax and AUC of digoxin were also decreased by 43% and 58%, respectively.[5481] It is recommended that digoxin concentrations be monitored if used with any of these drugs concomitantly.

Digoxin (Digitek™) **and Atropine; Hyoscyamine; Phenobarbital; Scopolamine** (Donnatal®)

Severity: Moderate

Oral formulations of digoxin can produce higher serum concentrations when administered concurrently with antimuscarinics (e.g., propantheline) because of decreased GI motility induced by the antimuscarinic agent.[4999] [7704] This interaction has mostly occurred in the literature with slowly-dissolving, large-particle formulations of digoxin tablets; the manufacture of oral digoxin products today, utilizing liquid formulations and/or smaller particle sizes, theoretically reduces the potential for absorption interactions. However, there is wide variability expected in individual responses to many digoxin-drug interactions.[4999] [7704] Other pharmacodynamic and pharmacokinetic systemic interactions are possible between digoxin and select antimuscarinic agents. Anticholinergics, because of their ability to cause tachycardia [6824], can also antagonize the beneficial actions of digoxin in atrial fibrillation/flutter. Routine therapeutic monitoring should be continued when an antimuscarinic agent is prescribed with digoxin until the effects of combined use are known.

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antimuscarinic) and digoxin are eliminated by active renal tubular secretion;[4999] [5974] coadministration has the potential to increase serum concentrations of trospium or digoxin due to competition for the drug elimination pathway. Darifenacin (30 mg daily) coadministered with digoxin (0.25 mg daily) resulted in a 16% increase in digoxin exposure.[7474] Anticholinergics, because of their ability to cause tachycardia [6824], can also antagonize the beneficial actions of digoxin in atrial fibrillation/flutter. Routine therapeutic monitoring should be continued when an antimuscarinic agent is prescribed with digoxin until the effects of combined use are known.

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Digoxin (Digitek™) **and Acetaminophen; Chlorpheniramine; Phenylephrine; Phenyltoloxamine** (Norel®SR)

Severity: High

Concomitant use of digoxin or cardiac glycosides with sympathomimetics can cause arrhythmias [4999] because sympathomimetics enhance ectopic pacemaker activity. Caution is advised during concurrent use with acetaminophen; chlorpheniramine; phenylephrine; phenyltoloxamine.

Concomitant use of digoxin with sympathomimetics can cause arrhythmias [4999] because sympathomimetics enhance ectopic pacemaker activity. Digoxin can also induce arrhythmias in patients receiving succinylcholine; succinylcholine causes extrusion of potassium from the muscle cells.[4999]

Digoxin (Digitek™) **and Propafenone** (Rythmol)

Severity: High

Increases in digoxin serum concentrations may occur in over 80% of patients when propafenone is added to the regimen.[5001] Concomitant use of propafenone and digoxin has been reported to increase the steady-state AUC of digoxin by 60-270%, and decrease digoxin clearance by 31-67%.[5014] Although the exact mechanism for this interaction has not been established, several mechanisms have been proposed including reduced distribution volume and nonrenal clearance of digoxin, as well as potential inhibition of P-glycoprotein renal tubular transport of digoxin.[5001] [5471] [5472] [5473] A reduction in digoxin dosage (by approximately 25%) has been suggested for patients in whom propafenone is initiated during maintenance digoxin therapy.[5001] Monitor digoxin serum concentrations if propafenone is added, discontinued, or titrated during digoxin therapy.[5014] Adjust digoxin dosage to attain appropriate efficacy and safety endpoints for the individual patient.

Digoxin (Digitek™) **and Psyllium** (Metamucil®)

Severity: Moderate

Several drugs, if administered concomitantly with digoxin, can reduce GI absorption of orally administered digoxin.[4999] [5802] These drugs include: antacids containing aluminum hydroxide, magnesium hydroxide [5802]; flaxseed [4999] [5802]; kaolin; pectin [4999]; or psyllium [5802]. In most cases, staggering the administration times by two hours will minimize the magnitude of these interactions.

Psyllium can interfere with the absorption of certain oral drugs if administered concomitantly. For example, psyllium fiber can theoretically adsorb cardiac glycosides [4999] [5802]; oral anticoagulants (e.g., warfarin) [6100] or salicylates [6107]. A response to a single dose of warfarin was not affected by repeated administration (every 2 hours) of psyllium in a group (n=6) of healthy subjects.[6100] Per the psyllium manufacturers, administration of other prescribed oral drugs should be separated from the administration of psyllium by at least 2 hours.

Digoxin (Digitek™) **and Verapamil**

Severity: High

Interactions occur between digoxin and a variety of other cardiovascular agents. These can be categorized into two groups: a) pharmacokinetic interactions that reduce the clearance of digoxin and may lead to digoxin toxicity: amiodarone [5802], felodipine [5827], diltiazem [5802], propafenone [5001] [5014], quinidine [5802], quinine [6113] and verapamil [5802]; and b) pharmacodynamic interactions that may potentiate the actions of digoxin: amiodarone, dofetilide, sotalol, beta-blockers [5001], diltiazem, and verapamil. Digoxin is a substrate for P-glycoprotein.[4718] Quinidine and verapamil inhibit P-glycoprotein, an energy-dependent cellular drug efflux pump. The inhibition of p-glycoprotein in the intestinal cell wall may lead to increased oral absorption of digoxin; however, it has been shown that both quinidine and verapamil inhibit the secretion of digoxin by p-glycoprotein transporters in the kidney leading to decreased renal tubular elimination of digoxin and increased serum concentrations.[6114] It has been recommended that digoxin doses be reduced by 50% when adding quinidine therapy, and serum digoxin levels closely monitored thereafter.[5001] Despite potential for interactions, digoxin sometimes is intentionally used in combination with a beta-blocker, diltiazem, or verapamil to further

reduce conduction through the AV node. Nevertheless, these combinations should be used cautiously, and digoxin dosages may need adjustment in some patients.[4999]

Digoxin and verapamil interact pharmacokinetically and pharmacodynamically. Verapamil reduces the renal and nonrenal clearance of digoxin by 27% and 29%, respectively; serum levels of digoxin increase by 50-75% after verapamil is added.[5000] In addition, both drugs slow conduction through the AV node and for this reason, these drugs are sometimes used together for ventricular control in patients with atrial fibrillation or flutter. According to the labeling for verapamil, maintenance and loading doses for digoxin should be reduced when verapamil is administered, and the patient should be carefully monitored.[5000] In addition to serum concentration information, digoxin dosage should be adjusted according to clinical response, since digoxin serum concentrations may not accurately reflect response.

Digoxin (Digitek™) **and Levalbuterol** (Xopenex®)

Severity: Low

Mean decreases of 16% and 22% in serum digoxin levels were demonstrated after single-dose intravenous and oral administration of racemic albuterol, respectively, to normal volunteers who had received digoxin for 10 days.[5262] The clinical significance of these findings for patients with obstructive airway disease who are receiving albuterol or levalbuterol and digoxin on a chronic basis is unclear. Nevertheless, it would be prudent to carefully evaluate the serum digoxin levels in patients who are currently receiving digoxin and albuterol or levalbuterol therapy.[5262]

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Diphenhydramine and Clonazepam (Klonopin®)

Severity: Moderate

Because diphenhydramine can cause pronounced sedation,[6568] an enhanced CNS depressant effect may occur when it is combined with other CNS depressants [6568] including anxiolytics, sedatives, and hypnotics (such as barbiturates and benzodiazepines) [6946] [6948], buprenorphine [5278], butorphanol [5912], carisoprodol, clozapine [4989], dronabinol, THC, droperidol [5468], entacapone [5769], ethanol [6341] [6948], general anesthetics [6892], haloperidol [5036], methocarbamol, mirtazapine [5366], molindone [5553], nabilone [9044], nalbuphine [6778], nefazodone [5414], olanzapine [5517], opiate agonists, pentazocine [6777], phenothiazines [6946], pimozide [5250], pramipexole [7757], pregabalin [7523], procarbazine [5356], quetiapine [5855], risperidone [5144], ropinirole [8018], tolcapone [5578], tramadol [5043], trazodone [5450], tricyclic antidepressants [6947], or with other sedating H_1-blockers [6568]. In addition, concurrent use of cannabinoids with sedating H_1-blockers may result in additive tachycardia, which may be pronounced.

Concomitant administration of clonazepam with other CNS-depressant drugs [7168], including barbiturates, buprenorphine, butorphanol, dronabinol, THC [7185], entacapone [5769], ethanol [7198], sedating H_1-blockers, general anesthetics [6892], nabilone [9044], nalbuphine [6778], opiate agonists, pentazocine, phenothiazines, pregabalin [7523], tolcapone, tramadol, tricyclic antidepressants, or other anxiolytics, sedatives, and hypnotics, can potentiate the CNS effects (i.e., increased sedation or respiratory depression) of either agent.[5174]

Diphenhydramine and Ipratropium (Atrovent®)

Severity: Moderate

The anticholinergic effects of diphenhydramine may be significant and may be enhanced when combined with antimuscarinics [6338]. Other commonly used drugs with moderate to significant anticholinergic effects include amantadine, amoxapine, clozapine, cyclobenzaprine, disopyramide, maprotiline, olanzapine, orphenadrine, most phenothiazines, and most tricyclic antidepressants. Clinicians should note that antimuscarinic effects might be seen not only on GI smooth muscle, but also on bladder function, the eye, and temperature regulation. With many of the listed agents, additive drowsiness may also occur when combined with sedating antihistamines.

Diphenhydramine and Acetaminophen; Oxycodone (Percocet®)

Severity: Moderate

Concomitant use of oxycodone with sedating H_1-blockers can potentiate respiratory depression and/or sedation. In addition, chlorpheniramine and diphenhydramine inhibit CYP2D6, an enzyme responsible for the metabolism of oxycodone to oxymorphone,

which represents < 15% of the total administered dose.[4718] Close monitoring for potential side effects in patients receiving oxycodone and chlorpheniramine or diphenhydramine is recommended.

Because diphenhydramine can cause pronounced sedation,[6568] an enhanced CNS depressant effect may occur when it is combined with other CNS depressants [6568] including anxiolytics, sedatives, and hypnotics (such as barbiturates and benzodiazepines) [6946] [6948], buprenorphine [5278], butorphanol [5912], carisoprodol, clozapine [4989], dronabinol, THC, droperidol [5468], entacapone [5769], ethanol [6341] [6948], general anesthetics [6892], haloperidol [5036], methocarbamol, mirtazapine [5366], molindone [5553], nabilone [9044], nalbuphine [6778], nefazodone [5414], olanzapine [5517], opiate agonists, pentazocine [6777], phenothiazines [6946], pimozide [5250], pramipexole [7757], pregabalin [7523], procarbazine [5356], quetiapine [5855], risperidone [5144], ropinirole [8018], tolcapone [5578], tramadol [5043], trazodone [5450], tricyclic antidepressants [6947], or with other sedating H_1-blockers [6568]. In addition, concurrent use of cannabinoids with sedating H_1-blockers may result in additive tachycardia, which may be pronounced.

Concomitant use of acetaminophen-oxycodone with other CNS depressants can potentiate the respiratory depression and/or sedation effects of both of these agents. CNS depressants include amitriptyline, amoxapine, anxiolytics, sedatives, and hypnotics, clomipramine, clozapine, doxepin, dronabinol, THC, droperidol, entacapone, ethotoin, fosphenytoin, general anesthetics, sedating H_1-blockers, haloperidol, imipramine, MAOIs, maprotiline, mirtazapine, molindone, nabilone [9044], nefazodone, nortriptyline, olanzapine, other opiate agonists, phenothiazines, phenytoin, pimozide, pramipexole, pregabalin, quetiapine, risperidone, ropinirole, skeletal muscle relaxants, tolcapone, tramadol, and trazodone.

Diphenhydramine and Aspirin, ASA; Butalbital; Caffeine; Codeine (Fiorinal® with Codeine)

Severity: Moderate

Because diphenhydramine can cause pronounced sedation,[6568] an enhanced CNS depressant effect may occur when it is combined with other CNS depressants [6568] including anxiolytics, sedatives, and hypnotics (such as barbiturates and benzodiazepines) [6946] [6948], buprenorphine [5278], butorphanol [5912], carisoprodol, clozapine [4989], dronabinol, THC, droperidol [5468], entacapone [5769], ethanol [6341] [6948], general anesthetics [6892], haloperidol [5036], methocarbamol, mirtazapine [5366], molindone [5553], nabilone [9044], nalbuphine [6778], nefazodone [5414], olanzapine [5517], opiate agonists, pentazocine [6777], phenothiazines [6946], pimozide [5250], pramipexole [7757], pregabalin [7523], procarbazine [5356], quetiapine [5855], risperidone [5144], ropinirole [8018], tolcapone [5578], tramadol [5043], trazodone [5450], tricyclic antidepressants [6947], or with other sedating H_1-blockers [6568]. In addition, concurrent use of cannabinoids with sedating H_1-blockers may result in additive tachycardia, which may be pronounced.

Caution should be exercised during concomitant use of any CNS-depressant drugs and aspirin; butalbital; caffeine; codeine. Dosage reduction of aspirin; butalbital; caffeine; codeine may be necessary.[5232] Additive CNS depression may occur if aspirin; butalbital; caffeine; codeine combination products are used concomitantly with opiate agonists, mixed opiate agonists/antagonists, dronabinol, THC, sedating H_1-blockers, tramadol, phenothiazines, general anesthetics, amoxapine, carisoprodol, droperidol, entacapone, haloperidol, maprotiline, methocarbamol, mirtazapine, molindone, nabilone [9044], nefazodone, olanzapine, pramipexole, pregabalin [7523], quetiapine, pimozide, risperidone, ropinirole, tolcapone, trazodone, skeletal muscle relaxants, or anxiolytics, sedatives, and hypnotics (including benzodiazepines). Concomitant use of haloperidol with codeine-containing products may decrease the metabolism of codeine to morphine by inhibiting cytochrome CYP2D6.[4718] Additionally, barbiturates are known hepatic enzyme inducers and may increase metabolism of ramelteon (primarily metabolized by CYP1A2) over a longer period of time. Ramelteon efficacy may be reduced, although additive CNS depressant effects might overrule.[8143] [4718]

Diphenhydramine and Atropine; Hyoscyamine; Phenobarbital; Scopolamine (Donnatal®)

Severity: Moderate

The anticholinergic effects of diphenhydramine may be significant and may be enhanced when combined with antimuscarinics [6338]. Other commonly used drugs with moderate to significant anticholinergic effects include amantadine, amoxapine, clozapine, cyclobenzaprine, disopyramide, maprotiline, olanzapine, orphenadrine, most phenothiazines, and most tricyclic antidepressants. Clinicians should note that antimuscarinic effects might be seen not only on GI smooth muscle, but also on bladder function, the eye, and temperature regulation. With many of the listed agents, additive drowsiness may also occur when combined with sedating antihistamines.

Because diphenhydramine can cause pronounced sedation,[6568] an enhanced CNS depressant effect may occur when it is combined with other CNS depressants [6568] including anxiolytics, sedatives, and hypnotics (such as barbiturates and benzodiazepines) [6946] [6948], buprenorphine [5278], butorphanol [5912], carisoprodol, clozapine [4989], dronabinol, THC, droperidol [5468], entacapone [5769], ethanol [6341] [6948], general anesthetics [6892], haloperidol [5036], methocarbamol, mirtazapine [5366], molindone [5553], nabilone [9044], nalbuphine [6778], nefazodone [5414], olanzapine [5517], opiate agonists, pentazocine [6777], phenothiazines [6946], pimozide [5250], pramipexole [7757], pregabalin [7523], procarbazine [5356], quetiapine [5855], risperidone [5144], ropinirole [8018], tolcapone [5578], tramadol [5043], trazodone [5450], tricyclic antidepressants [6947], or

with other sedating H_1-blockers [6568]. In addition, concurrent use of cannabinoids with sedating H_1-blockers may result in additive tachycardia, which may be pronounced.

Scopolamine and phenobarbital both have CNS depressant effects in addition to antimuscarinic effects. Concurrent use of atropine; hyoscyamine; phenobarbital; scopolamine with other CNS depressants (such as ethanol, dronabinol, THC, nabilone [9044], and the anxiolytics, sedatives, and hypnotics) may lead to additive sedation. Concurrent use of cannabinoids with antimuscarinic agents may result in additive tachycardia, which may be pronounced. Additionally, barbiturates are known hepatic enzyme inducers and may increase metabolism of ramelteon (primarily metabolized by CYP1A2) over a longer period of time. Ramelteon efficacy may be reduced, although additive CNS depressant effects might overrule.[8143] [4718]

Additive anticholinergic effects may be seen when combinations of atropine; hyoscyamine; phenobarbital; scopolamine are used concomitantly with other antimuscarinics.[6338] [7179] Other commonly used drugs with moderate to significant anticholinergic effects include amantadine, amoxapine, bupropion, clozapine, cyclobenzaprine, maprotiline [5491], olanzapine, orphenadrine, the sedating H_1-blockers, most phenothiazines, and most tricyclic antidepressants. Clinicians should note that antimuscarinic effects might be seen not only on GI smooth muscle, but also on bladder function, the eye, and temperature regulation. Many of the agents with anticholinergic properties listed can increase the risk of CNS depression when combined with phenobarbital or scopolamine as well. Phenobarbital may also increase the metabolism of many antidepressants and antipsychotics listed.

Diphenhydramine and Albuterol; Ipratropium (Combivent®)

Severity: Moderate

The anticholinergic effects of diphenhydramine may be significant and may be enhanced when combined with antimuscarinics [6338]. Other commonly used drugs with moderate to significant anticholinergic effects include amantadine, amoxapine, clozapine, cyclobenzaprine, disopyramide, maprotiline, olanzapine, orphenadrine, most phenothiazines, and most tricyclic antidepressants. Clinicians should note that antimuscarinic effects might be seen not only on GI smooth muscle, but also on bladder function, the eye, and temperature regulation. With many of the listed agents, additive drowsiness may also occur when combined with sedating antihistamines.

Diphenhydramine and Doxylamine (Unisom® Sleeptabs™)

Severity: High

Because diphenhydramine causes pronounced sedation,[6568] an enhanced CNS depressant effect may occur when it is combined with other sedating H_1-blockers [6568] or with cetirizine [5607]. Due to the duplicative pharmacology and potential for additive side effects, combination of diphenhydramine with other antihistamines is not generally recommended.

Because diphenhydramine can cause pronounced sedation,[6568] an enhanced CNS depressant effect may occur when it is combined with other CNS depressants [6568] including anxiolytics, sedatives, and hypnotics (such as barbiturates and benzodiazepines) [6946] [6948], buprenorphine [5278], butorphanol [5912], carisoprodol, clozapine [4989], dronabinol, THC, droperidol [5468], entacapone [5769], ethanol [6341] [6948], general anesthetics [6892], haloperidol [5036], methocarbamol, mirtazapine [5366], molindone [5553], nabilone [9044], nalbuphine [6778], nefazodone [5414], olanzapine [5517], opiate agonists, pentazocine [6777], phenothiazines [6946], pimozide [5250], pramipexole [7757], pregabalin [7523], procarbazine [5356], quetiapine [5855], risperidone [5144], ropinirole [8018], tolcapone [5578], tramadol [5043], trazodone [5450], tricyclic antidepressants [6947], or with other sedating H_1-blockers [6568]. In addition, concurrent use of cannabinoids with sedating H_1-blockers may result in additive tachycardia, which may be pronounced.

Because doxylamine causes sedation,[7801] an enhanced CNS depressant effect may occur when it is combined with other other sedating H_1-blockers [6568] or with cetirizine [5607]. Due to the duplicative pharmacology and potential for additive side effects, combination of doxylamine with other antihistamines is not generally recommended.

Because doxylamine can cause pronounced sedation,[7801] an enhanced CNS depressant effect may occur when it is combined with other CNS depressants [6568] including anxiolytics, sedatives, and hypnotics (such as barbiturates and benzodiazepines) [6946] [6948], buprenorphine [5278], butorphanol [5912], carisoprodol, clozapine [4989], dronabinol, THC, droperidol [5468], entacapone [5769], ethanol [6341] [6948], general anesthetics [6892], haloperidol [5036], methocarbamol, mirtazapine [5366], molindone [5553], nabilone [9044], nalbuphine [6778], nefazodone [5414], olanzapine [5517], opiate agonists, pentazocine [6777], phenothiazines [6946], pimozide [5250], pramipexole [7757], pregabalin [7523], procarbazine [5356], quetiapine [5855], risperidone [5144], ropinirole [8018], tolcapone [5578], tramadol [5043], trazodone [5450], tricyclic antidepressants [6947], or with other sedating H_1-blockers [6568]. In addition, concurrent use of cannabinoids with sedating H_1-blockers may result in additive tachycardia, which may be pronounced.

Diphenhydramine and Carbinoxamine (Histex™ I/E)

Severity: High

Because diphenhydramine causes pronounced sedation,[6568] an enhanced CNS depressant effect may occur when it is combined with other sedating H_1-blockers [6568] or with cetirizine [5607]. Due to the duplicative pharmacology and potential for additive side effects, combination of diphenhydramine with other antihistamines is not generally recommended.

Carbinoxamine has potential for CNS depressant effects.[7585] An enhanced CNS depressant effect may occur when carbinoxamine is combined with other CNS depressants including anxiolytics, sedatives, and hypnotics (including barbiturates and benzodiazepines), butorphanol, entacapone, ethanol [6341], haloperidol, general anesthetics, nalbuphine, opiate agonists, pentazocine, pramipexole, pregabalin [7523], risperidone, ropinirole, tolcapone, trazodone, tramadol, or other sedating H_1-blockers [6568].

Diphenhydramine and Acetaminophen; Chlorpheniramine; Phenylephrine; Phenyltoloxamine (Norel®SR)

Severity: High

Because diphenhydramine causes pronounced sedation,[6568] an enhanced CNS depressant effect may occur when it is combined with other sedating H_1-blockers [6568] or with cetirizine [5607]. Due to the duplicative pharmacology and potential for additive side effects, combination of diphenhydramine with other antihistamines is not generally recommended.

Acetaminophen; chlorpheniramine; phenylephrine; phenyltoloxamine may cause CNS depression. An enhanced CNS depressant effect may occur when this product is combined with other CNS depressants [9107] including anxiolytics, sedatives, and hypnotics, barbiturates, buprenorphine, butorphanol, dronabinol, THC, droperidol, entacapone, ethanol, haloperidol, general anesthetics, mirtazapine, molindone, nalbuphine, nefazodone, opiate agonists, pentazocine, pimozide, pramipexole, pregabalin [7523], quetiapine, risperidone, ropinirole, skeletal muscle relaxants, tolcapone, trazodone, tramadol, or with other products containing sedating H_1-blockers. Additionally, concurrent use of dronabinol, THC with sympathomimetics such as phenylephrine may result in additive hypertension, tachycardia, and possibly cardiotoxicity.[3868] The risk of developing hepatotoxicity from acetaminophen appears to be increased in patients who regularly consume ethanol. In these patients, hepatotoxicity is possible even at normal, therapeutic dosages of acetaminophen.[1654] Acute or chronic ethanol use increases acetaminophen-induced hepatotoxicity by inducing CYP2E, leading to increased formation of the hepatotoxic metabolite of acetaminophen.[583] Administration of acetaminophen should be limited or avoided altogether in patients with alcoholism or patients who consume ethanol regularly.[4934]

Atropine; Hyoscyamine; Phenobarbital; Scopolamine (Donnatal®) **and Amlodipine** (Norvasc®)

Severity: Moderate

Concurrent use of phenobarbital with antihypertensive agents may lead to excessive hypotension. An exception may occur when barbiturates are administered to patients receiving either nifedipine or verapamil. Barbiturates have been shown to enhance the hepatic clearance of calcium-channel blockers (e.g., diltiazem [5004] [6953], nifedipine, and verapamil). The effect on oral verapamil is greater than for IV verapamil, but a significant increase in clearance has been noted for both verapamil dosage forms during concomitant administration of a barbiturate.

Rifampin [4718], rifabutin [4718], rifapentine [5213], carbamazepine [4718], barbiturates (e.g., phenobarbital or primidone) [4718], and phenytoin [4718] (or fosphenytoin which is metabolized to phenytoin [5265]) may induce the CYP3A4 metabolism of calcium-channel blockers such as amlodipine [4718] and thereby reduce their oral bioavailability. The dosage requirements of amlodipine may be increased in patients receiving concurrent enzyme inducers.

Atropine; Hyoscyamine; Phenobarbital; Scopolamine (Donnatal®) **and Clonazepam** (Klonopin®)

Severity: Moderate

Barbiturates, and specifically phenobarbital, can increase the hepatic metabolism of various drugs by induction of several cytochrome P450 enzymes . These drugs include but are not limited to alosetron [5112], some beta-blockers (betaxolol, labetalol, metoprolol, pindolol, propranolol, timolol) [4718], bexarotene [4791], carbamazepine [4754], clonazepam [4718], corticosteroids [5326], cyclophosphamide [4765] , cyclosporine [4718], digitoxin [6126], doxycycline [5326], doxorubicin [4718], cevimeline [4718] , estrogens [5326], ethanol, galantamine [4718], ifosfamide [4718], imatinib, STI-571 [4718], irinotecan [2788], levobupivacaine [5637], lidocaine [4718], metronidazole [5326], mexiletine [4718], oral contraceptives [5326], oxcarbazepine [7640], progestins [5326], quinidine [5626], tacrolimus [4718], thyroid hormones [4718], tramadol [4718], sirolimus [4718], some antidepressants, xanthines (caffeine or theophylline), or zonisamide [4718]. Clinicians should be alert for a decreased response to these agents with dosage adjustments, discontinuation or addition of barbiturates during therapy. (see Phenobarbital monograph)

Scopolamine and phenobarbital both have CNS depressant effects in addition to antimuscarinic effects. Concurrent use of atropine; hyoscyamine; phenobarbital; scopolamine with other CNS depressants (such as ethanol, dronabinol, THC, nabilone [9044], and the anxiolytics, sedatives, and hypnotics) may lead to additive sedation. Concurrent use of cannabinoids with antimuscarinic agents may

result in additive tachycardia, which may be pronounced. Additionally, barbiturates are known hepatic enzyme inducers and may increase metabolism of ramelteon (primarily metabolized by CYP1A2) over a longer period of time. Ramelteon efficacy may be reduced, although additive CNS depressant effects might overrule.[8143] [4718]

Concomitant administration of clonazepam with other CNS-depressant drugs [7168], including barbiturates, buprenorphine, butorphanol, dronabinol, THC [7185], entacapone [5769], ethanol [7198], sedating H_1-blockers, general anesthetics [6892], nabilone [9044], nalbuphine [6778], opiate agonists, pentazocine, phenothiazines, pregabalin [7523], tolcapone, tramadol, tricyclic antidepressants, or other anxiolytics, sedatives, and hypnotics, can potentiate the CNS effects (i.e., increased sedation or respiratory depression) of either agent.[5174]

Atropine; Hyoscyamine; Phenobarbital; Scopolamine (Donnatal®) **and Ergocalciferol, Vitamin D2** (Vitamin D)

Severity: Moderate

Anticonvulsants, such as phenobarbital, can decrease the activity of vitamin D and vitamin D analogs by increasing metabolism of the vitamins.[4686] In rare cases, this has caused anticonvulsant-induced rickets and osteomalacia. Vitamin D supplementation may be required in patients with inadequate dietary intake of vitamin D who are receiving chronic treatment with anticonvulsants.

Barbiturates (i.e., phenobarbital, primidone) and anticonvulsants, such phenytoin and fosphenytoin (which is metabolized to phenytoin [5685]), can decrease the activity of vitamin D by increasing its metabolism.[6923] [7204] In rare cases, this has caused anticonvulsant-induced rickets and osteomalacia. Vitamin D supplementation or dosage adjustments may be required in patients who are receiving chronic treatment with anticonvulsants.

Atropine; Hyoscyamine; Phenobarbital; Scopolamine (Donnatal®) **and Flunisolide**

Severity: Moderate

Barbiturates, and specifically phenobarbital, can increase the hepatic metabolism of various drugs by induction of several cytochrome P450 enzymes . These drugs include but are not limited to alosetron [5112], some beta-blockers (betaxolol, labetalol, metoprolol, pindolol, propranolol, timolol) [4718], bexarotene [4791], carbamazepine [4754], clonazepam [4718], corticosteroids [5326], cyclophosphamide [4765] , cyclosporine [4718], digitoxin [6126], doxycycline [5326], doxorubicin [4718], cevimeline [4718] , estrogens [5326], ethanol, galantamine [4718], ifosfamide [4718], imatinib, STI-571 [4718], irinotecan [2788], levobupivacaine [5637], lidocaine [4718], metronidazole [5326], mexiletine [4718], oral contraceptives [5326], oxcarbazepine [7640], progestins [5326], quinidine [5626], tacrolimus [4718], thyroid hormones [4718], tramadol [4718], sirolimus [4718], some antidepressants, xanthines (caffeine or theophylline), or zonisamide [4718]. Clinicians should be alert for a decreased response to these agents with dosage adjustments, discontinuation or addition of barbiturates during therapy. (see Phenobarbital monograph)

Atropine; Hyoscyamine; Phenobarbital; Scopolamine (Donnatal®) **and Verapamil**

Severity: Moderate

Concurrent use of phenobarbital with antihypertensive agents may lead to excessive hypotension. An exception may occur when barbiturates are administered to patients receiving either nifedipine or verapamil. Barbiturates have been shown to enhance the hepatic clearance of calcium-channel blockers (e.g., diltiazem [5004] [6953], nifedipine, and verapamil). The effect on oral verapamil is greater than for IV verapamil, but a significant increase in clearance has been noted for both verapamil dosage forms during concomitant administration of a barbiturate.

Rifampin, a potent hepatic enzyme inducer, significantly reduces the oral bioavailability of verapamil, presumably by increasing first-pass metabolism.[5000] Rifabutin [4718] and rifapentine [5213], enzyme inducers, may have a similar effect. Barbiturates such as phenobarbital [5000], phenytoin [5641] (or fosphenytoin which is metabolized to phenytoin [5265]) may also reduce verapamil serum concentrations via enzyme induction. Verapamil is a substrate for CYP3A4. Patients receiving verapamil should be monitored for loss of therapeutic effect if any of these hepatic enzyme inducing drugs are added.

Atropine; Hyoscyamine; Phenobarbital; Scopolamine (Donnatal®) **and Acetaminophen; Oxycodone** (Percocet®)

Severity: Moderate

Opiate agonists should be used cautiously with antimuscarinics since additive depressive effects on GI motility or bladder function may been seen.[5986] Opioids increase the tone and decrease the propulsive contractions of the smooth muscle of the gastrointestinal tract. Prolongation of the gastrointestinal transit time may be the mechanism of the constipating effect.[6365] Opiate analgesics combined with antimuscarinics can cause severe constipation or paralytic ileus, especially with chronic use. Additionally, additive sedative effects may occur with the addition of opiate agonists to phenobarbital. Some opiate agonists may become less effective with the addition of phenobarbital due to hepatic enzyme induction; for example, symptoms of opiate withdrawal have been noted when methadone-stabilized patients were administered phenobarbital.

Concurrent use of antidiarrheals and acetaminophen; oxycodone can lead to severe constipation and possibly additive CNS depression. Opiate analgesics combined with antimuscarinics can cause severe constipation or paralytic ileus, especially with chronic use.

Concomitant use of acetaminophen-oxycodone with other CNS depressants can potentiate the respiratory depression and/or sedation effects of both of these agents. CNS depressants include amitriptyline, amoxapine, anxiolytics, sedatives, and hypnotics, clomipramine, clozapine, doxepin, dronabinol, THC, droperidol, entacapone, ethotoin, fosphenytoin, general anesthetics, sedating H_1-blockers, haloperidol, imipramine, MAOIs, maprotiline, mirtazapine, molindone, nabilone [9044], nefazodone, nortriptyline, olanzapine, other opiate agonists, phenothiazines, phenytoin, pimozide, pramipexole, pregabalin, quetiapine, risperidone, ropinirole, skeletal muscle relaxants, tolcapone, tramadol, and trazodone.

Clinically significant interactions, including withdrawal reactions, have been reported with the concurrent use of oxycodone and inducers of cytochrome P-450 (CYP) 2D6. Concomitant use of barbiturates, carbamazepine, or rifampin with oxycodone may necessitate increased doses of to achieve analgesia and prevent withdrawal. In the case of acetaminophen, inducers CYP 2E1 or 1A2 may increase the risk of acetaminophen-induced hepatotoxicity. Potentiation of acetaminophen hepatotoxicity has occurred clinically when acetaminophen was chronically co-administered with isoniazid, INH [4930], rifampin, or phenobarbital. Additive CNS depression may be the more important issue initially when barbiturates are when given with acetaminophen-oxycodone combinations. Induction of acetaminophen and oxycodone metabolism may take several days. Close monitoring for excessive toxicity or decreased efficacy is recommended in patients receiving these drugs in combination with acetaminophen-oxycodone.

Atropine; Hyoscyamine; Phenobarbital; Scopolamine (Donnatal®) **and Aspirin, ASA; Butalbital; Caffeine; Codeine** (Fiorinal® with Codeine)

Severity: Moderate

Scopolamine and phenobarbital both have CNS depressant effects in addition to antimuscarinic effects. Concurrent use of atropine; hyoscyamine; phenobarbital; scopolamine with other CNS depressants (such as ethanol, dronabinol, THC, nabilone [9044], and the anxiolytics, sedatives, and hypnotics) may lead to additive sedation. Concurrent use of cannabinoids with antimuscarinic agents may result in additive tachycardia, which may be pronounced. Additionally, barbiturates are known hepatic enzyme inducers and may increase metabolism of ramelteon (primarily metabolized by CYP1A2) over a longer period of time. Ramelteon efficacy may be reduced, although additive CNS depressant effects might overrule.[8143] [4718]

Opiate agonists should be used cautiously with antimuscarinics since additive depressive effects on GI motility or bladder function may been seen.[5986] Opioids increase the tone and decrease the propulsive contractions of the smooth muscle of the gastrointestinal tract. Prolongation of the gastrointestinal transit time may be the mechanism of the constipating effect.[6365] Opiate analgesics combined with antimuscarinics can cause severe constipation or paralytic ileus, especially with chronic use. Additionally, additive sedative effects may occur with the addition of opiate agonists to phenobarbital. Some opiate agonists may become less effective with the addition of phenobarbital due to hepatic enzyme induction; for example, symptoms of opiate withdrawal have been noted when methadone-stabilized patients were administered phenobarbital.

Additive constipation may be seen with concurrent use of aspirin; butalbital; caffeine; codeine combination products (due to the codeine component) and antidiarrheals. Concurrent use of certain antidiarrheals can also lead to additive CNS depression. Opiate analgesics combined with antimuscarinics can cause severe constipation or paralytic ileus, especially with chronic use. Both drug classes decrease peristalsis.

Caution should be exercised during concomitant use of any CNS-depressant drugs and aspirin; butalbital; caffeine; codeine. Dosage reduction of aspirin; butalbital; caffeine; codeine may be necessary.[5232] Additive CNS depression may occur if aspirin; butalbital; caffeine; codeine combination products are used concomitantly with opiate agonists, mixed opiate agonists/antagonists, dronabinol, THC, sedating H_1-blockers, tramadol, phenothiazines, general anesthetics, amoxapine, carisoprodol, droperidol, entacapone, haloperidol, maprotiline, methocarbamol, mirtazapine, molindone, nabilone [9044], nefazodone, olanzapine, pramipexole, pregabalin [7523], quetiapine, pimozide, risperidone, ropinirole, tolcapone, trazodone, skeletal muscle relaxants, or anxiolytics, sedatives, and hypnotics (including benzodiazepines). Concomitant use of haloperidol with codeine-containing products may decrease the metabolism of codeine to morphine by inhibiting cytochrome CYP2D6.[4718] Additionally, barbiturates are known hepatic enzyme inducers and may increase metabolism of ramelteon (primarily metabolized by CYP1A2) over a longer period of time. Ramelteon efficacy may be reduced, although additive CNS depressant effects might overrule.[8143] [4718]

Use caution when combining aspirin, ASA; butalbital; caffeine; codeine combinations with other barbiturates, due to duplicative pharmacotherapy. Caution should be exercised during concomitant use of any CNS-depressant drugs and aspirin; butalbital; caffeine; codeine. Dosage reduction of aspirin; butalbital; caffeine; codeine may be necessary.[5232] In addition, agents that induce hepatic enzymes (e.g., barbiturates) may affect the clinical response to aspirin; butalbital; caffeine; codeine combination products. Codeine is metabolized by CYP2D6; therefore, its analgesic activity may vary greatly when it is combined with any other drugs that may induce CYP2D6.[4718]

Atropine; Hyoscyamine; Phenobarbital; Scopolamine (Donnatal®) **and Doxylamine** (Unisom® Sleeptabs™)

Severity: Moderate

Scopolamine and phenobarbital both have CNS depressant effects in addition to antimuscarinic effects. Concurrent use of atropine; hyoscyamine; phenobarbital; scopolamine with other CNS depressants (such as ethanol, dronabinol, THC, nabilone [9044], and the anxiolytics, sedatives, and hypnotics) may lead to additive sedation. Concurrent use of cannabinoids with antimuscarinic agents may result in additive tachycardia, which may be pronounced. Additionally, barbiturates are known hepatic enzyme inducers and may increase metabolism of ramelteon (primarily metabolized by CYP1A2) over a longer period of time. Ramelteon efficacy may be reduced, although additive CNS depressant effects might overrule.[8143] [4718]

Additive anticholinergic effects may be seen when combinations of atropine; hyoscyamine; phenobarbital; scopolamine are used concomitantly with other antimuscarinics.[6338] [7179] Other commonly used drugs with moderate to significant anticholinergic effects include amantadine, amoxapine, bupropion, clozapine, cyclobenzaprine, maprotiline [5491], olanzapine, orphenadrine, the sedating H_1-blockers, most phenothiazines, and most tricyclic antidepressants. Clinicians should note that antimuscarinic effects might be seen not only on GI smooth muscle, but also on bladder function, the eye, and temperature regulation. Many of the agents with anticholinergic properties listed can increase the risk of CNS depression when combined with phenobarbital or scopolamine as well. Phenobarbital may also increase the metabolism of many antidepressants and antipsychotics listed.

Doxylamine is a sedating antihistamine.[7801] The anticholinergic effects of doxylamine may be significant and may be enhanced when combined with antimuscarinics [6338]. Other commonly used drugs with moderate to significant anticholinergic effects include amantadine [4771], amoxapine [5288], clozapine [4989], cyclobenzaprine [5155], disopyramide [4954], maprotiline [5491], olanzapine [5517], orphenadrine [5982], most phenothiazines [6946], and most tricyclic antidepressants [6947]. Clinicians should note that antimuscarinic effects might be seen not only on GI smooth muscle, but also on bladder function, the eye, and temperature regulation. With many of the listed agents, additive drowsiness may also occur when combined with significantly sedating antihistamines like doxylamine.

Because doxylamine can cause pronounced sedation,[7801] an enhanced CNS depressant effect may occur when it is combined with other CNS depressants [6568] including anxiolytics, sedatives, and hypnotics (such as barbiturates and benzodiazepines) [6946] [6948], buprenorphine [5278], butorphanol [5912], carisoprodol, clozapine [4989], dronabinol, THC, droperidol [5468], entacapone [5769], ethanol [6341] [6948], general anesthetics [6892], haloperidol [5036], methocarbamol, mirtazapine [5366], molindone [5553], nabilone [9044], nalbuphine [6778], nefazodone [5414], olanzapine [5517], opiate agonists, pentazocine [6777], phenothiazines [6946], pimozide [5250], pramipexole [7757], pregabalin [7523], procarbazine [5356], quetiapine [5855], risperidone [5144], ropinirole [8018], tolcapone [5578], tramadol [5043], trazodone [5450], tricyclic antidepressants [6947], or with other sedating H_1-blockers [6568]. In addition, concurrent use of cannabinoids with sedating H_1-blockers may result in additive tachycardia, which may be pronounced.

Atropine; Hyoscyamine; Phenobarbital; Scopolamine (Donnatal®) **and Carbinoxamine** (Histex™ I/E)

Severity: Moderate

Additive anticholinergic effects may be seen when combinations of atropine; hyoscyamine; phenobarbital; scopolamine are used concomitantly with other antimuscarinics.[6338] [7179] Other commonly used drugs with moderate to significant anticholinergic effects include amantadine, amoxapine, bupropion, clozapine, cyclobenzaprine, maprotiline [5491], olanzapine, orphenadrine, the sedating H_1-blockers, most phenothiazines, and most tricyclic antidepressants. Clinicians should note that antimuscarinic effects might be seen not only on GI smooth muscle, but also on bladder function, the eye, and temperature regulation. Many of the agents with anticholinergic properties listed can increase the risk of CNS depression when combined with phenobarbital or scopolamine as well. Phenobarbital may also increase the metabolism of many antidepressants and antipsychotics listed.

Carbinoxamine has mild anticholinergic effects.[7585] The anticholinergic effects of carbinoxamine may be significant and may be enhanced when combined with antimuscarinics [6338]. Other commonly used drugs with moderate to significant anticholinergic effects include amantadine, amoxapine, clozapine, cyclobenzaprine, disopyramide, maprotiline, olanzapine, orphenadrine, most phenothiazines, and most tricyclic antidepressants. Clinicians should note that antimuscarinic effects might not only be seen on GI smooth muscle, but also on bladder function, the eye, and temperature regulation. With many of the listed agents, additive drowsiness may also occur when combined with sedating antihistamines.

Carbinoxamine has potential for CNS depressant effects.[7585] An enhanced CNS depressant effect may occur when carbinoxamine is combined with other CNS depressants including anxiolytics, sedatives, and hypnotics (including barbiturates and benzodiazepines), butorphanol, entacapone, ethanol [6341], haloperidol, general anesthetics, nalbuphine, opiate agonists, pentazocine, pramipexole, pregabalin [7523], risperidone, ropinirole, tolcapone, trazodone, tramadol, or other sedating H_1-blockers [6568].

Atropine; Hyoscyamine; Phenobarbital; Scopolamine (Donnatal®) **and Acetaminophen; Chlorpheniramine; Phenylephrine; Phenyltoloxamine** (Norel®SR)

Severity: Moderate

Additive anticholinergic effects may be seen when combinations of atropine; hyoscyamine; phenobarbital; scopolamine are used concomitantly with other antimuscarinics.[6338] [7179] Other commonly used drugs with moderate to significant anticholinergic effects include amantadine, amoxapine, bupropion, clozapine, cyclobenzaprine, maprotiline [5491], olanzapine, orphenadrine, the sedating H_1-blockers, most phenothiazines, and most tricyclic antidepressants. Clinicians should note that antimuscarinic effects might be seen not only on GI smooth muscle, but also on bladder function, the eye, and temperature regulation. Many of the agents with anticholinergic properties listed can increase the risk of CNS depression when combined with phenobarbital or scopolamine as well. Phenobarbital may also increase the metabolism of many antidepressants and antipsychotics listed.

Acetaminophen; chlorpheniramine; phenylephrine; phenyltoloxamine may interact with medications from a variety of classes due to the anticholinergic effects of chlorpheniramine or phenyltoloxamine and the sympathomimetic effects of phenylephrine.[9107] An interaction may occur when this product is combined with other drugs with anticholinergic activity, like the antimuscarinics.[6338] Commonly used drugs with moderate to significant anticholinergic effects include amantadine, amoxapine, clozapine, cyclobenzaprine, disopyramide, maprotiline, olanzapine, orphenadrine, most phenothiazines, and most tricyclic antidepressants. Clinicians should note that antimuscarinic effects might be seen not only on GI smooth muscle, but also on bladder function, the eye, and temperature regulation. With many of the listed agents, additive drowsiness may also occur when combined with chlorpheniramine and phenyltoloxamine. Additionally, the sympathomimetic effects of phenylephrine may interact with tricyclic antidepressants [5287] and maprotiline [5491], resulting in severe cardiovascular effects including arrhythmias, severe hypertension, hyperpyrexia, and/or severe headaches.

Acetaminophen; chlorpheniramine; phenylephrine; phenyltoloxamine may cause CNS depression. An enhanced CNS depressant effect may occur when this product is combined with other CNS depressants [9107] including anxiolytics, sedatives, and hypnotics, barbiturates, buprenorphine, butorphanol, dronabinol, THC, droperidol, entacapone, ethanol, haloperidol, general anesthetics, mirtazapine, molindone, nalbuphine, nefazodone, opiate agonists, pentazocine, pimozide, pramipexole, pregabalin [7523], quetiapine, risperidone, ropinirole, skeletal muscle relaxants, tolcapone, trazodone, tramadol, or with other products containing sedating H_1-blockers. Additionally, concurrent use of dronabinol, THC with sympathomimetics such as phenylephrine may result in additive hypertension, tachycardia, and possibly cardiotoxicity.[3868] The risk of developing hepatotoxicity from acetaminophen appears to be increased in patients who regularly consume ethanol. In these patients, hepatotoxicity is possible even at normal, therapeutic dosages of acetaminophen.[1654] Acute or chronic ethanol use increases acetaminophen-induced hepatotoxicity by inducing CYP2E, leading to increased formation of the hepatotoxic metabolite of acetaminophen.[583] Administration of acetaminophen should be limited or avoided altogether in patients with alcoholism or patients who consume ethanol regularly.[4934]

Atropine; Hyoscyamine; Phenobarbital; Scopolamine (Donnatal®) **and Theophylline, Aminophylline** (Theophylline)

Severity: Moderate

The metabolism of xanthines, such as caffeine or theophylline, can be increased by concurrent use with barbiturates.[7694] [7695] While it is clear that barbiturates can accelerate the clearance of theophylline, the magnitude of this interaction is uncertain. Patients should be monitored for loss of therapeutic effect if a barbiturate is added to theophylline therapy. Conversely, caffeine or theophylline can reduce the hypnotic effects of barbiturates. Patients that ingest theophylline or high amounts of caffeine from foods, beverages (e.g., coffee, green tea [6531], other teas, cola, and chocolate), or dietary supplements such as guarana [4679] should be monitored for therapeutic effect while taking barbiturates.

Theophylline is primarily metabolized in the liver by the CYP1A2 isoenzyme, and also by the CYP3A4 isoenzyme.[4718] The following drugs can stimulate the hepatic metabolism of theophylline if used concurrently: barbiturates [4722], carbamazepine [4743], ethotoin [4741], phenytoin or fosphenytoin [4742], primidone [4718], and rifampin [4718]. Due to the long half-life of phenobarbital, several days of phenobarbital therapy may be necessary before any effect on theophylline pharmacokinetics is seen. Theophylline doses may need to be increased if any of these drugs are added. More importantly, serious theophylline toxicity can result if any of these drugs are discontinued and the dose of theophylline is not correspondingly decreased. Theophylline, in turn, may inhibit the absorption of phenytoin.

Aspirin, ASA; Butalbital; Caffeine; Codeine (Fiorinal® with Codeine) **and Clonazepam** (Klonopin®)

Severity: Moderate

Caution should be exercised during concomitant use of any CNS-depressant drugs and aspirin; butalbital; caffeine; codeine. Dosage reduction of aspirin; butalbital; caffeine; codeine may be necessary.[5232] Additive CNS depression may occur if aspirin; butalbital; caffeine; codeine combination products are used concomitantly with opiate agonists, mixed opiate agonists/antagonists, dronabinol, THC, sedating H_1-blockers, tramadol, phenothiazines, general anesthetics, amoxapine, carisoprodol, droperidol, entacapone,

haloperidol, maprotiline, methocarbamol, mirtazapine, molindone, nabilone [9044], nefazodone, olanzapine, pramipexole, pregabalin [7523], quetiapine, pimozide, risperidone, ropinirole, tolcapone, trazodone, skeletal muscle relaxants, or anxiolytics, sedatives, and hypnotics (including benzodiazepines). Concomitant use of haloperidol with codeine-containing products may decrease the metabolism of codeine to morphine by inhibiting cytochrome CYP2D6.[4718] Additionally, barbiturates are known hepatic enzyme inducers and may increase metabolism of ramelteon (primarily metabolized by CYP1A2) over a longer period of time. Ramelteon efficacy may be reduced, although additive CNS depressant effects might overrule.[8143] [4718]

Concomitant administration of clonazepam with other CNS-depressant drugs [7168], including barbiturates, buprenorphine, butorphanol, dronabinol, THC [7185], entacapone [5769], ethanol [7198], sedating H_1-blockers, general anesthetics [6892], nabilone [9044], nalbuphine [6778], opiate agonists, pentazocine, phenothiazines, pregabalin [7523], tolcapone, tramadol, tricyclic antidepressants, or other anxiolytics, sedatives, and hypnotics, can potentiate the CNS effects (i.e., increased sedation or respiratory depression) of either agent.[5174]

Aspirin, ASA; Butalbital; Caffeine; Codeine (Fiorinal® with Codeine) **and Flunisolide**

Severity: Moderate

Dose adjustments may be necessary in patients receiving both corticosteroids and an aspirin; butalbital; caffeine; codeine product; butalbital may induce the metabolism of corticosteroids. Also, the efficacy of aspirin; butalbital; caffeine; codeine may be reduced, as corticosteroids enhance the renal clearance of salicylates.[5683] Conversely, withdrawal of corticosteroids may cause salicylism, especially if the patient is taking additional aspirin. While there is controversy regarding the ulcerogenic potential of corticosteroids alone, concomitant administration of corticosteroids with aspirin may increase the GI toxicity of aspirin.

Aspirin, ASA; Butalbital; Caffeine; Codeine (Fiorinal® with Codeine) **and Ipratropium** (Atrovent®)

Severity: Moderate

Additive constipation may be seen with concurrent use of aspirin; butalbital; caffeine; codeine combination products (due to the codeine component) and antidiarrheals. Concurrent use of certain antidiarrheals can also lead to additive CNS depression. Opiate analgesics combined with antimuscarinics can cause severe constipation or paralytic ileus, especially with chronic use. Both drug classes decrease peristalsis.

Aspirin, ASA; Butalbital; Caffeine; Codeine (Fiorinal® with Codeine) **and Phenylephrine** (found in Codimal® DH)

Severity: High

The CNS-stimulating actions of caffeine can be additive with other CNS stimulants or psychostimulants.[4666] Therefore, aspirin; butalbital; caffeine; codeine should be avoided or used cautiously with amphetamine, dextroamphetamine, methylphenidate, pemoline, pseudoephedrine, beta$_2$-agonists, nicotine, or other sympathomimetics. When combined with any of these medications, caffeine can cause nervousness, irritability, insomnia, and/or cardiac arrhythmias.

Aspirin, ASA; Butalbital; Caffeine; Codeine (Fiorinal® with Codeine) **and Clopidogrel** (Plavix®)

Severity: High

Aspirin, ASA; butalbital; caffeine; codeine combination products contain the antiplatelet agent aspirin. Additive platelet effects may occur if Aspirin, ASA; butalbital; caffeine; codeine is given in combination with other platelet inhibitors. In addition, anagrelide has been shown to inhibit CYP1A2. In theory, coadministration of anagrelide with substrates of CYP1A2, including caffeine, could lead to increases in the serum concentrations of these drugs and, thus, adverse effects. Finally, anagrelide is metabolized by CYP1A2. In theory, coadministration with barbiturates could lead to a decrease in efficacy of anagrelide. Monitor patients for changes in efficacy of anagrelide, for an increase in toxicity of caffeine, and for an increase in the risk of bleeding if these drugs are coadministered.[6912]

Concomitant administration of clopidogrel and aspirin (500 mg twice daily for 1 day) did not significantly increase bleeding time prolongation induced by clopidogrel. However, clopidogrel does potentiate the effect of aspirin on collagen-induced platelet aggregation.[5165] In patients with recent TIA or stroke who are at high risk for recurrent ischemic events, the combination of aspirin and clopidogrel has not been shown to be more effective than clopidogrel alone; however, the incidence of major bleeding (i.e., bleeding that was substantially disabling, intraocular, or required >= 2 units of transfused blood) is more common with combination therapy. In addition, large doses of salicylates (>= 3-4 g/day) can cause hypoprothrombinemia [5170], an additional risk factor for bleeding. The CHARISMA trial, a study that enrolled > 15,000 patients with established or at risk for cardiovascular disease, randomized patients to either clopidogrel plus low-dose aspirin or low-dose aspirin alone. The findings from this trial indicate that combination antiplatelet therapy does not reduce the risk of MI, stroke, or CV death; furthermore, combination therapy is associated with an increased risk of moderate bleeding (rate of 2.1% in the combination therapy group vs. 1.3% in the placebo group, p<0.001), but not severe bleeding. Data from a subgroup analysis of patients with established cardiovascular disease, which should be interpreted with caution, indicate that combination antiplatelet therapy reduces the relative risk of recurrent myocardial infarction,

stroke, or cardiovascular death by 12.5% when compared to aspirin therapy alone (n=12,153; p=0.046). However, in patients without established cardiovascular disease, but who have risk factors for cardiovascular disease including diabetes mellitus, hypertension, or hypercholesterolemia, combination antiplatelet therapy is not associated with a difference in clinical outcomes and may be associated with an increase in cardiovascular death.[8833] More data are needed to determine the role of combination antiplatelet therapy in patients with established cardiovascular disease; however, it may be prudent to avoid using clopidogrel and aspirin combination therapy in patients that do not have established cardiovascular disease. Regardless of the indication, patients receiving both aspirin and clopidogrel should be monitored for an increased risk of bleeding.

Rifampin, rifabutin, rifapentine, bosentan, carbamazepine or barbiturates (e.g., phenobarbital or primidone) may induce the CYP3A4 metabolism of clopidogrel to its active metabolite.[4718] Patients should be monitored for potential increased antiplatelet effects when clopidogrel is used in combination with CYP3A4 inducers.

Aspirin, ASA; Butalbital; Caffeine; Codeine (Fiorinal® with Codeine) **and Acetaminophen; Oxycodone** (Percocet®)

Severity: Moderate

Caution should be exercised during concomitant use of any CNS-depressant drugs and aspirin; butalbital; caffeine; codeine. Dosage reduction of aspirin; butalbital; caffeine; codeine may be necessary.[5232] Additive CNS depression may occur if aspirin; butalbital; caffeine; codeine combination products are used concomitantly with opiate agonists, mixed opiate agonists/antagonists, dronabinol, THC, sedating H_1-blockers, tramadol, phenothiazines, general anesthetics, amoxapine, carisoprodol, droperidol, entacapone, haloperidol, maprotiline, methocarbamol, mirtazapine, molindone, nabilone [9044], nefazodone, olanzapine, pramipexole, pregabalin [7523], quetiapine, pimozide, risperidone, ropinirole, tolcapone, trazodone, skeletal muscle relaxants, or anxiolytics, sedatives, and hypnotics (including benzodiazepines). Concomitant use of haloperidol with codeine-containing products may decrease the metabolism of codeine to morphine by inhibiting cytochrome CYP2D6.[4718] Additionally, barbiturates are known hepatic enzyme inducers and may increase metabolism of ramelteon (primarily metabolized by CYP1A2) over a longer period of time. Ramelteon efficacy may be reduced, although additive CNS depressant effects might overrule.[8143] [4718]

Concomitant use of oxycodone with other opiate agonists may lead to additive respiratory depression and/or sedation. Propoxyphene should be especially avoided in combination with oxycodone due propoxyphene-induced inhibition of CYP2D6, an enzyme responsible for the metabolism of oxycodone.[4718] Also, propoxyphene will only partially suppress the withdrawal syndrome in patients physically dependent on morphine or other opiate agonists.[7070]

Concomitant use of acetaminophen-oxycodone with other CNS depressants can potentiate the respiratory depression and/or sedation effects of both of these agents. CNS depressants include amitriptyline, amoxapine, anxiolytics, sedatives, and hypnotics, clomipramine, clozapine, doxepin, dronabinol, THC, droperidol, entacapone, ethotoin, fosphenytoin, general anesthetics, sedating H_1-blockers, haloperidol, imipramine, MAOIs, maprotiline, mirtazapine, molindone, nabilone [9044], nefazodone, nortriptyline, olanzapine, other opiate agonists, phenothiazines, phenytoin, pimozide, pramipexole, pregabalin, quetiapine, risperidone, ropinirole, skeletal muscle relaxants, tolcapone, tramadol, and trazodone.

Clinically significant interactions, including withdrawal reactions, have been reported with the concurrent use of oxycodone and inducers of cytochrome P-450 (CYP) 2D6. Concomitant use of barbiturates, carbamazepine, or rifampin with oxycodone may necessitate increased doses of to achieve analgesia and prevent withdrawal. In the case of acetaminophen, inducers CYP 2E1 or 1A2 may increase the risk of acetaminophen-induced hepatotoxicity. Potentiation of acetaminophen hepatotoxicity has occurred clinically when acetaminophen was chronically co-administered with isoniazid, INH [4930], rifampin, or phenobarbital. Additive CNS depression may be the more important issue initially when barbiturates are when given with acetaminophen-oxycodone combinations. Induction of acetaminophen and oxycodone metabolism may take several days. Close monitoring for excessive toxicity or decreased efficacy is recommended in patients receiving these drugs in combination with acetaminophen-oxycodone.

Aspirin, ASA; Butalbital; Caffeine; Codeine (Fiorinal® with Codeine) **and Caffeine; Ergotamine** (Cafergot®)

Severity: High

The CNS-stimulating actions of caffeine can be additive with other CNS stimulants or psychostimulants.[4666] Therefore, aspirin; butalbital; caffeine; codeine should be avoided or used cautiously with amphetamine, dextroamphetamine, methylphenidate, pemoline, pseudoephedrine, beta$_2$-agonists, nicotine, or other sympathomimetics. When combined with any of these medications, caffeine can cause nervousness, irritability, insomnia, and/or cardiac arrhythmias.

Aspirin, ASA; Butalbital; Caffeine; Codeine (Fiorinal® with Codeine) **and Albuterol; Ipratropium** (Combivent®)

Severity: Moderate

Additive constipation may be seen with concurrent use of aspirin; butalbital; caffeine; codeine combination products (due to the codeine component) and antidiarrheals. Concurrent use of certain antidiarrheals can also lead to additive CNS depression. Opiate

analgesics combined with antimuscarinics can cause severe constipation or paralytic ileus, especially with chronic use. Both drug classes decrease peristalsis.

Aspirin, ASA; Butalbital; Caffeine; Codeine (Fiorinal® with Codeine) **and Doxylamine** (Unisom® Sleeptabs™)

Severity: High

Caution should be exercised during concomitant use of any CNS-depressant drugs and aspirin; butalbital; caffeine; codeine. Dosage reduction of aspirin; butalbital; caffeine; codeine may be necessary.[5232] Additive CNS depression may occur if aspirin; butalbital; caffeine; codeine combination products are used concomitantly with opiate agonists, mixed opiate agonists/antagonists, dronabinol, THC, sedating H_1-blockers, tramadol, phenothiazines, general anesthetics, amoxapine, carisoprodol, droperidol, entacapone, haloperidol, maprotiline, methocarbamol, mirtazapine, molindone, nabilone [9044], nefazodone, olanzapine, pramipexole, pregabalin [7523], quetiapine, pimozide, risperidone, ropinirole, tolcapone, trazodone, skeletal muscle relaxants, or anxiolytics, sedatives, and hypnotics (including benzodiazepines). Concomitant use of haloperidol with codeine-containing products may decrease the metabolism of codeine to morphine by inhibiting cytochrome CYP2D6.[4718] Additionally, barbiturates are known hepatic enzyme inducers and may increase metabolism of ramelteon (primarily metabolized by CYP1A2) over a longer period of time. Ramelteon efficacy may be reduced, although additive CNS depressant effects might overrule.[8143] [4718]

Because doxylamine can cause pronounced sedation,[7801] an enhanced CNS depressant effect may occur when it is combined with other CNS depressants [6568] including anxiolytics, sedatives, and hypnotics (such as barbiturates and benzodiazepines) [6946] [6948], buprenorphine [5278], butorphanol [5912], carisoprodol, clozapine [4989], dronabinol, THC, droperidol [5468], entacapone [5769], ethanol [6341] [6948], general anesthetics [6892], haloperidol [5036], methocarbamol, mirtazapine [5366], molindone [5553], nabilone [9044], nalbuphine [6778], nefazodone [5414], olanzapine [5517], opiate agonists, pentazocine [6777], phenothiazines [6946], pimozide [5250], pramipexole [7757], pregabalin [7523], procarbazine [5356], quetiapine [5855], risperidone [5144], ropinirole [8018], tolcapone [5578], tramadol [5043], trazodone [5450], tricyclic antidepressants [6947], or with other sedating H_1-blockers [6568]. In addition, concurrent use of cannabinoids with sedating H_1-blockers may result in additive tachycardia, which may be pronounced.

Aspirin, ASA; Butalbital; Caffeine; Codeine (Fiorinal® with Codeine) **and Carbinoxamine** (Histex™ I/E)

Severity: High

Caution should be exercised during concomitant use of any CNS-depressant drugs and aspirin; butalbital; caffeine; codeine. Dosage reduction of aspirin; butalbital; caffeine; codeine may be necessary.[5232] Additive CNS depression may occur if aspirin; butalbital; caffeine; codeine combination products are used concomitantly with opiate agonists, mixed opiate agonists/antagonists, dronabinol, THC, sedating H_1-blockers, tramadol, phenothiazines, general anesthetics, amoxapine, carisoprodol, droperidol, entacapone, haloperidol, maprotiline, methocarbamol, mirtazapine, molindone, nabilone [9044], nefazodone, olanzapine, pramipexole, pregabalin [7523], quetiapine, pimozide, risperidone, ropinirole, tolcapone, trazodone, skeletal muscle relaxants, or anxiolytics, sedatives, and hypnotics (including benzodiazepines). Concomitant use of haloperidol with codeine-containing products may decrease the metabolism of codeine to morphine by inhibiting cytochrome CYP2D6.[4718] Additionally, barbiturates are known hepatic enzyme inducers and may increase metabolism of ramelteon (primarily metabolized by CYP1A2) over a longer period of time. Ramelteon efficacy may be reduced, although additive CNS depressant effects might overrule.[8143] [4718]

Carbinoxamine has potential for CNS depressant effects.[7585] An enhanced CNS depressant effect may occur when carbinoxamine is combined with other CNS depressants including anxiolytics, sedatives, and hypnotics (including barbiturates and benzodiazepines), butorphanol, entacapone, ethanol [6341], haloperidol, general anesthetics, nalbuphine, opiate agonists, pentazocine, pramipexole, pregabalin [7523], risperidone, ropinirole, tolcapone, trazodone, tramadol, or other sedating H_1-blockers [6568].

Aspirin, ASA; Butalbital; Caffeine; Codeine (Fiorinal® with Codeine) **and Acetaminophen; Chlorpheniramine; Phenylephrine; Phenyltoloxamine** (Norel®SR)

Severity: High

Caution should be exercised during concomitant use of any CNS-depressant drugs and aspirin; butalbital; caffeine; codeine. Dosage reduction of aspirin; butalbital; caffeine; codeine may be necessary.[5232] Additive CNS depression may occur if aspirin; butalbital; caffeine; codeine combination products are used concomitantly with opiate agonists, mixed opiate agonists/antagonists, dronabinol, THC, sedating H_1-blockers, tramadol, phenothiazines, general anesthetics, amoxapine, carisoprodol, droperidol, entacapone, haloperidol, maprotiline, methocarbamol, mirtazapine, molindone, nabilone [9044], nefazodone, olanzapine, pramipexole, pregabalin [7523], quetiapine, pimozide, risperidone, ropinirole, tolcapone, trazodone, skeletal muscle relaxants, or anxiolytics, sedatives, and hypnotics (including benzodiazepines). Concomitant use of haloperidol with codeine-containing products may decrease the metabolism of codeine to morphine by inhibiting cytochrome CYP2D6.[4718] Additionally, barbiturates are known hepatic enzyme inducers and may increase metabolism of ramelteon (primarily metabolized by CYP1A2) over a longer period of time. Ramelteon efficacy may be reduced, although additive CNS depressant effects might overrule.[8143] [4718]

The CNS-stimulating actions of caffeine can be additive with other CNS stimulants or psychostimulants.[4666] Therefore, aspirin; butalbital; caffeine; codeine should be avoided or used cautiously with amphetamine, dextroamphetamine, methylphenidate, pemoline, pseudoephedrine, beta$_2$-agonists, nicotine, or other sympathomimetics. When combined with any of these medications, caffeine can cause nervousness, irritability, insomnia, and/or cardiac arrhythmias.

Acetaminophen; chlorpheniramine; phenylephrine; phenyltoloxamine may cause CNS depression. An enhanced CNS depressant effect may occur when this product is combined with other CNS depressants [9107] including anxiolytics, sedatives, and hypnotics, barbiturates, buprenorphine, butorphanol, dronabinol, THC, droperidol, entacapone, ethanol, haloperidol, general anesthetics, mirtazapine, molindone, nalbuphine, nefazodone, opiate agonists, pentazocine, pimozide, pramipexole, pregabalin [7523], quetiapine, risperidone, ropinirole, skeletal muscle relaxants, tolcapone, trazodone, tramadol, or with other products containing sedating H_1-blockers. Additionally, concurrent use of dronabinol, THC with sympathomimetics such as phenylephrine may result in additive hypertension, tachycardia, and possibly cardiotoxicity.[3868] The risk of developing hepatotoxicity from acetaminophen appears to be increased in patients who regularly consume ethanol. In these patients, hepatotoxicity is possible even at normal, therapeutic dosages of acetaminophen.[1654] Acute or chronic ethanol use increases acetaminophen-induced hepatotoxicity by inducing CYP2E, leading to increased formation of the hepatotoxic metabolite of acetaminophen.[583] Administration of acetaminophen should be limited or avoided altogether in patients with alcoholism or patients who consume ethanol regularly.[4934]

Prolonged concurrent use of salicylates with products containing acetaminophen is not recommended. High-dose, chronic administration of the combined analgesics significantly increases the risk of analgesic nephropathy, renal papillary necrosis, and end-stage renal disease. In a case-controlled study of patients with early renal failure, the regular use of aspirin and acetaminophen was associated with an odds ratio of 2.2 (95% confidence interval 1.4 to 3.5) when regular aspirin users were the reference group.[4064] The trend toward greater risk with an increasing cumulative life-time dose of acetaminophen was statistically significant with a risk that was 2.4-times as high for subjects who had consumed a total > 500 g of acetaminophen in combination with aspirin than for those who had used aspirin alone. Do not exceed the recommended individual maximum doses when these agents are given concurrently for short-term therapy.

Aspirin, ASA; Butalbital; Caffeine; Codeine (Fiorinal® with Codeine) **and Alendronate** (Fosamax®)

Severity: High

Aspirin; butalbital; caffeine; codeine should be used with caution in patients who are taking alendronate. In clinical trials, the incidence of upper gastrointestinal adverse events was increased in patients that received aspirin-containing medicines with alendronate 10 mg daily or higher. One patient with a history of peptic ulcer disease and gastrectomy that received alendronate 10 mg daily and aspirin got an anastomotic ulcer with mild hemorrhage. The patient recovered upon alendronate and aspirin discontinuation.[5375]

Aspirin, ASA; Butalbital; Caffeine; Codeine (Fiorinal® with Codeine) **and Propafenone** (Rythmol)

Severity: Low

Concomitant use of amiodarone or propafenone with codeine-containing products may decrease the metabolism of codeine to morphine by inhibiting cytochrome CYP2D6 (the list is not be inclusive of all agents that inhibit CYP2D6).[4718]

Aspirin, ASA; Butalbital; Caffeine; Codeine (Fiorinal® with Codeine) **and Psyllium** (Metamucil®)

Severity: Moderate

Psyllium can interfere with the absorption of certain oral drugs if administered concomitantly. For example, psyllium fiber can adsorb salicylates [6107]. Per the psyllium manufacturers, administration of other prescribed oral drugs should be separated from the administration of psyllium by at least 2 hours.

Psyllium can interfere with the absorption of certain oral drugs if administered concomitantly. For example, psyllium fiber can theoretically adsorb cardiac glycosides [4999] [5802]; oral anticoagulants (e.g., warfarin) [6100] or salicylates [6107]. A response to a single dose of warfarin was not affected by repeated administration (every 2 hours) of psyllium in a group (n=6) of healthy subjects.[6100] Per the psyllium manufacturers, administration of other prescribed oral drugs should be separated from the administration of psyllium by at least 2 hours.

Aspirin, ASA; Butalbital; Caffeine; Codeine (Fiorinal® with Codeine) **and Theophylline, Aminophylline** (Theophylline)

Severity: Moderate

If aspirin; butalbital; caffeine; codeine is used on a chronic basis, monitor for reduced efficacy of concomitantly used drugs that undergo oxidative metabolism, especially drugs with a narrow therapeutic range (e.g., theophylline). Barbiturates, such as butalbital are inducers of cytochrome P450 isoenzymes 1A2, 2C9, 2C19, and 3A4.[4718] However, clinically significant barbiturate enzyme-

induction occurs after several days and may not be clinically significant with short-term use. The extended use of aspirin; butalbital; caffeine; codeine is not recommended, as butalbital is habit-forming and potentially abusable.

Theophylline is primarily metabolized in the liver by the CYP1A2 isoenzyme, and also by the CYP3A4 isoenzyme.[4718] The following drugs can stimulate the hepatic metabolism of theophylline if used concurrently: barbiturates [4722], carbamazepine [4743], ethotoin [4741], phenytoin or fosphenytoin [4742], primidone [4718], and rifampin [4718]. Due to the long half-life of phenobarbital, several days of phenobarbital therapy may be necessary before any effect on theophylline pharmacokinetics is seen. Theophylline doses may need to be increased if any of these drugs are added. More importantly, serious theophylline toxicity can result if any of these drugs are discontinued and the dose of theophylline is not correspondingly decreased. Theophylline, in turn, may inhibit the absorption of phenytoin.

Formoterol (Foradil® Aerolizer) **and Flunisolide**

Severity: Moderate

Methylxanthine derivatives (such as theophylline, aminophylline [5277]) and corticosteroids [3085] may aggravate the hypokalemic effect which could be seen with formoterol.[5038] Consider checking potassium levels if clinically indicated. However, formoterol is commonly used in conjunction with theophylline, aminophylline and corticosteroid therapy.

Formoterol (Foradil® Aerolizer) **and Phenylephrine** (found in Codimal® DH)

Severity: Moderate

If asthma symptoms occur between formoterol controller doses, short-acting beta-2 agonists (e.g., albuterol) may be used safely for the symptomatic relief of acute asthma symptoms.[5038] When beginning treatment with formoterol, patients who have been taking inhaled, short-acting beta-2 agonists on a regular basis (e.g., four times a day) should be instructed to discontinue the regular, scheduled use of these drugs and use them only for the symptomatic relief of acute asthma symptoms. Patients should be cautioned that increasing short-acting inhaled beta-2 agonist use is a signal of deteriorating asthma. Due to the pharmacology of formoterol [5038], the concomitant use of formoterol with other long-acting beta-agonists (e.g., salmeterol-containing products [5197]) is NOT recommended due to the increased risk of adverse cardiovascular effects (considered duplicate therapy). Caution and close observation should be used when formoterol is used concurrently with other adrenergic sympathomimetics, administered by any route, to avoid potential for increased cardiovascular effects based on the pharmacology of formoterol.[5038]

Formoterol (Foradil® Aerolizer) **and Levalbuterol** (Xopenex®)

Severity: High

If asthma symptoms occur between the use of long-acting beta-agonists (e.g., salmeterol or formoterol), short-acting beta$_2$-agonists (e.g., levalbuterol) may be used safely for the symptomatic relief of acute asthma symptoms.[5047] [5197] When beginning treatment with a long-acting beta-agonist, patients who have been taking inhaled, short-acting beta$_2$-agonists on a regular basis (e.g., four times a day) should be instructed to discontinue the regular, scheduled use of these drugs and use them only for the symptomatic relief of acute asthma symptoms. Patients should be cautioned that increasing short-acting inhaled beta$_2$-agonist use is a signal of deteriorating asthma. Due to the pharmacology of levalbuterol [5047], the concomitant use of levalbuterol with other short-acting beta-agonists or short-acting sympathomimetic aerosol bronchodilators is NOT recommended due to the increased risk of adverse cardiovascular effects (considered duplicate therapy). Caution and close observation should also be used when levalbuterol is used concurrently with other adrenergic sympathomimetics, administered by any route, to avoid potential for increased cardiovascular effects.[5047]

If asthma symptoms occur between formoterol controller doses, short-acting beta-2 agonists (e.g., albuterol) may be used safely for the symptomatic relief of acute asthma symptoms.[5038] When beginning treatment with formoterol, patients who have been taking inhaled, short-acting beta-2 agonists on a regular basis (e.g., four times a day) should be instructed to discontinue the regular, scheduled use of these drugs and use them only for the symptomatic relief of acute asthma symptoms. Patients should be cautioned that increasing short-acting inhaled beta-2 agonist use is a signal of deteriorating asthma. Due to the pharmacology of formoterol [5038], the concomitant use of formoterol with other long-acting beta-agonists (e.g., salmeterol-containing products [5197]) is NOT recommended due to the increased risk of adverse cardiovascular effects (considered duplicate therapy). Caution and close observation should be used when formoterol is used concurrently with other adrenergic sympathomimetics, administered by any route, to avoid potential for increased cardiovascular effects based on the pharmacology of formoterol.[5038]

Formoterol (Foradil® Aerolizer) **and Acetaminophen; Chlorpheniramine; Phenylephrine; Phenyltoloxamine** (Norel®SR)

Severity: Moderate

If asthma symptoms occur between formoterol controller doses, short-acting beta-2 agonists (e.g., albuterol) may be used safely for the symptomatic relief of acute asthma symptoms.[5038] When beginning treatment with formoterol, patients who have been taking

inhaled, short-acting beta-2 agonists on a regular basis (e.g., four times a day) should be instructed to discontinue the regular, scheduled use of these drugs and use them only for the symptomatic relief of acute asthma symptoms. Patients should be cautioned that increasing short-acting inhaled beta-2 agonist use is a signal of deteriorating asthma. Due to the pharmacology of formoterol [5038], the concomitant use of formoterol with other long-acting beta-agonists (e.g., salmeterol-containing products [5197]) is NOT recommended due to the increased risk of adverse cardiovascular effects (considered duplicate therapy). Caution and close observation should be used when formoterol is used concurrently with other adrenergic sympathomimetics, administered by any route, to avoid potential for increased cardiovascular effects based on the pharmacology of formoterol.[5038]

Formoterol (Foradil® Aerolizer) **and Propafenone** (Rythmol)

Severity: High

The manufacturer warns that formoterol should be used with extreme caution with drugs known to prolong the QTc interval which may increase the risk of ventricular arrhythmias during beta-agonist therapy.[5038] In addition, beta-agonists should be avoided in patients with congenital long QT syndrome.[4951] Beta-agonists may be associated with adverse cardiovascular effects, usually at higher doses and/or when associated with hypokalemia.[5038] Beta-agonists should be administered with extreme caution to patients being treated with drugs known to prolong the QTc interval because the action of beta-agonists on the cardiovascular system may be potentiated.[5038] [5047] Drugs known to increase the QT interval include Class IA antiarrhythmics, Class III antiarrhythmics, flecainide, and propafenone. In addition to antiarrhythmic drugs, other drugs which can result in QT prolongation include: some antipsychotics (e.g., phenothiazines, pimozide, haloperidol [5036], risperidone, sertindole, ziprasidone [4959]), amoxapine, arsenic trioxide [4952], astemizole [140], bepridil [4953], cisapride [4951], chloroquine, clarithromycin [4964], dasatinib [9211], dolasetron [5036], droperidol [3610] [4951] [4963], erythromycin [328] [4978], halofantrine [4951] [4968], halogenated anesthetics [5187] [5188] [5486] [5487] [5488], levomethadyl, maprotiline, methadone, some quinolone antibiotics (e.g. ofloxacin, gatifloxacin, gemifloxacin, grepafloxacin, levofloxacin, moxifloxacin, sparfloxacin [4951] [4958]), ondansetron [8046], palonosetron [8716], pentamidine [168] [335] [4951], probucol, ranolazine [8747], terfenadine [141] [231], tricyclic antidepressants [5145] [5146], and vorinostat [8046]. This list is not inclusive of all agents known to prolong the QT interval. Tricyclic antidepressants (TCAs) can also potentiate the vascular effects of beta-agonists.

Propafenone is a Class IC antiarrhythmic which increases the QT interval, but largely due to prolongation of the QRS interval.[5014] The use of propafenone in conjunction with other drugs that prolong the QT interval has not been studied and is not recommended by the manufacturer due to potential risk for ventricular tachycardia, including torsade de pointes (TdP) and monomorphic ventricular tachycardia.[5014] According to the manufacturer, propafenone coadministration with tricyclic antidepressants is not recommended.[5014] In addition, drugs which directly prolong the QT interval are not recommended during propafenone therapy. Drugs which have been established to have a causal association with QT prolongation and TdP include: Class IA antiarrhythmics (disopyramide, procainamide, quinidine) [4951] [4952] [5187], Class III antiarrhythmics (amiodarone, bretylium, dofetilide, ibutilide, sotalol) [4951] [4952] [5187], astemizole [140], arsenic trioxide [4951] [4977], bepridil [4951] [4953], cisapride [4951], chloroquine [4951] [4955] [4956], clarithromycin [4951] [4964], droperidol [3610] [4951] [4963], erythromycin [228] [4951] [4978], grepafloxacin [5149], halofantrine [4951] [4968], haloperidol [42] [336] [4951] [5036], levomethadyl [4951] [5079] [5081] [5146], methadone [4951] [5048] [5049] [5050] [5051], pentamidine [168] [335] [4951] [5149], certain phenothiazines (chlorpromazine [4951], mesoridazine [4951] [5831], and thioridazine [4951] [5022]), pimozide [4951], probucol [5145], sparfloxacin [4951] [4958], and terfenadine [141] [231]. Other agents associated with a lower, but possible risk for QT prolongation and TdP based on varying levels of documentation (see separate drug monographs) include: abarelix [5392], alfuzosin [4988], amoxapine [5145], apomorphine [5136], beta-agonists [4951] [5038] [5047], ofloxacin [7501], ciprofloxacin [4951] [5149] [5496] [5507] [6579], clozapine [5146], cyclobenzaprine [5155] [5156], dasatinib [9211], dolasetron [5037], gatifloxacin [5149] [5150] [5152], gemifloxacin [5154], halogenated anesthetics [5187] [5188] [5486] [5487] [5488], levofloxacin [5149] [5150] [5151], local anesthetics, maprotiline [5145], mefloquine [6617] [7535], moxifloxacin [5149] [5150] [5153], olanzapine [9575] [9576], ondansetron [8046], norfloxacin [6564], octreotide [4951], palonosetron [5148], some phenothiazines (fluphenazine [5145], perphenazine [5145], prochlorperazine [5145], and trifluoperazine [5145]), propafenone [5014] [5146], ranolazine [8747], risperidone [4951] [5144], sertindole [5187], tacrolimus [4049] [4050] [4951], telithromycin [4880], tricyclic antidepressants when given in excessive doses or overdosage [5145] [5146], troleandomycin (based on interactions with macrolides) [5149], vardenafil [4942], vorinostat [9633], or ziprasidone [4959]. This list is not inclusive of all agents that can cause QT interval prolongation. In addition, some of the listed drugs are CYP2D6 inhibitors (e.g., amiodarone, chloroquine, chlorpromazine, haloperidol, perphenazine, quinidine, ranolazine, and thioridazine) with potential to inhibit the metabolism of propafenone. In addition to potential for additive QT prolongation, concomitant administration of propafenone with desipramine (tricyclic antidepressant) may result in elevated serum desipramine levels.[5014] In addition to avoiding concurrent drug interactions, the potential for TdP can be reduced by avoiding the use of QT prolonging drugs in patients at substantial risk for TdP.[5162] Examples of general risk factors for TdP include congenital long QT syndrome, female sex, elderly patients, significant bradycardia, hypokalemia, hypomagnesemia, and underlying cardiac disease (e.g., arrhythmias, cardiomyopathy, acute myocardial ischemia).

Formoterol (Foradil® Aerolizer) **and Theophylline, Aminophylline** (Theophylline)

Severity: Moderate

Methylxanthine derivatives (such as theophylline, aminophylline [5277]) and corticosteroids [3085] may aggravate the hypokalemic effect which could be seen with formoterol.[5038] Consider checking potassium levels if clinically indicated. However, formoterol is commonly used in conjunction with theophylline, aminophylline and corticosteroid therapy.

Methylxanthine derivatives, (such as theophylline [5277] and aminophylline) and corticosteroids [3085] may aggravate the hypokalemic effect that may be seen with beta-agonists.[5197] Consider checking potassium levels if clinically indicated. However, beta-agonists are commonly used in conjunction with aminophylline, theophylline, and corticosteroid therapy.[5197]

Alendronate (Fosamax®) **and Ranitidine** (Zantac 150™)

Severity: Moderate

Although the clinical significance has not been determined, the bioavailability of oral alendronate is doubled by concomitant administration of intravenous ranitidine.[5375] Investigations have not been undertaken to determine if other H_2-antagonists have a similar effect on bioavailability.[5375] Patients should be closely monitored when antiulcer medications, such as proton pump inhibitors (PPIs), gastric mucosal agents, and H2-blockers, or other medications for GI disorders, are coadministered as they may affect the bioavailability of alendronate, leading to a higher likelihood of developing GI adverse effects while taking alendronate.

Alendronate (Fosamax®) **and Magnesium Salts** (found in Calcium Magnesium Zinc Tablets)

Severity: Moderate

Antacids are likely to interfere with the absorption of alendronate. At least 30 minutes should elapse after an alendronate dose before taking antacids or any other drugs.[5375] Concomitant administration of oral alendronate with vitamin supplements; mineral supplements; or other medications that contain calcium salts (e.g., calcium carbonate), iron salts such as ferrous sulfate or polysaccharide-iron complex, aluminum salts (i.e., aluminum hydroxide), or magnesium salts may interfere with the absorption of alendronate.[5375] Even though calcium salts are not to be administered with alendronate, patients need to maintain an adequate intake of calcium and vitamin D to avoid hypocalcemia. Due to the action of alendronate on bone, hypocalcemia and associated adverse effects can develop. The ingestion of high-calcium foods can interfere with the absorption of alendronate, and should not be eaten before, or for at least 30 minutes after, administration of alendronate.

Carbinoxamine (Histex™ I/E) **and Clonazepam** (Klonopin®)

Severity: Moderate

Carbinoxamine has potential for CNS depressant effects.[7585] An enhanced CNS depressant effect may occur when carbinoxamine is combined with other CNS depressants including anxiolytics, sedatives, and hypnotics (including barbiturates and benzodiazepines), butorphanol, entacapone, ethanol [6341], haloperidol, general anesthetics, nalbuphine, opiate agonists, pentazocine, pramipexole, pregabalin [7523], risperidone, ropinirole, tolcapone, trazodone, tramadol, or other sedating H_1-blockers [6568].

Concomitant administration of clonazepam with other CNS-depressant drugs [7168], including barbiturates, buprenorphine, butorphanol, dronabinol, THC [7185], entacapone [5769], ethanol [7198], sedating H_1-blockers, general anesthetics [6892], nabilone [9044], nalbuphine [6778], opiate agonists, pentazocine, phenothiazines, pregabalin [7523], tolcapone, tramadol, tricyclic antidepressants, or other anxiolytics, sedatives, and hypnotics, can potentiate the CNS effects (i.e., increased sedation or respiratory depression) of either agent.[5174]

Carbinoxamine (Histex™ I/E) **and Ipratropium** (Atrovent®)

Severity: Moderate

Carbinoxamine has mild anticholinergic effects.[7585] The anticholinergic effects of carbinoxamine may be significant and may be enhanced when combined with antimuscarinics [6338]. Other commonly used drugs with moderate to significant anticholinergic effects include amantadine, amoxapine, clozapine, cyclobenzaprine, disopyramide, maprotiline, olanzapine, orphenadrine, most phenothiazines, and most tricyclic antidepressants. Clinicians should note that antimuscarinic effects might not only be seen on GI smooth muscle, but also on bladder function, the eye, and temperature regulation. With many of the listed agents, additive drowsiness may also occur when combined with sedating antihistamines.

Carbinoxamine (Histex™ I/E) **and Acetaminophen; Oxycodone** (Percocet®)

Severity: Moderate

Carbinoxamine has potential for CNS depressant effects.[7585] An enhanced CNS depressant effect may occur when carbinoxamine is combined with other CNS depressants including anxiolytics, sedatives, and hypnotics (including barbiturates and benzodiazepines),

butorphanol, entacapone, ethanol [6341], haloperidol, general anesthetics, nalbuphine, opiate agonists, pentazocine, pramipexole, pregabalin [7523], risperidone, ropinirole, tolcapone, trazodone, tramadol, or other sedating H_1-blockers [6568].

Concomitant use of oxycodone with sedating H_1-blockers can potentiate respiratory depression and/or sedation. In addition, chlorpheniramine and diphenhydramine inhibit CYP2D6, an enzyme responsible for the metabolism of oxycodone to oxymorphone, which represents < 15% of the total administered dose.[4718] Close monitoring for potential side effects in patients receiving oxycodone and chlorpheniramine or diphenhydramine is recommended.

Carbinoxamine (Histex™ I/E) **and Albuterol; Ipratropium** (Combivent®)

Severity: Moderate

Carbinoxamine has mild anticholinergic effects.[7585] The anticholinergic effects of carbinoxamine may be significant and may be enhanced when combined with antimuscarinics [6338]. Other commonly used drugs with moderate to significant anticholinergic effects include amantadine, amoxapine, clozapine, cyclobenzaprine, disopyramide, maprotiline, olanzapine, orphenadrine, most phenothiazines, and most tricyclic antidepressants. Clinicians should note that antimuscarinic effects might not only be seen on GI smooth muscle, but also on bladder function, the eye, and temperature regulation. With many of the listed agents, additive drowsiness may also occur when combined with sedating antihistamines.

Carbinoxamine (Histex™ I/E) **and Doxylamine** (Unisom® Sleeptabs™)

Severity: High

Carbinoxamine has potential for CNS depressant effects.[7585] An enhanced CNS depressant effect may occur when carbinoxamine is combined with other CNS depressants including anxiolytics, sedatives, and hypnotics (including barbiturates and benzodiazepines), butorphanol, entacapone, ethanol [6341], haloperidol, general anesthetics, nalbuphine, opiate agonists, pentazocine, pramipexole, pregabalin [7523], risperidone, ropinirole, tolcapone, trazodone, tramadol, or other sedating H_1-blockers [6568].

Because doxylamine causes sedation,[7801] an enhanced CNS depressant effect may occur when it is combined with other other sedating H_1-blockers [6568] or with cetirizine [5607]. Due to the duplicative pharmacology and potential for additive side effects, combination of doxylamine with other antihistamines is not generally recommended.

Carbinoxamine (Histex™ I/E) **and Acetaminophen; Chlorpheniramine; Phenylephrine; Phenyltoloxamine** (Norel®SR)

Severity: High

Carbinoxamine has potential for CNS depressant effects.[7585] An enhanced CNS depressant effect may occur when carbinoxamine is combined with other CNS depressants including anxiolytics, sedatives, and hypnotics (including barbiturates and benzodiazepines), butorphanol, entacapone, ethanol [6341], haloperidol, general anesthetics, nalbuphine, opiate agonists, pentazocine, pramipexole, pregabalin [7523], risperidone, ropinirole, tolcapone, trazodone, tramadol, or other sedating H_1-blockers [6568].

Acetaminophen; chlorpheniramine; phenylephrine; phenyltoloxamine may cause CNS depression. An enhanced CNS depressant effect may occur when this product is combined with other CNS depressants [9107] including anxiolytics, sedatives, and hypnotics, barbiturates, buprenorphine, butorphanol, dronabinol, THC, droperidol, entacapone, ethanol, haloperidol, general anesthetics, mirtazapine, molindone, nalbuphine, nefazodone, opiate agonists, pentazocine, pimozide, pramipexole, pregabalin [7523], quetiapine, risperidone, ropinirole, skeletal muscle relaxants, tolcapone, trazodone, tramadol, or with other products containing sedating H_1-blockers. Additionally, concurrent use of dronabinol, THC with sympathomimetics such as phenylephrine may result in additive hypertension, tachycardia, and possibly cardiotoxicity.[3868] The risk of developing hepatotoxicity from acetaminophen appears to be increased in patients who regularly consume ethanol. In these patients, hepatotoxicity is possible even at normal, therapeutic dosages of acetaminophen.[1654] Acute or chronic ethanol use increases acetaminophen-induced hepatotoxicity by inducing CYP2E, leading to increased formation of the hepatotoxic metabolite of acetaminophen.[583] Administration of acetaminophen should be limited or avoided altogether in patients with alcoholism or patients who consume ethanol regularly.[4934]

Clonazepam (Klonopin®) **and Acetaminophen; Oxycodone** (Percocet®)

Severity: Moderate

Concomitant administration of clonazepam with other CNS-depressant drugs [7168], including barbiturates, buprenorphine, butorphanol, dronabinol, THC [7185], entacapone [5769], ethanol [7198], sedating H_1-blockers, general anesthetics [6892], nabilone [9044], nalbuphine [6778], opiate agonists, pentazocine, phenothiazines, pregabalin [7523], tolcapone, tramadol, tricyclic antidepressants, or other anxiolytics, sedatives, and hypnotics, can potentiate the CNS effects (i.e., increased sedation or respiratory depression) of either agent.[5174]

Concomitant use of acetaminophen-oxycodone with other CNS depressants can potentiate the respiratory depression and/or sedation effects of both of these agents. CNS depressants include amitriptyline, amoxapine, anxiolytics, sedatives, and hypnotics, clomipramine, clozapine, doxepin, dronabinol, THC, droperidol, entacapone, ethotoin, fosphenytoin, general anesthetics, sedating H_1-blockers, haloperidol, imipramine, MAOIs, maprotiline, mirtazapine, molindone, nabilone [9044], nefazodone, nortriptyline, olanzapine, other opiate agonists, phenothiazines, phenytoin, pimozide, pramipexole, pregabalin, quetiapine, risperidone, ropinirole, skeletal muscle relaxants, tolcapone, tramadol, and trazodone.

Clonazepam (Klonopin®) **and Doxylamine** (Unisom® Sleeptabs™)

Severity: High

Concomitant administration of clonazepam with other CNS-depressant drugs [7168], including barbiturates, buprenorphine, butorphanol, dronabinol, THC [7185], entacapone [5769], ethanol [7198], sedating H_1-blockers, general anesthetics [6892], nabilone [9044], nalbuphine [6778], opiate agonists, pentazocine, phenothiazines, pregabalin [7523], tolcapone, tramadol, tricyclic antidepressants, or other anxiolytics, sedatives, and hypnotics, can potentiate the CNS effects (i.e., increased sedation or respiratory depression) of either agent.[5174]

Because doxylamine can cause pronounced sedation,[7801] an enhanced CNS depressant effect may occur when it is combined with other CNS depressants [6568] including anxiolytics, sedatives, and hypnotics (such as barbiturates and benzodiazepines) [6946] [6948], buprenorphine [5278], butorphanol [5912], carisoprodol, clozapine [4989], dronabinol, THC, droperidol [5468], entacapone [5769], ethanol [6341] [6948], general anesthetics [6892], haloperidol [5036], methocarbamol, mirtazapine [5366], molindone [5553], nabilone [9044], nalbuphine [6778], nefazodone [5414], olanzapine [5517], opiate agonists, pentazocine [6777], phenothiazines [6946], pimozide [5250], pramipexole [7757], pregabalin [7523], procarbazine [5356], quetiapine [5855], risperidone [5144], ropinirole [8018], tolcapone [5578], tramadol [5043], trazodone [5450], tricyclic antidepressants [6947], or with other sedating H_1-blockers [6568]. In addition, concurrent use of cannabinoids with sedating H_1-blockers may result in additive tachycardia, which may be pronounced.

Clonazepam (Klonopin®) **and Acetaminophen; Chlorpheniramine; Phenylephrine; Phenyltoloxamine** (Norel®SR)

Severity: Moderate

Concomitant administration of clonazepam with other CNS-depressant drugs [7168], including barbiturates, buprenorphine, butorphanol, dronabinol, THC [7185], entacapone [5769], ethanol [7198], sedating H_1-blockers, general anesthetics [6892], nabilone [9044], nalbuphine [6778], opiate agonists, pentazocine, phenothiazines, pregabalin [7523], tolcapone, tramadol, tricyclic antidepressants, or other anxiolytics, sedatives, and hypnotics, can potentiate the CNS effects (i.e., increased sedation or respiratory depression) of either agent.[5174]

Acetaminophen; chlorpheniramine; phenylephrine; phenyltoloxamine may cause CNS depression. An enhanced CNS depressant effect may occur when this product is combined with other CNS depressants [9107] including anxiolytics, sedatives, and hypnotics, barbiturates, buprenorphine, butorphanol, dronabinol, THC, droperidol, entacapone, ethanol, haloperidol, general anesthetics, mirtazapine, molindone, nalbuphine, nefazodone, opiate agonists, pentazocine, pimozide, pramipexole, pregabalin [7523], quetiapine, risperidone, ropinirole, skeletal muscle relaxants, tolcapone, trazodone, tramadol, or with other products containing sedating H_1-blockers. Additionally, concurrent use of dronabinol, THC with sympathomimetics such as phenylephrine may result in additive hypertension, tachycardia, and possibly cardiotoxicity.[3868] The risk of developing hepatotoxicity from acetaminophen appears to be increased in patients who regularly consume ethanol. In these patients, hepatotoxicity is possible even at normal, therapeutic dosages of acetaminophen.[1654] Acute or chronic ethanol use increases acetaminophen-induced hepatotoxicity by inducing CYP2E, leading to increased formation of the hepatotoxic metabolite of acetaminophen.[583] Administration of acetaminophen should be limited or avoided altogether in patients with alcoholism or patients who consume ethanol regularly.[4934]

Clonazepam (Klonopin®) **and Theophylline, Aminophylline** (Theophylline)

Severity: Moderate

Theophylline has been reported to counteract the pharmacodynamic effects (e.g., sedative and anxiolytic effects) of diazepam.[4764] A proposed mechanism is competitive binding of theophylline to adenosine receptors in the brain. Whether a similar interaction occurs with other benzodiazepines is not known. If theophylline therapy is initiated or discontinued, monitor the clinical response to benzodiazepines.

Theophylline has been reported to counteract the pharmacodynamic effects (e.g., sedative and anxiolytic effects) of diazepam. A proposed mechanism is competitive binding of theophylline to adenosine receptors in the brain. Whether a similar interaction occurs with other benzodiazepines is not known. If theophylline therapy is initiated or discontinued, monitor the clinical response to benzodiazepines.[4764]

Clonazepam (Klonopin®) **and Verapamil**

Severity: Moderate

CYP3A4 inhibitors may reduce the metabolism of clonazepam and increase the potential for benzodiazepine toxicity.[5174] Examples of CYP3A4 inhibitors include: amiodarone [5629], anti-retroviral protease inhibitors [4718], systemic azole antifungals, cimetidine, clarithromycin [4718], dalfopristin; quinupristin [5221], delavirdine [4718] [1800], diltiazem [4718], efavirenz (inducer or inhibitor) [4718], erythromycin [4718], fluoxetine [6130] [5915], fluvoxamine [6130] [649], imatinib, STI-571 [4718], nefazodone [4718], nicardipine (weak) [4718], ranolazine [8747], troleandomycin [4718], verapamil [4718], zafirlukast [4718], and zileuton [5415]. This list is not inclusive of all CYP3A4 inhibitors. In addition, telithromycin [4880], a ketolide antibiotic, can theoretically compete with clonazepam for metabolism by CYP3A4. Monitor patients closely who receive concurrent therapy.

A clinically significant interaction has occurred with verapamil (CYP3A4 inhibitor) and oral midazolam (CYP3A4 substrate).[647] When verapamil and midazolam are coadministered, the AUC and half-life of midazolam are increased and the associated sedation is more pronounced.[647] The significance of an interaction between verapamil and IV midazolam is uncertain, however, but may be less significant due to absence of an effect by verapamil on presystemic midazolam clearance. Verapamil inhibits CYP3A4 metabolism [4718] [5000], and therefore may inhibit the metabolism of other oxidized benzodiazepines (e.g., alprazolam [4718], chlordiazepoxide [5286], clonazepam [4718], clorazepate [4718], diazepam [4718], estazolam [7167], flurazepam [4718], prazepam [4718], quazepam [7807], and triazolam [4718]).

Clonazepam (Klonopin®) **and Melatonin**

Severity: Moderate

It appears prudent to recommend caution when clonazepam is prescribed in conjunction with melatonin. In animal studies, melatonin has been shown to increase benzodiazepine binding to receptor sites, and this may result in clinically significant drug interactions. Case reports exist of concomitant benzodiazepine and melatonin use in humans; the cases resulted in lethargy, short-term amnestic responses, or prolonged benzodiazepine activity. These apparent interactions could have been the result of a pharmacokinetic or pharmacodynamic enhancement of benzodiazepine activity by melatonin.

In animal studies, melatonin has been shown to increase benzodiazepine binding to receptor sites, and this may result in clinically significant drug interactions. One case report noted that nightly melatonin administration allowed a benzodiazepine-dependent woman with an 11 year history of insomnia to wean and discontinue her benzodiazepine prescription within a few days without rebound insomnia or apparent benzodiazepine withdrawal.[2106] Another case report of excessive melatonin ingestion along with normal doses of chlordiazepoxide and amitriptyline resulted in lethargy and short-term amnestic responses.[2107] (see Adverse Reactions). Both cases could have been the result of a pharmacokinetic or pharmacodynamic enhancement of benzodiazepine activity by melatonin. Until more data are available, use caution when combining melatonin with other traditional anxiolytics, sedatives, and hypnotics, including benzodiazepines. Additionally, melatonin should not be combined with the use of ramelteon until interaction studies demonstrate safety. These two agents may be used for similar indications (quicker sleep onset) and the combined use could produce additive sedative effects or additive adverse effects.

Melatonin and Amlodipine (Norvasc®)

Severity: High

Melatonin may impair the efficacy of some calcium-channel blockers, and caution is advised with concurrent use. In one placebo-controlled study, melatonin ingestion led to significant increases in blood pressure throughout the day in patients taking nifedipine.[3549] The mechanism of this interaction is unclear. It may be prudent to avoid melatonin use during calcium-channel blocker therapy.

Melatonin may impair the efficacy of some calcium-channel blockers, and caution is advised with concurrent use. In one placebo-controlled study, melatonin evening ingestion led to significant increases in blood pressure (6.5 mmHg systolic and 4.9 mmHg diastolic) and heart rate (3.9 bpm) throughout the day in patients taking nifedipine (GITS formulation).[3549] Melatonin appeared to antagonize the antihypertensive effects of nifedipine. The mechanism of this interaction is unclear. It may be prudent to avoid melatonin use during calcium-channel blocker therapy.

Melatonin and Diphenhydramine

Severity: Moderate

In animal studies, melatonin has been shown to increase benzodiazepine binding to receptor sites, and this may result in clinically significant drug interactions. One case report noted that nightly melatonin administration allowed a benzodiazepine-dependent woman with an 11 year history of insomnia to wean and discontinue her benzodiazepine prescription within a few days without rebound insomnia or apparent benzodiazepine withdrawal.[2106] Another case report of excessive melatonin ingestion along with normal doses of chlordiazepoxide and amitriptyline resulted in lethargy and short-term amnestic responses.[2107] (see Adverse Reactions).

Both cases could have been the result of a pharmacokinetic or pharmacodynamic enhancement of benzodiazepine activity by melatonin. Until more data are available, use caution when combining melatonin with other traditional anxiolytics, sedatives, and hypnotics, including benzodiazepines. Additionally, melatonin should not be combined with the use of ramelteon until interaction studies demonstrate safety. These two agents may be used for similar indications (quicker sleep onset) and the combined use could produce additive sedative effects or additive adverse effects.

Melatonin and Verapamil

Severity: High

Melatonin may impair the efficacy of some calcium-channel blockers, and caution is advised with concurrent use. In one placebo-controlled study, melatonin ingestion led to significant increases in blood pressure throughout the day in patients taking nifedipine.[3549] The mechanism of this interaction is unclear. It may be prudent to avoid melatonin use during calcium-channel blocker therapy.

Melatonin may impair the efficacy of some calcium-channel blockers, and caution is advised with concurrent use. In one placebo-controlled study, melatonin evening ingestion led to significant increases in blood pressure (6.5 mmHg systolic and 4.9 mmHg diastolic) and heart rate (3.9 bpm) throughout the day in patients taking nifedipine (GITS formulation).[3549] Melatonin appeared to antagonize the antihypertensive effects of nifedipine. The mechanism of this interaction is unclear. It may be prudent to avoid melatonin use during calcium-channel blocker therapy.

Melatonin and Aspirin, ASA; Butalbital; Caffeine; Codeine (Fiorinal® with Codeine)

Severity: Moderate

In animal studies, melatonin has been shown to increase benzodiazepine binding to receptor sites, and this may result in clinically significant drug interactions. One case report noted that nightly melatonin administration allowed a benzodiazepine-dependent woman with an 11 year history of insomnia to wean and discontinue her benzodiazepine prescription within a few days without rebound insomnia or apparent benzodiazepine withdrawal.[2106] Another case report of excessive melatonin ingestion along with normal doses of chlordiazepoxide and amitriptyline resulted in lethargy and short-term amnestic responses.[2107] (see Adverse Reactions). Both cases could have been the result of a pharmacokinetic or pharmacodynamic enhancement of benzodiazepine activity by melatonin. Until more data are available, use caution when combining melatonin with other traditional anxiolytics, sedatives, and hypnotics, including benzodiazepines. Additionally, melatonin should not be combined with the use of ramelteon until interaction studies demonstrate safety. These two agents may be used for similar indications (quicker sleep onset) and the combined use could produce additive sedative effects or additive adverse effects.

Melatonin and Atropine; Hyoscyamine; Phenobarbital; Scopolamine (Donnatal®)

Severity: Moderate

In animal studies, melatonin has been shown to increase benzodiazepine binding to receptor sites, and this may result in clinically significant drug interactions. One case report noted that nightly melatonin administration allowed a benzodiazepine-dependent woman with an 11 year history of insomnia to wean and discontinue her benzodiazepine prescription within a few days without rebound insomnia or apparent benzodiazepine withdrawal.[2106] Another case report of excessive melatonin ingestion along with normal doses of chlordiazepoxide and amitriptyline resulted in lethargy and short-term amnestic responses.[2107] (see Adverse Reactions). Both cases could have been the result of a pharmacokinetic or pharmacodynamic enhancement of benzodiazepine activity by melatonin. Until more data are available, use caution when combining melatonin with other traditional anxiolytics, sedatives, and hypnotics, including benzodiazepines. Additionally, melatonin should not be combined with the use of ramelteon until interaction studies demonstrate safety. These two agents may be used for similar indications (quicker sleep onset) and the combined use could produce additive sedative effects or additive adverse effects.

Melatonin and Doxylamine (Unisom® Sleeptabs™)

Severity: Moderate

In animal studies, melatonin has been shown to increase benzodiazepine binding to receptor sites, and this may result in clinically significant drug interactions. One case report noted that nightly melatonin administration allowed a benzodiazepine-dependent woman with an 11 year history of insomnia to wean and discontinue her benzodiazepine prescription within a few days without rebound insomnia or apparent benzodiazepine withdrawal.[2106] Another case report of excessive melatonin ingestion along with normal doses of chlordiazepoxide and amitriptyline resulted in lethargy and short-term amnestic responses.[2107] (see Adverse Reactions). Both cases could have been the result of a pharmacokinetic or pharmacodynamic enhancement of benzodiazepine activity by melatonin. Until more data are available, use caution when combining melatonin with other traditional anxiolytics, sedatives, and hypnotics, including benzodiazepines. Additionally, melatonin should not be combined with the use of ramelteon until interaction studies demonstrate safety. These two agents may be used for similar indications (quicker sleep onset) and the combined use could produce additive sedative effects or additive adverse effects.

Acetaminophen; Chlorpheniramine; Phenylephrine; Phenyltoloxamine (Norel®SR) **and Amlodipine** (Norvasc®)

Severity: Moderate

The cardiovascular effects of sympathomimetics such as phenylephrine may reduce the effectiveness of antihypertensive agents such as reserpine, alpha-blockers, beta-blockers, central-acting adrenergic agents (e.g., clonidine, guanfacine, guanabenz, methyldopa), mecamylamine, and treprostinil.[2843] [6289] In addition, the alpha-receptor agonist effects of phenylephrine may be more pronounced with concurrent beta-blocker therapy. The effect of unopposed alpha vasoconstriction can result in hypertension and/or reflex bradycardia. The effect may be more likely to occur with non-selective beta-blockers like propranolol. Blood pressure and heart rates should be monitored closely in patients receiving acetaminophen; chlorpheniramine; phenylephrine; phenyltoloxamine to confirm that the desired antihypertensive effect is achieved.

Acetaminophen; Chlorpheniramine; Phenylephrine; Phenyltoloxamine (Norel®SR) **and Ipratropium** (Atrovent®)

Severity: Moderate

Acetaminophen; chlorpheniramine; phenylephrine; phenyltoloxamine may interact with medications from a variety of classes due to the anticholinergic effects of chlorpheniramine or phenyltoloxamine and the sympathomimetic effects of phenylephrine.[9107] An interaction may occur when this product is combined with other drugs with anticholinergic activity, like the antimuscarinics.[6338] Commonly used drugs with moderate to significant anticholinergic effects include amantadine, amoxapine, clozapine, cyclobenzaprine, disopyramide, maprotiline, olanzapine, orphenadrine, most phenothiazines, and most tricyclic antidepressants. Clinicians should note that antimuscarinic effects might be seen not only on GI smooth muscle, but also on bladder function, the eye, and temperature regulation. With many of the listed agents, additive drowsiness may also occur when combined with chlorpheniramine and phenyltoloxamine. Additionally, the sympathomimetic effects of phenylephrine may interact with tricyclic antidepressants [5287] and maprotiline [5491], resulting in severe cardiovascular effects including arrhythmias, severe hypertension, hyperpyrexia, and/or severe headaches.

Acetaminophen; Chlorpheniramine; Phenylephrine; Phenyltoloxamine (Norel®SR) **and Verapamil**

Severity: Moderate

The cardiovascular effects of sympathomimetics such as phenylephrine may reduce the effectiveness of antihypertensive agents such as reserpine, alpha-blockers, beta-blockers, central-acting adrenergic agents (e.g., clonidine, guanfacine, guanabenz, methyldopa), mecamylamine, and treprostinil.[2843] [6289] In addition, the alpha-receptor agonist effects of phenylephrine may be more pronounced with concurrent beta-blocker therapy. The effect of unopposed alpha vasoconstriction can result in hypertension and/or reflex bradycardia. The effect may be more likely to occur with non-selective beta-blockers like propranolol. Blood pressure and heart rates should be monitored closely in patients receiving acetaminophen; chlorpheniramine; phenylephrine; phenyltoloxamine to confirm that the desired antihypertensive effect is achieved.

Acetaminophen; Chlorpheniramine; Phenylephrine; Phenyltoloxamine (Norel®SR) **and Acetaminophen; Oxycodone** (Percocet®)

Severity: Moderate

Acetaminophen; chlorpheniramine; phenylephrine; phenyltoloxamine may cause CNS depression. An enhanced CNS depressant effect may occur when this product is combined with other CNS depressants [9107] including anxiolytics, sedatives, and hypnotics, barbiturates, buprenorphine, butorphanol, dronabinol, THC, droperidol, entacapone, ethanol, haloperidol, general anesthetics, mirtazapine, molindone, nalbuphine, nefazodone, opiate agonists, pentazocine, pimozide, pramipexole, pregabalin [7523], quetiapine, risperidone, ropinirole, skeletal muscle relaxants, tolcapone, trazodone, tramadol, or with other products containing sedating H_1-blockers. Additionally, concurrent use of dronabinol, THC with sympathomimetics such as phenylephrine may result in additive hypertension, tachycardia, and possibly cardiotoxicity.[3868] The risk of developing hepatotoxicity from acetaminophen appears to be increased in patients who regularly consume ethanol. In these patients, hepatotoxicity is possible even at normal, therapeutic dosages of acetaminophen.[1654] Acute or chronic ethanol use increases acetaminophen-induced hepatotoxicity by inducing CYP2E, leading to increased formation of the hepatotoxic metabolite of acetaminophen.[583] Administration of acetaminophen should be limited or avoided altogether in patients with alcoholism or patients who consume ethanol regularly.[4934]

Concomitant use of oxycodone with sedating H_1-blockers can potentiate respiratory depression and/or sedation. In addition, chlorpheniramine and diphenhydramine inhibit CYP2D6, an enzyme responsible for the metabolism of oxycodone to oxymorphone, which represents < 15% of the total administered dose.[4718] Close monitoring for potential side effects in patients receiving oxycodone and chlorpheniramine or diphenhydramine is recommended.

Acetaminophen; Chlorpheniramine; Phenylephrine; Phenyltoloxamine (Norel®SR) **and Caffeine; Ergotamine** (Cafergot®)

Severity: Very High. This drug combination should be avoided.

Some ergot alkaloids [5066], notably ergotamine and, to a lesser extent, ergonovine, may produce peripheral vasoconstriction due to alpha-receptor agonist effects in the peripheral circulation. Although no data are available, it is possible that concomitant use of phenylephrine with ergotamine could cause additive and possibly severe peripheral vasoconstriction. Similar problems have been observed when ergot alkaloids were used in combination with other drugs known to cause peripheral vasoconstriction (e.g., ergonovine with dopamine; ergotamine with propranolol). Hypertension, headache, myocardial ectopy, and seizures have occurred when bromocriptine, an ergot derivative, was combined with various sympathomimetics. Acetaminophen; chlorpheniramine; phenylephrine; phenyltoloxamine use should be avoided in patients receiving ergot alkaloids or bromocriptine whenever possible.[5066]

Acetaminophen; Chlorpheniramine; Phenylephrine; Phenyltoloxamine (Norel®SR) **and Doxylamine** (Unisom® Sleeptabs™)

Severity: High

Acetaminophen; chlorpheniramine; phenylephrine; phenyltoloxamine may cause CNS depression. An enhanced CNS depressant effect may occur when this product is combined with other CNS depressants [9107] including anxiolytics, sedatives, and hypnotics, barbiturates, buprenorphine, butorphanol, dronabinol, THC, droperidol, entacapone, ethanol, haloperidol, general anesthetics, mirtazapine, molindone, nalbuphine, nefazodone, opiate agonists, pentazocine, pimozide, pramipexole, pregabalin [7523], quetiapine, risperidone, ropinirole, skeletal muscle relaxants, tolcapone, trazodone, tramadol, or with other products containing sedating H_1-blockers. Additionally, concurrent use of dronabinol, THC with sympathomimetics such as phenylephrine may result in additive hypertension, tachycardia, and possibly cardiotoxicity.[3868] The risk of developing hepatotoxicity from acetaminophen appears to be increased in patients who regularly consume ethanol. In these patients, hepatotoxicity is possible even at normal, therapeutic dosages of acetaminophen.[1654] Acute or chronic ethanol use increases acetaminophen-induced hepatotoxicity by inducing CYP2E, leading to increased formation of the hepatotoxic metabolite of acetaminophen.[583] Administration of acetaminophen should be limited or avoided altogether in patients with alcoholism or patients who consume ethanol regularly.[4934]

Because doxylamine causes sedation,[7801] an enhanced CNS depressant effect may occur when it is combined with other other sedating H_1-blockers [6568] or with cetirizine [5607]. Due to the duplicative pharmacology and potential for additive side effects, combination of doxylamine with other antihistamines is not generally recommended.

Acetaminophen; Chlorpheniramine; Phenylephrine; Phenyltoloxamine (Norel®SR) **and Theophylline, Aminophylline** (Theophylline)

Severity: High

Concurrent administration of caffeine, a CNS stimulant [4666], with phenylephrine-containing products can produce excessive stimulatory effects such as nervousness, irritability, insomnia, or tremor. Other xanthines, such as theophylline or dyphylline, can interact in a similar way.[5241] Excessive caffeine ingestion should be avoided while taking phenylephrine products concurrently. This includes ingestion of foods and beverages that contain high amounts of caffeine such as coffee, teas, green tea, colas, and chocolate and dietary supplements such as guarana [4679].

Concurrent administration of theophylline or aminophylline with some sympathomimetics can produce excessive stimulation and effects such as nervousness, irritability, or insomnia. Seizures or cardiac arrhythmias are also possible. The herbal sympathomimetic ephedra, Ma huang may potentially increase the risk of developing cardiac arrhythmias if this herb is taken with theophylline.[5241]

Amlodipine (Norvasc®) **and Verapamil**

Severity: Moderate

Diltiazem (CYP3A4 inhibitor) may increase the plasma level of amlodipine via CYP3A4 inhibition [5004], and because both drugs reduce blood pressure [5004] [5825], additive hypotensive effects may occur. Other examples of CYP3A4 inhibitors which theoretically may decrease the hepatic metabolism of amlodipine (a CYP3A4 substrate) include: amiodarone [5629], anti-retroviral protease inhibitors [4718], aprepitant [7438], systemic azole antifungals [4718], clarithromycin [4718], dalfopristin; quinupristin [5221], delavirdine [4718], diltiazem [4718], efavirenz (inducer or inhibitor) [5172], erythromycin [4718], fluoxetine [4718], fluvoxamine [4718], mifepristone, RU-486 [4718], nefazodone [4718], troleandomycin [4718], verapamil [4718], zafirlukast [4948], and zileuton [5415]. This list is not inclusive of all CYP3A4 inhibitors. Coadministration of cimetidine (a nonspecific cytochrome P-450 inhibitor) with amlodipine does not change the pharmacokinetics of amlodipine.[5825] Caution should be used when CYP3A4 inhibitors are co-administered with calcium-channel blockers; monitor therapeutic response.

Clinicians should be aware that food interactions with some calcium channel blockers are possible.[5822] Grapefruit juice contains an unknown compound that can inhibit the cytochrome P-450 CYP3A4 isozyme in the gut wall. Grapefruit juice can increase the serum concentrations and oral bioavailability of most calcium-channel blockers (e.g., amlodipine, felodipine, nicardipine, nifedipine, nimodipine, nisoldipine, and verapamil); no significant effect on diltiazem bioavailability has been reported. Compared to orange juice, co-administration of oral verapamil with grapefruit juice significantly increases the AUC and peak plasma concentrations of verapamil

(both isomers affected, with a 36% AUC increase in the S-isomer vs. 28% for the R-isomer); the half-life and renal clearance of verapamil are not affected.[5633] To avoid increased drug bioavailability, it is generally recommended to avoid grapefruit juice during calcium-channel blocker therapy.

Amlodipine can have additive hypotensive effects with other antihypertensive agents [5825] including alpha-blockers, other calcium-channel blockers, vasodilators, and diuretics. This additive effect can be desirable, but the patient should be monitored carefully and the dosage should be adjusted based on clinical response. The concomitant use of dihydropyridine calcium-channel blockers and beta-blockers can reduce angina and improve exercise tolerance. When these drugs are given together, however, hypotension and impaired cardiac performance can occur, especially in patients with left ventricular dysfunction, cardiac arrhythmias, or aortic stenosis.

Calcium-channel blockers can have additive hypotensive effects with other antihypertensive agents (including diuretics).[5000] Additive pharmacodynamic effects are especially prominent when verapamil is co-administered with alpha-blockers or beta-blockers.[5000] The use of alpha-blockers with verapamil can lead to excessive hypotension; verapamil also reportedly increases the AUC and Cmax of prazosin [6962] and terazosin [6961]. Verapamil can inhibit the metabolism of some beta-blockers (e.g., metoprolol, propranolol), and can cause additive effects on slowing of AV conduction and depression of blood pressure.[5000] Oral calcium-channel blockers and beta-blockers are used together for their therapeutic benefits to reduce angina and improve exercise tolerance.[5000] However, concomitant administration of beta-adrenergic blocking agents and verapamil can lead to significant AV nodal blockade. This can manifest as heart block, bradycardia, cardiac conduction abnormalities and/or prolonged PR interval. Congestive heart failure or severe hypotension also can occur. The combination of beta-blockers and verapamil should be avoided in patients with poor ventricular function due to increased negative inotropic effects. Clonidine can produce bradycardia [5017] and should be used cautiously in patients who are receiving calcium channel blockers that lower the heart rate such verapamil or diltiazem. Complete AV block resulting in a nodal rhythm has been reported during combination therapy of clonidine with verapamil. This additive effect can be desirable, but the patient should be monitored carefully and the dosage should be adjusted based on clinical response.

Amlodipine (Norvasc®) **and Aspirin, ASA; Butalbital; Caffeine; Codeine** (Fiorinal® with Codeine)

Severity: Moderate

Rifampin [4718], rifabutin [4718], rifapentine [5213], carbamazepine [4718], barbiturates (e.g., phenobarbital or primidone) [4718], and phenytoin [4718] (or fosphenytoin which is metabolized to phenytoin [5265]) may induce the CYP3A4 metabolism of calcium-channel blockers such as amlodipine [4718] and thereby reduce their oral bioavailability. The dosage requirements of amlodipine may be increased in patients receiving concurrent enzyme inducers.

Amlodipine (Norvasc®) **and Calcium Salts** (found in Calcium Magnesium Zinc Tablets)

Severity: Low

Calcium salts are used in the treatment of calcium channel blocker overdose.[5801] In general, high doses of calcium salts are needed to overcome the hypotensive effects of calcium channel blocker overdose. However, the exogenous administration of intravenous calcium salts in non-overdose situations may attenuate the pharmacodynamic response to calcium-channel antagonists. If patients receive intravenous calcium salts during concomitant calcium channel blocker therapy, therapeutic response should be monitored.

Acetaminophen; Oxycodone (Percocet®) **and Ipratropium** (Atrovent®)

Severity: Moderate

Concurrent use of antidiarrheals and acetaminophen; oxycodone can lead to severe constipation and possibly additive CNS depression. Opiate analgesics combined with antimuscarinics can cause severe constipation or paralytic ileus, especially with chronic use.

Acetaminophen; Oxycodone (Percocet®) **and Albuterol; Ipratropium** (Combivent®)

Severity: Moderate

Concurrent use of antidiarrheals and acetaminophen; oxycodone can lead to severe constipation and possibly additive CNS depression. Opiate analgesics combined with antimuscarinics can cause severe constipation or paralytic ileus, especially with chronic use.

Acetaminophen; Oxycodone (Percocet®) **and Doxylamine** (Unisom® Sleeptabs™)

Severity: Moderate

Concomitant use of acetaminophen-oxycodone with other CNS depressants can potentiate the respiratory depression and/or sedation effects of both of these agents. CNS depressants include amitriptyline, amoxapine, anxiolytics, sedatives, and hypnotics, clomipramine, clozapine, doxepin, dronabinol, THC, droperidol, entacapone, ethotoin, fosphenytoin, general anesthetics, sedating H_1-

blockers, haloperidol, imipramine, MAOIs, maprotiline, mirtazapine, molindone, nabilone [9044], nefazodone, nortriptyline, olanzapine, other opiate agonists, phenothiazines, phenytoin, pimozide, pramipexole, pregabalin, quetiapine, risperidone, ropinirole, skeletal muscle relaxants, tolcapone, tramadol, and trazodone.

Concomitant use of oxycodone with sedating H_1-blockers can potentiate respiratory depression and/or sedation. In addition, chlorpheniramine and diphenhydramine inhibit CYP2D6, an enzyme responsible for the metabolism of oxycodone to oxymorphone, which represents < 15% of the total administered dose.[4718] Close monitoring for potential side effects in patients receiving oxycodone and chlorpheniramine or diphenhydramine is recommended.

Because doxylamine can cause pronounced sedation,[7801] an enhanced CNS depressant effect may occur when it is combined with other CNS depressants [6568] including anxiolytics, sedatives, and hypnotics (such as barbiturates and benzodiazepines) [6946] [6948], buprenorphine [5278], butorphanol [5912], carisoprodol, clozapine [4989], dronabinol, THC, droperidol [5468], entacapone [5769], ethanol [6341] [6948], general anesthetics [6892], haloperidol [5036], methocarbamol, mirtazapine [5366], molindone [5553], nabilone [9044], nalbuphine [6778], nefazodone [5414], olanzapine [5517], opiate agonists, pentazocine [6777], phenothiazines [6946], pimozide [5250], pramipexole [7757], pregabalin [7523], procarbazine [5356], quetiapine [5855], risperidone [5144], ropinirole [8018], tolcapone [5578], tramadol [5043], trazodone [5450], tricyclic antidepressants [6947], or with other sedating H_1-blockers [6568]. In addition, concurrent use of cannabinoids with sedating H_1-blockers may result in additive tachycardia, which may be pronounced.

Clopidogrel (Plavix®) **and Atropine; Hyoscyamine; Phenobarbital; Scopolamine** (Donnatal®)

Severity: Low

Rifampin, rifabutin, rifapentine, bosentan, carbamazepine or barbiturates (e.g., phenobarbital or primidone) may induce the CYP3A4 metabolism of clopidogrel to its active metabolite.[4718] Patients should be monitored for potential increased antiplatelet effects when clopidogrel is used in combination with CYP3A4 inducers.

Clopidogrel (Plavix®) **and Verapamil**

Severity: Low

Clopidogrel requires hepatic biotransformation to an active metabolite; the activation is thought to be mediated by the CYP3A4 isoenzyme.[5163] As a result, drugs that inhibit CYP3A4 theoretically may decrease the hepatic metabolism of clopidogrel to its active metabolite. CYP3A4 inhibitors may include: amiodarone [5629], anti-retroviral protease inhibitors [4718], aprepitant [7438], systemic azole antifungals [4718], clarithromycin [4718], conivaptan [8569], dalfopristin; quinupristin [4718], danazol [4718], delavirdine [4718], diltiazem [4718], efavirenz (inducer or inhibitor) [5172], erythromycin [4718], fluoxetine [4718], fluvoxamine [4718], imatinib, STI-571 [4718], mifepristone, RU-486 [4718], nefazodone [4718], troleandomycin [4718], verapamil [4718], and zafirlukast [4718]. This list is not inclusive of all CYP3A4 inhibitors.

Propafenone (Rythmol) **and Levalbuterol** (Xopenex®)

Severity: Moderate

Drugs known to prolong the QTc interval have an increased risk of ventricular arrhythmias. Beta-agonists may be associated with adverse cardiovascular effects (including QTc interval prolongation), usually at higher doses and/or when associated with hypokalemia.[5038] [5047] [5262] In addition, beta-agonists should be avoided in patients with congenital long QT syndrome.[4951] Beta-agonists should be administered with extreme caution to patients being treated with drugs known to prolong the QTc interval because the action of beta-agonists on the cardiovascular system may be potentiated.[5038] [5047] Drugs known to increase the QT interval include Class IA antiarrhythmics, Class III antiarrhythmics, flecainide, and propafenone. In addition to antiarrhythmic drugs, other drugs which can result in QT prolongation include: some antipsychotics (e.g., phenothiazines, pimozide, haloperidol, risperidone, sertindole, ziprasidone), amoxapine, arsenic trioxide, astemizole, bepridil, cisapride, chloroquine, clarithromycin, dasatinib [8211], dolasetron [5036], droperidol, halofantrine, halogenated anesthetics, erythromycin, levomethadyl, maprotiline, methadone, ondansetron [8046], palonosetron [8716], some quinolone antibiotics [4951] [5149] [5150] [5507] [6579] (e.g., ofloxacin [7501], ciprofloxacin [5496], gatifloxacin [5152] [5149] [5150] [6579], gemifloxacin [5154], grepafloxacin [5149], levofloxacin [5151], moxifloxacin [5153], norfloxacin [6564], and sparfloxacin [4958]); pentamidine, probucol, ranolazine, terfenadine, tricyclic antidepressants, and vorinostat [9633]. This list is not inclusive of all agents that may prolong the QT interval. Tricyclic antidepressants (TCAs) can also potentiate the vascular effects of beta-agonists.

Propafenone is a Class IC antiarrhythmic which increases the QT interval, but largely due to prolongation of the QRS interval.[5014] The use of propafenone in conjunction with other drugs that prolong the QT interval has not been studied and is not recommended by the manufacturer due to potential risk for ventricular tachycardia, including torsade de pointes (TdP) and monomorphic ventricular tachycardia.[5014] According to the manufacturer, propafenone coadministration with tricyclic antidepressants is not recommended.[5014] In addition, drugs which directly prolong the QT interval are not recommended during propafenone therapy.

Drugs which have been established to have a causal association with QT prolongation and TdP include: Class IA antiarrhythmics (disopyramide, procainamide, quinidine) [4951] [4952] [5187], Class III antiarrhythmics (amiodarone, bretylium, dofetilide, ibutilide, sotalol) [4951] [4952] [5187], astemizole [140], arsenic trioxide [4951] [4977], bepridil [4951] [4953], cisapride [4951], chloroquine [4951] [4955] [4956], clarithromycin [4951] [4964], droperidol [3610] [4951] [4963], erythromycin [228] [4951] [4978], grepafloxacin [5149], halofantrine [4951] [4968], haloperidol [42] [336] [4951] [5036], levomethadyl [4951] [5079] [5081] [5146], methadone [4951] [5048] [5049] [5050] [5051], pentamidine [168] [335] [4951] [5149], certain phenothiazines (chlorpromazine [4951], mesoridazine [4951] [5831], and thioridazine [4951] [5022]), pimozide [4951], probucol [5145], sparfloxacin [4951] [4958], and terfenadine [141] [231]. Other agents associated with a lower, but possible risk for QT prolongation and TdP based on varying levels of documentation (see separate drug monographs) include: abarelix [5392], alfuzosin [4988], amoxapine [5145], apomorphine [5136], beta-agonists [4951] [5038] [5047], ofloxacin [7501], ciprofloxacin [4951] [5149] [5496] [5507] [6579], clozapine [5146], cyclobenzaprine [5155] [5156], dasatinib [9211], dolasetron [5037], gatifloxacin [5149] [5150] [5152], gemifloxacin [5154], halogenated anesthetics [5187] [5188] [5486] [5487] [5488], levofloxacin [5149] [5150] [5151], local anesthetics, maprotiline [5145], mefloquine [6617] [7535], moxifloxacin [5149] [5150] [5153], olanzapine [9575] [9576], ondansetron [8046], norfloxacin [6564], octreotide [4951], palonosetron [5148], some phenothiazines (fluphenazine [5145], perphenazine [5145], prochlorperazine [5145], and trifluoperazine [5145]), propafenone [5014] [5146], ranolazine [8747], risperidone [4951] [5144], sertindole [5187], tacrolimus [4049] [4050] [4951], telithromycin [4880], tricyclic antidepressants when given in excessive doses or overdosage [5145] [5146], troleandomycin (based on interactions with macrolides) [5149], vardenafil [4942], vorinostat [9633], or ziprasidone [4959]. This list is not inclusive of all agents that can cause QT interval prolongation. In addition, some of the listed drugs are CYP2D6 inhibitors (e.g., amiodarone, chloroquine, chlorpromazine, haloperidol, perphenazine, quinidine, ranolazine, and thioridazine) with potential to inhibit the metabolism of propafenone. In addition to potential for additive QT prolongation, concomitant administration of propafenone with desipramine (tricyclic antidepressant) may result in elevated serum desipramine levels.[5014] In addition to avoiding concurrent drug interactions, the potential for TdP can be reduced by avoiding the use of QT prolonging drugs in patients at substantial risk for TdP.[5162] Examples of general risk factors for TdP include congenital long QT syndrome, female sex, elderly patients, significant bradycardia, hypokalemia, hypomagnesemia, and underlying cardiac disease (e.g., arrhythmias, cardiomyopathy, acute myocardial ischemia).

Propafenone (Rythmol) **and Theophylline, Aminophylline** (Theophylline)

Severity: Moderate

Although limited data are available, it appears that propafenone may affect theophylline clearance.[6996] In several patients, theophylline concentrations increased after the addition of propafenone and in at least one patient, symptoms of theophylline toxicity were suspected. Until more data are available, lower doses of theophylline should be considered in patients receiving propafenone.

Although limited data are available, it appears that propafenone affects theophylline clearance.[6996] In several patients, theophylline concentrations increased after the addition of propafenone and in at least one patient, symptoms of theophylline toxicity were suspected. Until more data are available, lower doses of theophylline should be considered in patients receiving propafenone.

Propafenone (Rythmol) **and Verapamil**

Severity: High

Coadministration of propafenone [5014] with diltiazem [5004] or verapamil [5000] has the potential to cause additive decreases in AV conduction and/or negative inotropic effects. In addition, certain calcium-channel blockers (e.g., diltiazem, verapamil, and nicardipine) inhibit CYP3A4, a partial pathway for propafenone metabolism.[4718] [5014] Bepridil has been noted to cause QT prolongation,[4951] [4953] [5162] and concurrent use with propafenone is contraindicated by the manufacturer [5014].

Theophylline, Aminophylline (Theophylline) **and Levalbuterol** (Xopenex®)

Severity: Moderate

Methylxanthine derivatives, (such as theophylline, aminophylline [5277]) and corticosteroids [3085] may aggravate the hypokalemic effect that may be seen with beta-agonists.[5197] Consider checking potassium levels if clinically indicated. However, beta-agonists are commonly used in conjunction with aminophylline, theophylline, and corticosteroid therapy.

Methylxanthine derivatives, (such as theophylline [5277] and aminophylline) and corticosteroids [3085] may aggravate the hypokalemic effect that may be seen with beta-agonists.[5197] Consider checking potassium levels if clinically indicated. However, beta-agonists are commonly used in conjunction with aminophylline, theophylline, and corticosteroid therapy.[5197]

Theophylline, Aminophylline (Theophylline) **and Ranitidine** (Zantac 150™)

Severity: Moderate

Theophylline is primarily metabolized in the liver by the CYP1A2 isoenzyme. Cimetidine is well-known to inhibit the hepatic metabolism theophylline. In general, other H_2-antagonists, such as ranitidine or famotidine, do not interact with theophylline, but at least one report

exists of theophylline toxicity occurring during ranitidine therapy and a small study documented a significant decrease in theophylline clearance after therapy with famotidine.[321]

Reports in the literature have suggested ranitidine increases theophylline serum concentrations [7885] [7886], but clinical studies in healthy subjects have failed to identify this effect [7887] [7888]. Furthermore, a clinical study in 12 healthy subjects demonstrated a lack of effect of ranitidine doses up to 4200 mg/day on theophylline metabolism.[7889] However, caution should be exercised when using even larger doses, such as in the treatment of Zollinger-Ellison syndrome (see dosage), since the occurrence of cimetidine-like drug interactions at these doses is unknown.

Theophylline, Aminophylline (Theophylline) **and Verapamil**

Severity: Moderate

The calcium channel blockers diltiazem, nifedipine (conflicting data), and verapamil [3742] [5000] have been reported to decrease theophylline clearance. The mechanism if most likely reduced cytochrome P-450 metabolism of theophylline. Diltiazem and verapamil are known CYP3A4 inhibitors. Theophylline is partially metabolized by CYP3A4; however, CYP1A2 is the primary metabolic pathway. An interaction with theophylline is unlikely to be clinically important for nifedipine, and the reduction in theophylline clearance is modest (about 10-20%) for verapamil and diltiazem. The interaction between theophylline and verapamil appears to be dose-related; verapamil has been reported to reduce theophylline clearance by 8-18% when given in doses ranging from 40 to 120 mg.[3742] In several studies, diltiazem has been shown to modestly reduce (range 11-22%) the total clearance of theophylline, with an associated increase in half-life. In one small clinical study, diltiazem did not significantly increase theophylline serum concentrations during chronic therapy (i.e., mean serum theophylline level 13.6 vs. 14 mcg/ml with and without diltiazem, respectively).[3743] Since the therapeutic range is narrow for theophylline, it is prudent to monitor theophylline serum concentrations during diltiazem or verapamil therapy.

Verapamil has been reported to decrease theophylline clearance.[3742] [5000] The mechanism is most likely reduced cytochrome P-450 metabolism of theophylline (CYP1A2 and CYP3A4 substrate). The interaction between theophylline and verapamil appears to be dose-related; verapamil has been reported to reduce theophylline clearance by 8-18% when given in doses ranging from 40 to 120 mg.[3742] Since the therapeutic range is narrow for theophylline, it is prudent to monitor theophylline serum concentrations during verapamil therapy.

Trimethobenzamide (Tigan®) **and Clonazepam** (Klonopin®)

Severity: Moderate

Trimethobenzamide has CNS depressant effects and may cause drowsiness.[7086] The concurrent use of trimethobenzamide with other medications that cause CNS depression [e.g., anxiolytics, sedatives, and hypnotics (including barbiturates) [7086], antimuscarinics derived from the belladonna alkaloids (e.g., atropine, homatropine, hyoscyamine, scopolamine)[7086], buprenorphine [5278], butorphanol [5912], dronabinol, THC [7185], nabilone [9044], nalbuphine [6778] , opiate agonists, pentazocine [6969], the phenothiazines [7086], or tramadol [5043] may potentiate the effects of either trimethobenzamide or these other medications.[7086] Ethanol and alcoholic beverages should be avoided while trimethobenzamide is used.[7086] In addition, the administration of trimethobenzamide to patients who have recently received CNS-depressive drugs has resulted in opisthotonus, seizures, coma, and extrapyramidal symptoms.[7086]

Trimethobenzamide (Tigan®) **and Diphenhydramine**

Severity: Moderate

Trimethobenzamide has CNS depressant effects and may cause drowsiness.[7086] The concurrent use of trimethobenzamide with other medications that cause CNS depression [e.g., anxiolytics, sedatives, and hypnotics (including barbiturates) [7086], antimuscarinics derived from the belladonna alkaloids (e.g., atropine, homatropine, hyoscyamine, scopolamine)[7086], buprenorphine [5278], butorphanol [5912], dronabinol, THC [7185], nabilone [9044], nalbuphine [6778] , opiate agonists, pentazocine [6969], the phenothiazines [7086], or tramadol [5043] may potentiate the effects of either trimethobenzamide or these other medications.[7086] Ethanol and alcoholic beverages should be avoided while trimethobenzamide is used.[7086] In addition, the administration of trimethobenzamide to patients who have recently received CNS-depressive drugs has resulted in opisthotonus, seizures, coma, and extrapyramidal symptoms.[7086]

Trimethobenzamide (Tigan®) **and Hydrocodone** (found in Codimal® DH)

Severity: Moderate

Trimethobenzamide has CNS depressant effects and may cause drowsiness.[7086] The concurrent use of trimethobenzamide with other medications that cause CNS depression [e.g., anxiolytics, sedatives, and hypnotics (including barbiturates) [7086], antimuscarinics derived from the belladonna alkaloids (e.g., atropine, homatropine, hyoscyamine, scopolamine)[7086], buprenorphine [5278], butorphanol [5912], dronabinol, THC [7185], nabilone [9044], nalbuphine [6778] , opiate agonists, pentazocine [6969], the

phenothiazines [7086], or tramadol [5043] may potentiate the effects of either trimethobenzamide or these other medications.[7086] Ethanol and alcoholic beverages should be avoided while trimethobenzamide is used.[7086] In addition, the administration of trimethobenzamide to patients who have recently received CNS-depressive drugs has resulted in opisthotonus, seizures, coma, and extrapyramidal symptoms.[7086]

Trimethobenzamide (Tigan®) **and Ipratropium** (Atrovent®)

Severity: Moderate

Trimethobenzamide has CNS depressant effects and may cause drowsiness.[7086] The concurrent use of trimethobenzamide with other medications that cause CNS depression [e.g., anxiolytics, sedatives, and hypnotics (including barbiturates) [7086], antimuscarinics derived from the belladonna alkaloids (e.g., atropine, homatropine, hyoscyamine, scopolamine)[7086], buprenorphine [5278], butorphanol [5912], dronabinol, THC [7185], nabilone [9044], nalbuphine [6778] , opiate agonists, pentazocine [6969], the phenothiazines [7086], or tramadol [5043] may potentiate the effects of either trimethobenzamide or these other medications.[7086] Ethanol and alcoholic beverages should be avoided while trimethobenzamide is used.[7086] In addition, the administration of trimethobenzamide to patients who have recently received CNS-depressive drugs has resulted in opisthotonus, seizures, coma, and extrapyramidal symptoms.[7086]

Trimethobenzamide (Tigan®) **and Acetaminophen; Oxycodone** (Percocet®)

Severity: Moderate

Trimethobenzamide has CNS depressant effects and may cause drowsiness.[7086] The concurrent use of trimethobenzamide with other medications that cause CNS depression [e.g., anxiolytics, sedatives, and hypnotics (including barbiturates) [7086], antimuscarinics derived from the belladonna alkaloids (e.g., atropine, homatropine, hyoscyamine, scopolamine)[7086], buprenorphine [5278], butorphanol [5912], dronabinol, THC [7185], nabilone [9044], nalbuphine [6778] , opiate agonists, pentazocine [6969], the phenothiazines [7086], or tramadol [5043] may potentiate the effects of either trimethobenzamide or these other medications.[7086] Ethanol and alcoholic beverages should be avoided while trimethobenzamide is used.[7086] In addition, the administration of trimethobenzamide to patients who have recently received CNS-depressive drugs has resulted in opisthotonus, seizures, coma, and extrapyramidal symptoms.[7086]

Trimethobenzamide (Tigan®) **and Aspirin, ASA; Butalbital; Caffeine; Codeine** (Fiorinal® with Codeine)

Severity: Moderate

Trimethobenzamide has CNS depressant effects and may cause drowsiness.[7086] The concurrent use of trimethobenzamide with other medications that cause CNS depression [e.g., anxiolytics, sedatives, and hypnotics (including barbiturates) [7086], antimuscarinics derived from the belladonna alkaloids (e.g., atropine, homatropine, hyoscyamine, scopolamine)[7086], buprenorphine [5278], butorphanol [5912], dronabinol, THC [7185], nabilone [9044], nalbuphine [6778] , opiate agonists, pentazocine [6969], the phenothiazines [7086], or tramadol [5043] may potentiate the effects of either trimethobenzamide or these other medications.[7086] Ethanol and alcoholic beverages should be avoided while trimethobenzamide is used.[7086] In addition, the administration of trimethobenzamide to patients who have recently received CNS-depressive drugs has resulted in opisthotonus, seizures, coma, and extrapyramidal symptoms.[7086]

Trimethobenzamide (Tigan®) **and Atropine; Hyoscyamine; Phenobarbital; Scopolamine** (Donnatal®)

Severity: Moderate

Trimethobenzamide has CNS depressant effects and may cause drowsiness.[7086] The concurrent use of trimethobenzamide with other medications that cause CNS depression [e.g., anxiolytics, sedatives, and hypnotics (including barbiturates) [7086], antimuscarinics derived from the belladonna alkaloids (e.g., atropine, homatropine, hyoscyamine, scopolamine)[7086], buprenorphine [5278], butorphanol [5912], dronabinol, THC [7185], nabilone [9044], nalbuphine [6778] , opiate agonists, pentazocine [6969], the phenothiazines [7086], or tramadol [5043] may potentiate the effects of either trimethobenzamide or these other medications.[7086] Ethanol and alcoholic beverages should be avoided while trimethobenzamide is used.[7086] In addition, the administration of trimethobenzamide to patients who have recently received CNS-depressive drugs has resulted in opisthotonus, seizures, coma, and extrapyramidal symptoms.[7086]

Trimethobenzamide (Tigan®) **and Albuterol; Ipratropium** (Combivent®)

Severity: Moderate

Trimethobenzamide has CNS depressant effects and may cause drowsiness.[7086] The concurrent use of trimethobenzamide with other medications that cause CNS depression [e.g., anxiolytics, sedatives, and hypnotics (including barbiturates) [7086], antimuscarinics derived from the belladonna alkaloids (e.g., atropine, homatropine, hyoscyamine, scopolamine)[7086], buprenorphine [5278], butorphanol [5912], dronabinol, THC [7185], nabilone [9044], nalbuphine [6778] , opiate agonists, pentazocine [6969], the

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Trimethobenzamide (Tigan®) **and Doxylamine** (Unisom® Sleeptabs™)

Severity: Moderate

Trimethobenzamide has CNS depressant effects and may cause drowsiness.[7086] The concurrent use of trimethobenzamide with other medications that cause CNS depression [e.g., anxiolytics, sedatives, and hypnotics (including barbiturates) [7086], antimuscarinics derived from the belladonna alkaloids (e.g., atropine, homatropine, hyoscyamine, scopolamine)[7086], buprenorphine [5278], butorphanol [5912], dronabinol, THC [7185], nabilone [9044], nalbuphine [6778] , opiate agonists, pentazocine [6969], the phenothiazines [7086], or tramadol [5043] may potentiate the effects of either trimethobenzamide or these other medications.[7086] Ethanol and alcoholic beverages should be avoided while trimethobenzamide is used.[7086] In addition, the administration of trimethobenzamide to patients who have recently received CNS-depressive drugs has resulted in opisthotonus, seizures, coma, and extrapyramidal symptoms.[7086]

Doxylamine (Unisom® Sleeptabs™) **and Ipratropium** (Atrovent®)

Severity: Moderate

Doxylamine is a sedating antihistamine.[7801] The anticholinergic effects of doxylamine may be significant and may be enhanced when combined with antimuscarinics [6338]. Other commonly used drugs with moderate to significant anticholinergic effects include amantadine [4771], amoxapine [5288], clozapine [4989], cyclobenzaprine [5155], disopyramide [4954], maprotiline [5491], olanzapine [5517], orphenadrine [5982], most phenothiazines [6946], and most tricyclic antidepressants [6947]. Clinicians should note that antimuscarinic effects might be seen not only on GI smooth muscle, but also on bladder function, the eye, and temperature regulation. With many of the listed agents, additive drowsiness may also occur when combined with significantly sedating antihistamines like doxylamine.

Doxylamine (Unisom® Sleeptabs™) **and Albuterol; Ipratropium** (Combivent®)

Severity: Moderate

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Verapamil and Aspirin, ASA; Butalbital; Caffeine; Codeine (Fiorinal® with Codeine)

Severity: Moderate

Rifampin, a potent hepatic enzyme inducer, significantly reduces the oral bioavailability of verapamil, presumably by increasing first-pass metabolism.[5000] Rifabutin [4718] and rifapentine [5213], enzyme inducers, may have a similar effect. Barbiturates such as phenobarbital [5000], phenytoin [5641] (or fosphenytoin which is metabolized to phenytoin [5265]) may also reduce verapamil serum concentrations via enzyme induction. Verapamil is a substrate for CYP3A4. Patients receiving verapamil should be monitored for loss of therapeutic effect if any of these hepatic enzyme inducing drugs are added.

Ergocalciferol, Vitamin D2 (Vitamin D) **and Digoxin** (Digitek™)

Severity: Moderate

Ergocalciferol should be administered with caution to patients with cardiac disease or those receiving cardiac glycosides. Ergocalciferol may cause hypercalcemia which may affect the actions of the cardiac glycoside and/or lead to cardiac arrhythmias.[6916] [4999]

Ergocalciferol, Vitamin D2 (Vitamin D) **and Flunisolide**

Severity: Low

Vitamin D plus calcium supplements are generally recommended for the prevention of osteoporosis in patients taking long-term corticosteroids.[6905] A relationship of functional antagonism exists between vitamin D analogs, which promote calcium absorption,

and corticosteroids, which inhibit calcium absorption.[6916] [1441] Therapeutic effect of vitamin D analogs should be monitored when used concomitantly with corticosteroids.

Ergocalciferol, Vitamin D2 (Vitamin D) **and Aspirin, ASA; Butalbital; Caffeine; Codeine** (Fiorinal® with Codeine)

Severity: Moderate

Barbiturates (i.e., phenobarbital, primidone) and anticonvulsants, such phenytoin and fosphenytoin (which is metabolized to phenytoin [5685]), can decrease the activity of vitamin D by increasing its metabolism.[6923] [7204] In rare cases, this has caused anticonvulsant-induced rickets and osteomalacia. Vitamin D supplementation or dosage adjustments may be required in patients who are receiving chronic treatment with anticonvulsants.

Levalbuterol (Xopenex®) **and Flunisolide**

Severity: Moderate

Methylxanthine derivatives, (such as theophylline, aminophylline [5277]) and corticosteroids [3085] may aggravate the hypokalemic effect that may be seen with beta-agonists.[5197] Consider checking potassium levels if clinically indicated. However, beta-agonists are commonly used in conjunction with aminophylline, theophylline, and corticosteroid therapy.

Levalbuterol (Xopenex®) **and Phenylephrine** (found in Codimal® DH)

Severity: High

If asthma symptoms occur between the use of long-acting beta-agonists (e.g., salmeterol or formoterol), short-acting beta$_2$-agonists (e.g., levalbuterol) may be used safely for the symptomatic relief of acute asthma symptoms.[5047] [5197] When beginning treatment with a long-acting beta-agonist, patients who have been taking inhaled, short-acting beta$_2$-agonists on a regular basis (e.g., four times a day) should be instructed to discontinue the regular, scheduled use of these drugs and use them only for the symptomatic relief of acute asthma symptoms. Patients should be cautioned that increasing short-acting inhaled beta$_2$-agonist use is a signal of deteriorating asthma. Due to the pharmacology of levalbuterol [5047], the concomitant use of levalbuterol with other short-acting beta-agonists or short-acting sympathomimetic aerosol bronchodilators is NOT recommended due to the increased risk of adverse cardiovascular effects (considered duplicate therapy). Caution and close observation should also be used when levalbuterol is used concurrently with other adrenergic sympathomimetics, administered by any route, to avoid potential for increased cardiovascular effects.[5047]

Levalbuterol (Xopenex®) **and Acetaminophen; Chlorpheniramine; Phenylephrine; Phenyltoloxamine** (Norel®SR)

Severity: High

If asthma symptoms occur between the use of long-acting beta-agonists (e.g., salmeterol or formoterol), short-acting beta$_2$-agonists (e.g., levalbuterol) may be used safely for the symptomatic relief of acute asthma symptoms.[5047] [5197] When beginning treatment with a long-acting beta-agonist, patients who have been taking inhaled, short-acting beta$_2$-agonists on a regular basis (e.g., four times a day) should be instructed to discontinue the regular, scheduled use of these drugs and use them only for the symptomatic relief of acute asthma symptoms. Patients should be cautioned that increasing short-acting inhaled beta$_2$-agonist use is a signal of deteriorating asthma. Due to the pharmacology of levalbuterol [5047], the concomitant use of levalbuterol with other short-acting beta-agonists or short-acting sympathomimetic aerosol bronchodilators is NOT recommended due to the increased risk of adverse cardiovascular effects (considered duplicate therapy). Caution and close observation should also be used when levalbuterol is used concurrently with other adrenergic sympathomimetics, administered by any route, to avoid potential for increased cardiovascular effects.[5047]

Adverse Reactions

• abdominal pain (Fosamax® | Norvasc® | Bactrim™ DS | Digitek™ | Diphenhydramine | Vitamin D | Metamucil® | Zantac 150™ | Theophylline | Verapamil | Plavix® | Percocet® | Fiorinal® with Codeine | Cafergot® | Melatonin | Unisom® Sleeptabs™ | Foradil® Aerolizer | Histex™ I/E)
• acneiform rash (Fiorinal® with Codeine | Donnatal®)
• acute generalized exanthematous pustulosis (AGEP) (Bactrim™ DS | Percocet® | Norel®SR)
• agitation (Diphenhydramine | Zantac 150™ | Theophylline | Unisom® Sleeptabs™)
• agranulocytosis (Bactrim™ DS | Zantac 150™ | Plavix® | Percocet® | Fiorinal® with Codeine | Tigan® | Norel®SR)
• alopecia (Zantac 150™)
• anaphylactic shock (Cyanocobalamin, Vitamin B12 | Percocet® | Norel®SR)

• anaphylactoid reactions (Albuterol | Atrovent® | Zantac 150™ | Plavix® | Percocet® | Fiorinal® with Codeine | Combivent® | Foradil® Aerolizer | Xopenex® | Norel®SR)
• anemia (Vitamin D | Fiorinal® with Codeine)
• angina (Albuterol | Norvasc® | Rythmol | Donnatal® | Cafergot® | Combivent® | Foradil® Aerolizer | Xopenex® | Norel®SR)
• angioedema (Albuterol | Norvasc® | Bactrim™ DS | Atrovent® | Zantac 150™ | Plavix® | Percocet® | Fiorinal® with Codeine | Combivent® | Foradil® Aerolizer | Xopenex®)
• anorexia (Norvasc® | Bactrim™ DS | Digitek™ | Vitamin D | Theophylline | Percocet® | Histex™ I/E | Norel®SR)
• anuria (Bactrim™ DS)
• anxiety (Albuterol | Klonopin® | Cyanocobalamin, Vitamin B12 | Digitek™ | Theophylline | Fiorinal® with Codeine | Donnatal® | Xopenex® | Norel®SR)
• aplastic anemia (Bactrim™ DS | Zantac 150™ | Plavix® | Norel®SR)
• appetite stimulation (Diphenhydramine | Unisom® Sleeptabs™)
• arrhythmia exacerbation (Albuterol | Rythmol | Combivent® | Foradil® Aerolizer | Xopenex® | Norel®SR)
• arthralgia (Fosamax® | Bactrim™ DS | Vitamin D | Zantac 150™)
• aseptic meningitis (Bactrim™ DS)
• asphyxia (Metamucil®)
• asthenia (Norvasc® | Diphenhydramine | Verapamil | Cafergot® | Unisom® Sleeptabs™ | Xopenex®)
• asystole (Rythmol | Verapamil)
• ataxia (Klonopin® | Bactrim™ DS | Cyanocobalamin, Vitamin B12 | Diphenhydramine | Vitamin D | Donnatal® | Unisom® Sleeptabs™ | Histex™ I/E | Norel®SR)
• atrial fibrillation (Digitek™ | Theophylline)
• atrial flutter (Theophylline)
• atrial tachycardia (Digitek™ | Theophylline)
• AV block (Digitek™ | Zantac 150™ | Verapamil | Norel®SR)
• azotemia (Vitamin D | Fiorinal® with Codeine)
• back pain (Atrovent®)
• bleeding (Plavix® | Percocet® | Fiorinal® with Codeine | Norel®SR)
• blurred vision (Norvasc® | Digitek™ | Diphenhydramine | Atrovent® | Rythmol | Zantac 150™ | Donnatal® | Tigan® | Combivent® | Unisom® Sleeptabs™ | Histex™ I/E | Norel®SR)
• bone pain (Fosamax® | Fiorinal® with Codeine)
• bradycardia (Norvasc® | Digitek™ | Rythmol | Zantac 150™ | Verapamil | Percocet® | Donnatal® | Cafergot® | Norel®SR)
• bronchial secretions (Norel®SR)
• bronchospasm (Albuterol | Flunisolide | Atrovent® | Zantac 150™ | Plavix® | Fiorinal® with Codeine | Combivent® | Xopenex®)
• bullous rash (Bactrim™ DS | Donnatal®)
• candidiasis (Flunisolide)
• cardiac arrest (Theophylline | Percocet®)
• cardiac valvulopathy (Cafergot®)
• cataracts (Flunisolide)
• chest pain (unspecified) (Atrovent® | Metamucil® | Cafergot®)
• chills (Bactrim™ DS)
• cholestasis (Rythmol)
• colitis (Plavix® | Cafergot® | Norel®SR)
• coma (Tigan®)
• confusion (Klonopin® | Digitek™ | Diphenhydramine | Zantac 150™ | Verapamil | Plavix® | Percocet® | Fiorinal® with Codeine | Donnatal® | Cafergot® | Melatonin | Unisom® Sleeptabs™ | Histex™ I/E)
• conjunctivitis (Fosamax® | Atrovent® | Combivent®)
• constipation (Fosamax® | Norvasc® | Digitek™ | Diphenhydramine | Vitamin D | Atrovent® | Rythmol | Zantac 150™ | Verapamil | Percocet® | Fiorinal® with Codeine | Donnatal® | Combivent® | Unisom® Sleeptabs™ | Histex™ I/E | Norel®SR)
• contact dermatitis (Diphenhydramine | Percocet® | Norel®SR)
• coronary vasospasm (Cafergot®)
• cough (Albuterol | Bactrim™ DS | Flunisolide | Atrovent® | Combivent® | Xopenex®)
• crystalluria (Bactrim™ DS)
• cycloplegia (Atrovent® | Donnatal® | Combivent®)
• dehydration (Vitamin D | Fiorinal® with Codeine)
• delirium (Digitek™ | Zantac 150™ | Fiorinal® with Codeine | Donnatal® | Unisom® Sleeptabs™)
• depression (Klonopin® | Bactrim™ DS | Digitek™ | Zantac 150™ | Fiorinal® with Codeine | Donnatal® | Cafergot® | Melatonin)
• diaphoresis (Albuterol | Fiorinal® with Codeine)
• diarrhea (Fosamax® | Norvasc® | Bactrim™ DS | Cyanocobalamin, Vitamin B12 | Digitek™ | Diphenhydramine | Vitamin D | Rythmol | Metamucil® | Zantac 150™ | Plavix® | Fiorinal® with Codeine | Cafergot® | Tigan® | Unisom® Sleeptabs™ | Histex™ I/E | Xopenex®)
• disseminated intravascular coagulation (DIC) (Fiorinal® with Codeine)
• diuresis (Bactrim™ DS | Theophylline)

• dizziness (Albuterol | Norvasc® | Klonopin® | Bactrim™ DS | Digitek™ | Diphenhydramine | Flunisolide | Atrovent® | Rythmol | Zantac 150™ | Theophylline | Verapamil | Percocet® | Fiorinal® with Codeine | Donnatal® | Tigan® | Combivent® | Unisom® Sleeptabs™ | Foradil® Aerolizer | Histex™ I/E | Xopenex® | Norel®SR)
• drowsiness (Albuterol | Norvasc® | Klonopin® | Digitek™ | Diphenhydramine | Atrovent® | Verapamil | Percocet® | Fiorinal® with Codeine | Cafergot® | Tigan® | Combivent® | Melatonin | Unisom® Sleeptabs™ | Histex™ I/E | Norel®SR)
• dysarthria (Klonopin® | Diphenhydramine | Unisom® Sleeptabs™)
• dysgeusia (Fosamax® | Flunisolide | Atrovent® | Rythmol | Combivent®)
• dyskinesia (Diphenhydramine | Unisom® Sleeptabs™)
• dysosmia (Flunisolide)
• dyspepsia (Albuterol | Fosamax® | Atrovent® | Verapamil | Plavix® | Fiorinal® with Codeine | Donnatal® | Combivent® | Melatonin | Foradil® Aerolizer | Histex™ I/E | Xopenex®)
• dysphagia (Fosamax® | Norvasc® | Donnatal®)
• dysphonia (Flunisolide | Combivent® | Foradil® Aerolizer)
• dyspnea (Bactrim™ DS)
• dystonic reaction (Diphenhydramine | Unisom® Sleeptabs™)
• dysuria (Atrovent® | Combivent® | Histex™ I/E | Norel®SR)
• edema (Norvasc® | Rythmol | Verapamil | Percocet® | Cafergot® | Norel®SR)
• elevated hepatic enzymes (Norvasc® | Bactrim™ DS | Rythmol | Zantac 150™ | Verapamil | Plavix® | Percocet® | Norel®SR)
• encephalopathy (Percocet® | Norel®SR)
• eosinophilia (Bactrim™ DS | Flunisolide | Zantac 150™)
• epiphora (Flunisolide)
• epistaxis (Albuterol | Norvasc® | Atrovent®)
• erythema (Digitek™ | Percocet® | Norel®SR)
• erythema multiforme (Norvasc® | Bactrim™ DS | Zantac 150™ | Plavix®)
• erythema nodosum (Bactrim™ DS | Fiorinal® with Codeine)
• esophageal stricture (Fosamax® | Fiorinal® with Codeine)
• esophageal ulceration (Fosamax® | Fiorinal® with Codeine)
• esophagitis (Fosamax® | Fiorinal® with Codeine)
• euphoria (Klonopin®)
• excitability (Albuterol | Fiorinal® with Codeine | Histex™ I/E | Norel®SR)
• exfoliative dermatitis (Bactrim™ DS | Percocet® | Norel®SR)
• fatigue (Norvasc® | Klonopin® | Bactrim™ DS | Digitek™ | Diphenhydramine | Vitamin D | Verapamil | Unisom® Sleeptabs™ | Foradil® Aerolizer)
• fetal abortion (Cafergot®)
• fetal death (Cafergot®)
• fever (Plavix® | Percocet® | Fiorinal® with Codeine | Donnatal® | Tigan® | Xopenex® | Norel®SR)
• flatulence (Fosamax® | Norvasc® | Metamucil®)
• flushing (Albuterol | Norvasc® | Flunisolide | Verapamil | Donnatal®)
• gastritis (Fosamax® | Plavix® | Fiorinal® with Codeine)
• gastroesophageal reflux (Fosamax®)
• GI bleeding (Fosamax® | Plavix® | Norel®SR)
• GI obstruction (Metamucil®)
• GI perforation (Fosamax®)
• glomerulonephritis (Plavix®)
• glossitis (Bactrim™ DS)
• goiter (Bactrim™ DS)
• growth inhibition (Vitamin D | Flunisolide)
• gynecomastia (Norvasc® | Digitek™ | Zantac 150™ | Verapamil)
• hallucinations (Bactrim™ DS | Digitek™ | Diphenhydramine | Zantac 150™ | Plavix® | Percocet® | Fiorinal® with Codeine | Donnatal® | Unisom® Sleeptabs™ | Histex™ I/E | Norel®SR)
• headache (Albuterol | Fosamax® | Norvasc® | Klonopin® | Bactrim™ DS | Cyanocobalamin, Vitamin B12 | Digitek™ | Diphenhydramine | Vitamin D | Flunisolide | Atrovent® | Rythmol | Zantac 150™ | Theophylline | Verapamil | Percocet® | Fiorinal® with Codeine | Donnatal® | Tigan® | Combivent® | Melatonin | Unisom® Sleeptabs™ | Foradil® Aerolizer | Histex™ I/E | Xopenex®)
• hearing loss (Fiorinal® with Codeine)
• heart failure (Rythmol | Verapamil)
• hematemesis (Theophylline)
• hematuria (Bactrim™ DS)
• hemolysis (Percocet® | Fiorinal® with Codeine | Norel®SR)
• hemolytic anemia (Bactrim™ DS | Zantac 150™ | Percocet® | Fiorinal® with Codeine | Norel®SR)
• hepatic encephalopathy (Fiorinal® with Codeine)
• hepatic failure (Plavix®)
• hepatic necrosis (Bactrim™ DS | Percocet® | Fiorinal® with Codeine | Norel®SR)

• hepatitis (Norvasc® | Bactrim™ DS | Rythmol | Zantac 150™ | Plavix® | Fiorinal® with Codeine | Melatonin)
• hoarseness (Albuterol | Flunisolide | Atrovent® | Combivent® | Foradil® Aerolizer | Xopenex®)
• hostility (Albuterol)
• hyperammonemia (Fiorinal® with Codeine)
• hyperbilirubinemia (Fiorinal® with Codeine)
• hypercalcemia (Vitamin D)
• hypercalciuria (Vitamin D)
• hypercholesterolemia (Vitamin D)
• hyperglycemia (Albuterol | Fiorinal® with Codeine | Combivent® | Foradil® Aerolizer | Xopenex®)
• hyperkalemia (Bactrim™ DS | Digitek™)
• hyperkinesis (Albuterol)
• hypernatremia (Fiorinal® with Codeine)
• hyperphosphatemia (Vitamin D)
• hyperreflexia (Klonopin®)
• hypersalivation (Klonopin®)
• hypertension (Albuterol | Vitamin D | Fiorinal® with Codeine | Combivent® | Foradil® Aerolizer | Histex™ I/E | Xopenex® | Norel®SR)
• hyperthermia (Vitamin D)
• hyperuricemia (Fiorinal® with Codeine)
• hyperventilation (Fiorinal® with Codeine)
• hypervitaminosis D (Vitamin D)
• hypocalcemia (Fosamax®)
• hypoglycemia (Bactrim™ DS | Fiorinal® with Codeine)
• hypokalemia (Albuterol | Cyanocobalamin, Vitamin B12 | Digitek™ | Theophylline | Fiorinal® with Codeine | Combivent® | Foradil® Aerolizer | Xopenex®)
• hypophosphatemia (Fosamax®)
• hypoprothrombinemia (Percocet® | Fiorinal® with Codeine | Norel®SR)
• hypotension (Albuterol | Norvasc® | Diphenhydramine | Atrovent® | Theophylline | Verapamil | Plavix® | Percocet® | Tigan® | Combivent® | Unisom® Sleeptabs™ | Foradil® Aerolizer | Histex™ I/E | Xopenex®)
• hypothalamic-pituitary-adrenal (HPA) suppression (Flunisolide)
• hypothermia (Cafergot®)
• ileus (Donnatal®)
• impaired cognition (Digitek™ | Diphenhydramine | Unisom® Sleeptabs™)
• impaired wound healing (Flunisolide)
• impotence (erectile dysfunction) (Digitek™ | Zantac 150™ | Verapamil | Fiorinal® with Codeine)
• infection (Cyanocobalamin, Vitamin B12 | Zantac 150™ | Foradil® Aerolizer | Xopenex®)
• infertility (Melatonin)
• influenza (Xopenex®)
• injection site reaction (Tigan®)
• insomnia (Albuterol | Bactrim™ DS | Diphenhydramine | Atrovent® | Zantac 150™ | Theophylline | Verapamil | Fiorinal® with Codeine | Donnatal® | Combivent® | Unisom® Sleeptabs™ | Foradil® Aerolizer | Histex™ I/E | Xopenex® | Norel®SR)
• interstitial nephritis (Bactrim™ DS | Percocet® | Fiorinal® with Codeine | Donnatal® | Norel®SR)
• intracranial bleeding (Plavix®)
• irritability (Albuterol | Vitamin D | Unisom® Sleeptabs™ | Histex™ I/E)
• jaundice (Norvasc® | Bactrim™ DS | Zantac 150™ | Percocet® | Fiorinal® with Codeine | Tigan® | Norel®SR)
• laryngospasm (Atrovent® | Combivent®)
• lethargy (Fiorinal® with Codeine | Melatonin | Norel®SR)
• leukocytosis (Fiorinal® with Codeine | Donnatal®)
• leukopenia (Norvasc® | Bactrim™ DS | Zantac 150™ | Fiorinal® with Codeine | Tigan®)
• libido decrease (Digitek™ | Zantac 150™ | Fiorinal® with Codeine | Donnatal®)
• lupus-like symptoms (Bactrim™ DS)
• lymphadenopathy (Xopenex®)
• maculopapular rash (Albuterol | Bactrim™ DS | Digitek™ | Atrovent® | Zantac 150™ | Plavix® | Percocet® | Fiorinal® with Codeine | Donnatal® | Combivent® | Norel®SR)
• malaise (Foradil® Aerolizer)
• mania (Klonopin®)
• megaloblastic anemia (Bactrim™ DS | Donnatal®)
• metabolic acidosis (Vitamin D | Theophylline | Fiorinal® with Codeine | Foradil® Aerolizer)
• metallic taste (Vitamin D | Rythmol)
• methemoglobinemia (Bactrim™ DS | Percocet® | Norel®SR)
• miosis (Percocet® | Donnatal®)
• muscle cramps (Albuterol | Cafergot® | Tigan® | Foradil® Aerolizer | Xopenex®)
• musculoskeletal pain (Fosamax® | Vitamin D)

• myalgia (Fosamax® | Bactrim™ DS | Vitamin D | Zantac 150™ | Plavix® | Cafergot®)
• myasthenia (Unisom® Sleeptabs™)
• mydriasis (Diphenhydramine | Atrovent® | Fiorinal® with Codeine | Donnatal® | Combivent® | Unisom® Sleeptabs™ | Norel®SR)
• myocardial infarction (Cafergot® | Norel®SR)
• myocarditis (Bactrim™ DS | Norel®SR)
• nasal congestion (Flunisolide | Atrovent®)
• nasal dryness (Flunisolide | Atrovent®)
• nasal irritation (Flunisolide | Atrovent®)
• nausea/vomiting (Albuterol | Fosamax® | Norvasc® | Bactrim™ DS | Cyanocobalamin, Vitamin B12 | Digitek™ | Vitamin D | Flunisolide | Atrovent® | Rythmol | Metamucil® | Zantac 150™ | Theophylline | Verapamil | Percocet® | Fiorinal® with Codeine | Donnatal® | Cafergot® | Combivent® | Foradil® Aerolizer | Histex™ I/E | Xopenex® | Norel®SR)
• neonatal abstinence syndrome (Percocet® | Fiorinal® with Codeine)
• neuritis (Bactrim™ DS)
• neutropenia (Bactrim™ DS | Zantac 150™ | Plavix® | Percocet®)
• nightmares (Albuterol | Klonopin® | Donnatal® | Melatonin)
• nocturia (Vitamin D)
• nystagmus (Fiorinal® with Codeine | Donnatal®)
• ocular hemorrhage (Plavix®)
• ocular hypertension (Atrovent® | Donnatal® | Combivent® | Norel®SR)
• ocular inflammation (Fosamax®)
• ocular irritation (Atrovent® | Combivent®)
• ocular pain (Fosamax® | Atrovent® | Combivent®)
• odynophagia (Fiorinal® with Codeine)
• oliguria (Bactrim™ DS)
• oral ulceration (Fosamax® | Atrovent® | Foradil® Aerolizer)
• orthostatic hypotension (Norvasc® | Percocet®)
• osteonecrosis (Fosamax®)
• osteopenia (Fiorinal® with Codeine | Donnatal®)
• osteoporosis (Vitamin D)
• pallor (Norel®SR)
• palpitations (Albuterol | Norvasc® | Diphenhydramine | Atrovent® | Theophylline | Percocet® | Fiorinal® with Codeine | Cafergot® | Combivent® | Unisom® Sleeptabs™ | Foradil® Aerolizer | Histex™ I/E | Xopenex® | Norel®SR)
• pancreatitis (Norvasc® | Bactrim™ DS | Zantac 150™ | Plavix® | Cafergot®)
• pancytopenia (Bactrim™ DS | Zantac 150™ | Plavix® | Percocet® | Fiorinal® with Codeine | Norel®SR)
• paranoia (Zantac 150™)
• paresthesias (Norvasc® | Cyanocobalamin, Vitamin B12 | Digitek™ | Cafergot® | Foradil® Aerolizer | Xopenex®)
• peptic ulcer (Plavix®)
• periarteritis (Bactrim™ DS)
• peripheral edema (Norvasc® | Verapamil)
• peripheral vasoconstriction (Cafergot®)
• peripheral vasodilation (Albuterol | Norvasc® | Verapamil | Combivent® | Xopenex®)
• pharyngitis (Flunisolide | Foradil® Aerolizer | Xopenex®)
• photophobia (Digitek™ | Vitamin D | Donnatal® | Norel®SR)
• photosensitivity (Fosamax® | Bactrim™ DS | Diphenhydramine | Fiorinal® with Codeine | Donnatal® | Foradil® Aerolizer | Histex™ I/E)
• physiological dependence (Klonopin® | Percocet® | Fiorinal® with Codeine | Cafergot®)
• platelet dysfunction (Plavix®)
• pneumonitis (Plavix®)
• polydipsia (Vitamin D)
• polyuria (Vitamin D | Fiorinal® with Codeine | Cafergot®)
• PR prolongation (Digitek™)
• premature ventricular contractions (PVCs) (Digitek™ | Zantac 150™ | Theophylline)
• prolonged bleeding time (Plavix®)
• proteinuria (Fiorinal® with Codeine)
• pruritus (Bactrim™ DS | Cyanocobalamin, Vitamin B12 | Digitek™ | Atrovent® | Plavix® | Percocet® | Fiorinal® with Codeine | Cafergot® | Combivent® | Melatonin | Norel®SR)
• pseudomembranous colitis (Bactrim™ DS)
• pseudoparkinsonism (Tigan®)
• psychological dependence (Fiorinal® with Codeine)
• psychosis (Digitek™ | Diphenhydramine | Melatonin | Unisom® Sleeptabs™ | Histex™ I/E | Norel®SR)
• ptosis (Fiorinal® with Codeine | Donnatal®)
• pulmonary edema (Cyanocobalamin, Vitamin B12 | Verapamil | Fiorinal® with Codeine)

• pulmonary fibrosis (Cafergot®)
• purpura (Bactrim™ DS | Flunisolide | Plavix® | Percocet® | Fiorinal® with Codeine | Donnatal® | Norel®SR)
• pyrosis (heartburn) (Fosamax® | Fiorinal® with Codeine | Donnatal®)
• QT prolongation (Albuterol | Rythmol | Combivent® | Foradil® Aerolizer | Xopenex®)
• rash (unspecified) (Fosamax® | Diphenhydramine | Plavix® | Percocet® | Tigan® | Foradil® Aerolizer | Xopenex® | Norel®SR)
• renal failure (unspecified) (Bactrim™ DS | Vitamin D | Percocet® | Fiorinal® with Codeine | Norel®SR)
• renal papillary necrosis (Percocet® | Fiorinal® with Codeine | Norel®SR)
• renal tubular necrosis (Bactrim™ DS | Percocet® | Fiorinal® with Codeine | Cafergot® | Norel®SR)
• respiratory depression (Percocet® | Fiorinal® with Codeine)
• restlessness (Albuterol | Klonopin® | Diphenhydramine | Theophylline | Percocet® | Unisom® Sleeptabs™ | Histex™ I/E | Xopenex® | Norel®SR)
• retinal hemorrhage (Plavix®)
• retroperitoneal bleeding (Plavix®)
• retroperitoneal fibrosis (Cafergot®)
• Reye's syndrome (Fiorinal® with Codeine)
• rhabdomyolysis (Bactrim™ DS)
• rhinitis (Cyanocobalamin, Vitamin B12 | Atrovent® | Fiorinal® with Codeine | Foradil® Aerolizer | Xopenex®)
• rhinorrhea (Atrovent®)
• seizures (Bactrim™ DS | Diphenhydramine | Theophylline | Verapamil | Fiorinal® with Codeine | Cafergot® | Tigan® | Unisom® Sleeptabs™ | Histex™ I/E | Norel®SR)
• serum sickness (Bactrim™ DS | Plavix®)
• sinus tachycardia (Albuterol | Norvasc® | Digitek™ | Diphenhydramine | Atrovent® | Zantac 150™ | Theophylline | Verapamil | Fiorinal® with Codeine | Donnatal® | Cafergot® | Combivent® | Melatonin | Unisom® Sleeptabs™ | Foradil® Aerolizer | Histex™ I/E | Xopenex® | Norel®SR)
• sneezing (Flunisolide)
• spermatogenesis inhibition (Melatonin)
• Stevens-Johnson syndrome (Bactrim™ DS | Digitek™ | Zantac 150™ | Plavix® | Fiorinal® with Codeine | Donnatal®)
• stomatitis (Bactrim™ DS | Plavix®)
• stroke (Norel®SR)
• ST-T wave changes (Albuterol | Digitek™ | Foradil® Aerolizer | Xopenex®)
• supraventricular tachycardia (SVT) (Theophylline)
• syncope (Albuterol | Norvasc® | Klonopin® | Digitek™ | Verapamil | Percocet® | Xopenex®)
• tardive dyskinesia (Diphenhydramine | Unisom® Sleeptabs™)
• teratogenesis (Klonopin® | Cafergot®)
• throat irritation (Albuterol | Atrovent® | Combivent® | Xopenex®)
• thrombocytopenia (Norvasc® | Bactrim™ DS | Digitek™ | Zantac 150™ | Percocet® | Fiorinal® with Codeine | Donnatal® | Norel®SR)
• thrombocytosis (Cyanocobalamin, Vitamin B12 | Percocet®)
• thrombosis (Cafergot®)
• thrombotic thrombocytopenic purpura (TTP) (Plavix®)
• tinnitus (Bactrim™ DS | Vitamin D | Verapamil | Fiorinal® with Codeine)
• tissue necrosis (Cafergot®)
• tolerance (Klonopin® | Percocet® | Fiorinal® with Codeine | Foradil® Aerolizer)
• torsade de pointes (Rythmol)
• toxic epidermal necrolysis (Bactrim™ DS | Zantac 150™ | Plavix® | Percocet® | Fiorinal® with Codeine | Norel®SR)
• tremor (Albuterol | Norvasc® | Klonopin® | Diphenhydramine | Atrovent® | Fiorinal® with Codeine | Cafergot® | Tigan® | Combivent® | Unisom® Sleeptabs™ | Foradil® Aerolizer | Xopenex®)
• urinary retention (Albuterol | Diphenhydramine | Atrovent® | Donnatal® | Combivent® | Unisom® Sleeptabs™ | Histex™ I/E | Norel®SR)
• urticaria (Albuterol | Fosamax® | Bactrim™ DS | Flunisolide | Atrovent® | Theophylline | Percocet® | Fiorinal® with Codeine | Donnatal® | Combivent® | Foradil® Aerolizer | Xopenex® | Norel®SR)
• uterine contractions (Cafergot®)
• uveitis (Fosamax®)
• vasculitis (Bactrim™ DS | Zantac 150™ | Plavix®)
• ventricular fibrillation (Rythmol | Verapamil)
• ventricular tachycardia (Digitek™ | Rythmol | Theophylline)
• vertigo (Norvasc® | Klonopin® | Bactrim™ DS | Vitamin D)
• visual impairment (Fosamax® | Digitek™ | Atrovent® | Fiorinal® with Codeine | Combivent® | Histex™ I/E)
• weakness (Bactrim™ DS | Digitek™ | Diphenhydramine | Vitamin D | Rythmol | Unisom® Sleeptabs™ | Histex™ I/E | Xopenex®)
• weight loss (Vitamin D | Fiorinal® with Codeine)
• wheezing (Flunisolide | Fiorinal® with Codeine)
• withdrawal (Klonopin® | Percocet® | Fiorinal® with Codeine | Cafergot®)

• xanthopsia (Digitek™)
• xerophthalmia (Diphenhydramine | Unisom® Sleeptabs™ | Histex™ I/E | Norel®SR)
• xerostomia (Albuterol | Diphenhydramine | Vitamin D | Flunisolide | Atrovent® | Rythmol | Donnatal® | Cafergot® | Combivent® | Unisom® Sleeptabs™ | Foradil® Aerolizer | Histex™ I/E | Xopenex® | Norel®SR)

Precautions

Precaution: Albuterol in hypertension
Albuterol should be used with caution in patients with cardiovascular disorders including ischemic cardiac disease (coronary artery disease), hypertension, cardiac arrhythmias, tachycardia, or QT prolongation. In addition, beta-agonists should be avoided in patients with congenital long QT syndrome due to the risk of torsade de pointes.[4951] Significant changes in systolic and diastolic blood pressures and heart rate could be expected to occur in some patients after use of any beta-adrenergic bronchodilator. As with other beta-adrenergic agonist medications, albuterol may produce significant hypokalemia in some patients, possibly through intracellular shunting, which has the potential to produce adverse cardiovascular effects. The decrease is usually transient, not requiring supplementation. Correct pre-existing hypokalemia prior to beta-agonist administration.

Precaution: Albuterol in renal impairment
The pharmacokinetics of albuterol were studied in a small number of subjects with creatinine clearances between 7-53 mL/minute in comparison to healthy volunteers. The half-life was unchanged; however albuterol clearance was decreased by 67% in those with renal impairment. The manufacturer recommends caution during administration of high doses of inhaled albuterol to patients with renal impairment.[8628]

Precaution: Bactrim™ DS in renal impairment
Trimethoprim has a potassium-sparing effect on the distal nephron and may induce *hyperkalemia*, especially in patients with pre-existing risk factors (e.g., renal disease, elderly patients). Trimethoprim is contraindicated in patients with severe renal impairment, renal disease, or *renal failure* (creatinine clearance less than 15 ml/minute). Sulfamethoxazole; trimethoprim should be used cautiously in patients with moderate renal impairment (i.e., creatinine clearance less than 30 mL/min); the dosage should be adjusted to avoid drug accumulation and potential toxicity (see Dosage). Monitor serum potassium levels in patients with risk factors for developing drug-induced hyperkalemia (renal impairment, elderly, high-dose trimethoprim). In addition, use trimethoprim with caution in patients receiving drugs known to significantly increase serum potassium (see Drug Interactions).

Precaution: Cafergot® in hypertension
Caffeine; ergotamine is contraindicated in *peripheral vascular disease* (including *thromboangiitis obliterans (Buerger's disease)*, *luetic arteritis*, severe *arteriosclerosis*, *thrombophlebitis*, and *Raynaud's disease*), *coronary artery disease* (including unstable or vasospastic *angina,* or predisposition to vasospastic reactions), *sepsis*, history of *myocardial infarction*, or uncontrolled *hypertension*. It is recommended that ergotamine not be given to patients in whom unrecognized coronary artery disease (CAD) is predicted by the presence of cardiac disease risk factors (e.g., hypertension, hypercholesterolemia, current tobacco smoking, obesity, diabetes mellitus, strong family history of CAD, postmenopausal females, or males over 40 years of age), unless a cardiovascular evaluation provides sufficient evidence that the patient is reasonably free of ischemic heart disease. The elderly may be more susceptible to vasoconstrictive effects of ergot alkaloids. In general, dosing should be more cautious in the elderly, starting at the lower end of the dose range to account for differences in renal, hepatic, or cardiac systems as well as concomitant disease states and medications.

Precaution: Cafergot® in renal impairment
Renal impairment, including *renal failure*, is considered a contraindication to caffeine; ergotamine use by the manufacturer. Patients with severe renal impairment who receive ergotamine may develop symptoms of ergot poisoning because of impaired elimination. Use with caution in any patient with renal disease due to the vasoconstrictive effects of the drug.

Precaution: Calcium Magnesium Zinc Tablets in renal impairment
Magnesium salts should be used with caution in patients with renal disease, including patients with renal impairment or renal failure. Magnesium salts are renally eliminated, so patients with renal impairment have an increased risk of developing magnesium toxicity from decreased excretion of magnesium. In patients with severe renal dysfunction, no more than 20 grams (162 mEq) of magnesium should be administered within a 48-hour period. Parenteral magnesium should be avoided in patients with a creatinine clearance of less than 20 mL/minute. Up to 30% of an orally administered dose is absorbed systemically.

Precaution: Calcium Magnesium Zinc Tablets in renal impairment
Zinc Chloride injection contains aluminum which may reach toxic levels with prolonged administration in patients with renal impairment or renal failure. Neonates of neonatal prematurity are at particular risk for aluminum toxicity following administration of aluminum-containing injectables since they have immature kidneys. Research indicates that patients with renal impairment, including neonates, who receive parenteral aluminum at rates greater than 4-5 mcg/kg/day may accumulate aluminum at levels associated with CNS and bone toxicity. Tissue loading may occur at lower administration rates.

Precaution: Codimal® DH in constipation
Due to the effects of opiate agonists on the gastrointestinal tract, hydrocodone should be used cautiously in patients with GI disease including GI obstruction or ileus, ulcerative colitis, or pre-existing constipation. Opiate agonists may obscure the diagnosis or clinical course in patients with acute abdominal conditions. Patients with acute ulcerative colitis (UC) or other inflammatory bowel disease may be more sensitive to the constipating effects of opiate agonists. Hydrocodone should not be used in patients with suspected *paralytic ileus*. Although opiate agonists are contraindicated for use in patients with diarrhea secondary to *poisoning* or *infectious diarrhea*, antimotility agents have been used successfully in these patients. If possible, opiate agonists should not be given until the toxic substance has been eliminated.

Precaution: Codimal® DH in renal impairment
Hydrocodone and other opiate agonists can cause urinary retention and oliguria, due to increasing the tension of the detrusor muscle. Patients more prone to these effects include those with prostatic hypertrophy, urethral stricture, bladder obstruction, or pelvic tumors. Drug accumulation or prolonged duration of action can occur in patients with renal impairment, renal failure, or hepatic disease. In acute situations, patients require close monitoring to avoid excessive toxicity. Patients with chronic liver or renal disease may require less frequent dosing intervals.

Precaution: Codimal® DH in atrial fibrillation
Phenylephrine, particularly when administered intravenously, is absolutely contraindicated in patients with severe organic *cardiac disease* including *coronary artery disease* (e.g., *angina, history of myocardial infarction, acute myocardial infarction*), dilated *cardiomyopathy*, and/or *cardiac arrhythmias* associated with *tachycardia (atrial fibrillation, atrial flutter, ventricular fibrillation, ventricular tachycardia)* because of its detrimental cardiovascular effects in these conditions (i.e., increased myocardial oxygen demand, chronotropy, proarrhythmic potential, and vasoactivity). Phenylephrine should not be used in patients with *uncontrolled hypertension* (especially parenteral dosage forms) due to the increased likelihood of adverse cardiac events. Phenylephrine can cause a decrease in cardiac output, and extreme caution should be used when administering the drug, parenterally or orally, to patients with arteriosclerosis, to elderly patients, or to patients with *coronary artery disease* or heart failure. In general, elderly patients are more susceptible than younger adults to a reduction in cardiac output following sinus bradycardia. The baroreceptor reflex response to phenylephrine may decrease with age. Phenylephrine when administered by ophthalmic or nasal routes, should be also used with caution in patients with known or suspected cardiac disease or arteriosclerosis, including elderly patients. Elderly patients, especially those with pre-existing cardiac disease may experience adverse cardiovascular reactions including increased blood pressure, cardiac arrhythmias, or myocardial infarction following intraocular administration of 10% phenylephrine ophthalmic solution; therefore, use of the 2.5% ophthalmic solution is preferred for elderly patients.

Precaution: Codimal® DH in hypertension
Phenylephrine, particularly when administered intravenously, is absolutely contraindicated in patients with severe organic *cardiac disease* including *coronary artery disease* (e.g., *angina, history of myocardial infarction, acute myocardial infarction*), dilated *cardiomyopathy*, and/or *cardiac arrhythmias* associated with *tachycardia (atrial fibrillation, atrial flutter, ventricular fibrillation, ventricular tachycardia)* because of its detrimental cardiovascular effects in these conditions (i.e., increased myocardial oxygen demand, chronotropy, proarrhythmic potential, and vasoactivity). Phenylephrine should not be used in patients with *uncontrolled hypertension* (especially parenteral dosage forms) due to the increased likelihood of adverse cardiac events. Phenylephrine can cause a decrease in cardiac output, and extreme caution should be used when administering the drug, parenterally or orally, to patients with arteriosclerosis, to elderly patients, or to patients with *coronary artery disease* or heart failure. In general, elderly patients are more susceptible than younger adults to a reduction in cardiac output following sinus bradycardia. The baroreceptor reflex response to phenylephrine may decrease with age. Phenylephrine when administered by ophthalmic or nasal routes, should be also used with caution in patients with known or suspected cardiac disease or arteriosclerosis, including elderly patients. Elderly patients, especially those with pre-existing cardiac disease may experience adverse cardiovascular reactions including increased blood pressure, cardiac arrhythmias, or myocardial infarction following intraocular administration of 10% phenylephrine ophthalmic solution; therefore, use of the 2.5% ophthalmic solution is preferred for elderly patients.

Precaution: Combivent® in hypertension
Due to the sympathomimetic effects of albuterol, albuterol; ipratropium combinations should be used with caution in certain patient populations. Fatalities have been reported with the excessive use of sympathomimetic drugs in patients with asthma. Recommended dosages for albuterol; ipratropium should not be exceeded. In addition, beta agonists have been reported to produce ECG changes, such as flattening of the T-wave, QT prolongation, and ST segment depression. Albuterol should be used cautiously in any patient with cardiac disease, hypertension, angina, cardiac arrhythmias, tachycardia, or coronary artery disease since it has cardiostimulatory actions. In addition, beta-agonists should be avoided in patients with congenital long QT syndrome due to the risk of torsade de pointes.[4951] At excessive use or dosages, beta-agonists may produce a transient hypokalemia, which might produce adverse effects in susceptible individuals with cardiac disease, particularly those patients on non-potassium sparing diuretics.

Precaution: Combivent® in renal impairment
The use of albuterol; ipratropium has not been adequately studied in patients with renal impairment (including renal failure, renal disease) or hepatic disease.

Precaution: Digitek™ in hypertension
IV administration of digoxin can transiently increase blood pressure and should be used cautiously in patients with hypertension.

Precaution: Digitek™ in renal impairment
Patients with renal disease, such as acute glomerulonephritis, associated with heart failure should use digoxin with caution. Use of a lower daily dose is recommended with appropriate ECG monitoring based on clinical goals and patient conditions. Digoxin should be used with caution in patients with renal impairment including renal failure because 50% of digoxin is eliminated unchanged via the kidneys. Renal impairment reduces the excretion of the drug and can cause toxicity. Dosages should be decreased, and it should be kept in mind that the time required to reach steady-state concentrations can be prolonged in patients with renal failure.

Precaution: Donnatal® in hypertension
Atropine; Hyoscyamine; Phenobarbital; Scopolamine should be used with caution in patients with known cardiac disease. Antimuscarinics may alter the heart rate; the predominant clinical effect is tachycardia. Thus antimuscarinics should be used cautiously in patients with cardiac arrhythmias, congestive heart failure, coronary artery disease or other cardiac instability where an increase in heart rate could be detrimental. Antimuscarinics are relatively contraindicated in some patients with *acute myocardial infarction* because the drug can potentiate arrhythmias. In addition, the increase in heart rate caused by atropine increases the oxygen demand on the heart and can exacerbate myocardial ischemia. Increased heart rate is undesirable in patients with hyperthyroidism (*thyrotoxicosis*) or cardiovascular instability in *acute hemorrhage* (*bleeding*). Antimuscarinics should be used with caution in patients with mitral stenosis since tachycardia could exacerbate the clinical symptoms of this condition. Antimuscarinics should be used with caution in patients with hypertension since they have some actions on the heart and can exacerbate this condition.

Precaution: Donnatal® in renal impairment
Antimuscarinics and barbiturates should be used cautiously in patients with renal impairment. Metabolites and unchanged drug are excreted in the kidneys. Renal failure can lead to phenobarbital toxicity because >= 25% of the drug is excreted unchanged in the urine. Further, antimuscarinics can cause *urinary retention*. Atropine; Hyoscyamine; Phenobarbital; Scopolamine is therefore contraindicated in patients with *bladder obstruction*, *prostatic hypertrophy*, or other *urinary tract obstruction* because urinary retention may be aggravated. Urinary retention may also be aggravated in patients with autonomic neuropathy.

Precaution: Fiorinal® with Codeine in constipation
Aspirin can induce gastric or intestinal ulceration that can occasionally be accompanied by iron-deficiency from the resultant blood loss. Aspirin-butalbital-caffeine-codeine should not be used in patients with *peptic ulcer disease* and should be used cautiously, if at all, in patients with a history of or active GI disease including erosive esophagitis, gastritis, GI bleeding, *infectious diarrhea,* ulcerative colitis, or previous NSAID-induced bleeding. Such patients should be monitored closely, with special caution in tobacco smoking patients or in patients with alcoholism. All patients receiving chronic treatment should be routinely monitored for potential GI ulceration and bleeding. All products containing aspirin should be discontinued at least 1 week before surgery to minimize postoperative bleeding. Acetaminophen; butalbital; caffeine; codeine should also be avoided in those with acute abdomen (e.g., GI obstruction or *ileus*, including *paralytic ileus*). Opiate agonists like codeine can slow GI motility, aggravating constipation or leading to impaction.

Precaution: Fiorinal® with Codeine in hypertension
Aspirin; ASA; butalbital; caffeine; codeine should be used with caution in patients with mental status changes such as major depression or suicidal ideation due to exacerbation of these conditions by the CNS depressant effects. Aspirin; ASA; butalbital; caffeine; codeine should be prescribed cautiously to certain high risk patients such as elderly or debilitated patients, patients with cardiac disease (e.g., angina, cardiac arrhythmias, hypertension, hypotension, or immediately following an acute myocardial infarction) because of possible adverse hemodynamic effects. The risk of an aspirin-induced GI bleed is greater in the elderly. Elderly patients may experience increased side effects such as excitement, confusion or depression. In cases where an overdose of a barbiturate has occurred, symptoms may include: confusion, hypotension, incoherent speech, nystagmus, and tachycardia. Elderly patients are more sensitive to the analgesic effects of opiate agonists as they experience higher peak serum levels and a longer duration of relief. According to US federal OBRA regulations, butalbital is not to be used in a nursing home patient, unless started before admission to the nursing home, or given as a single dose for a medical or dental procedure. Discontinuation should be gradually attempted at least twice in one year before discontinuation is considered 'clinically contraindicated.'

Precaution: Fiorinal® with Codeine in osteoporosis
Use aspirin; ASA; butalbital; caffeine; codeine with caution in patients with low bone density. There may be an increased risk of osteopenia/osteoporosis with long-term barbiturate therapy. Osteomalacia has been noted in patients using barbiturates who have end-stage kidney disease.

Precaution: Fiorinal® with Codeine in renal impairment
Aspirin; ASA; butalbital; caffeine; codeine should be used carefully in patients with diabetes mellitus, inflammatory bowel disease, prostatic hypertrophy, urethral stricture or thyroid disease (i.e., hypothyroidism). Aspirin; butalbital; caffeine; codeine should be used with caution in patients with renal disease, renal impairment and with extreme caution, if at all, in patients with advanced, chronic renal failure since metabolites of aspirin, including salicylic acid, are renally excreted. In addition, these patients may be at increased risk of

developing salicylate-induced nephrotoxicity. Aspirin; butalbital; caffeine; codeine should also be used cautiously in patients with renal disease or systemic lupus erythematosus (SLE) due to the risk of decreased glomerular filtration rate in these patients. Dose adjustments of codeine are required in patients with CrCl < 50 ml/min; combination products such as aspirin; ASA; butalbital; caffeine; codeine make this extremely difficult. Codeine can cause urinary retention and oliguria, due to increased the tension of the detrusor muscle; patients more prone to these effects include those with prostatic hypertrophy, urethral stricture, bladder obstruction, urinary tract obstruction, or pelvic tumors.

Precaution: Flunisolide in osteoporosis
Detrimental effects on bone metabolism, such as osteoporosis are expected to be much lower with inhaled, rather than systemically-administered corticosteroids. Although not conclusive, some data suggest that high-dose inhaled steroids may also decrease bone formation and increased resorption. Some patients receiving inhaled steroids may be at increased risk of bone loss compared to healthy individuals. Prospective long-term trials are needed confirm these findings.[1159]

Precaution: Foradil® Aerolizer in hypertension
Formoterol should be used with caution in patients with cardiovascular disorders including ischemic cardiac disease (coronary artery disease), hypertension, cardiac arrhythmias (including tachycardia), or QT prolongation. In addition, beta-agonists should be avoided in patients with congenital long QT syndrome due to the risk of torsade de pointes.[4951] Significant changes in systolic and diastolic blood pressures and heart rate could be expected to occur in some patients after use of any beta-adrenergic bronchodilator. As with other beta-adrenergic agonist medications, formoterol may produce significant hypokalemia in some patients, possibly through intracellular shunting, which has the potential to produce adverse cardiovascular effects. The decrease is usually transient, not requiring supplementation. Correct pre-existing hypokalemia prior to beta-agonist administration. Elderly patients may be more sensitive to the side effects of beta-agonists, especially tremor and tachycardia; this risk is higher in patients with preexisting coronary artery disease. Although not clearly established, airway responsiveness to beta-agonist medications may also change with age.

Precaution: Fosamax® in renal impairment
About 50% of a single IV dose of alendronate is excreted in the urine. Studies in animals indicated that any alendronate not deposited in bone was rapidly excreted. Renal failure in animals led to increased amounts of alendronate in plasma, kidney, spleen, and tibia. No human study results are available, but it is likely that patients with severe renal impairment will accumulate alendronate. No dosage adjustment is recommended by the manufacturer if creatinine clearance is > 35 ml/min (mild to moderate renal insufficiency). Until further evidence is available alendronate is not recommended for patients with creatinine clearance < 35 ml/min (*renal failure*).

Precaution: Histex™ I/E in hypertension
Anticholinergic effects also warrant caution when carbinoxamine is used in patients who have hyperthyroidism, cardiac disease, or hypertension.

Precaution: Klonopin® in females
Clonazepam is classified as FDA pregnancy category D. Females of childbearing potential should discuss options with their prescriber or health care professional prior to beginning treatment with clonazepam. The possibility that a woman of child-bearing potential may be pregnant at the time of institution of therapy should be considered and/or ruled out. In general, the use of clonazepam in pregnant epileptic women should be considered only when the clinical situation outweighs any potential risk to the fetus. In the treatment of panic disorder, alternative treatments should be considered. Pregnant rabbits were given clonazepam doses lower or similar to maximum human doses during the period of organogenesis. Cleft palate, open eyelid, fused sternebrae and limb defects were observed in a low, non-dose related incidence in exposed litters from all dosage groups. No maternal or embryo-fetal anomalies were noted in mice and rats receiving 4 and 20 times the maximum recommended human dose. There may also be non-teratogenic risks associated with benzodiazepines during the perinatal period, including neonatal flaccidity, respiratory suppression, feeding difficulties, and hypothermia in infants born to mothers who received benzodiazepines late in pregnancy. In women with epilepsy, abrupt withdrawal of clonazepam may result in life-threatening status epilepticus. Additionally, even mild seizures may pose hazards to the developing fetus. If a woman becomes pregnant while taking clonazepam, she should be counseled regarding the potential risks to the fetus. Clonazepam has not been studied for use in obstetrical procedures or obstetric delivery, including cesarean section; however, other benzodiazepines have been associated with perinatal complications.

Precaution: Klonopin® in renal impairment
Clonazepam should be administered cautiously to patients with renal impairment or renal failure; in general, initial dose selection should be in the lower range and dosage titration should proceed cautiously. Assess renal function during prolonged therapy and adjust dosage as clinically indicated.

Precaution: Melatonin in females
At this time, melatonin should be considered contraindicated in females who are trying to conceive. As a hormone, melatonin modulates steroid hormone actions, including those in reproductive and mammary tissues. Melatonin has been shown to inhibit ovulation in higher doses and may affect reproductive capacity, thus it may impact infertility. In men, there is some evidence that melatonin is important in the regulation of sperm counts and use of melatonin may affect the proper production of sperm.

Precaution: Melatonin in insomnia
The American Sleep Disorder Association considers melatonin an experimental drug for insomnia and does not recommend its use without medical supervision. Due to a lack of scientific data and an unknown potential for side effects, melatonin is not recommended for use in neonates, infants, or children without the approval and observation of a health care professional. Caution is also warranted in the elderly due to limited study of melatonin in this patient population at this time. If an adult patient decides to self-treat insomnia with melatonin, it is recommended that use not exceed 2 weeks without consultation of a health care professional.

Precaution: Norel®SR in atrial fibrillation
Products containing phenylephrine are contraindicated in patients with *acute cardiac arrhythmias* (*tachycardia, ventricular tachycardia, ventricular fibrillation, atrial fibrillation, atrial flutter*), *severe or uncontrolled hypertension*, or *severe coronary artery disease* (including *acute myocardial infarction*, *angina*, or *history of myocardial infarction*). Products containing phenylephrine, chlorpheniramine, and phenyltoloxamine should be used with considerable caution in patients with bradycardia, partial heart block (AV block, bundle-branch block), controlled or mild hypertension, heart failure, cardiomyopathy, ischemic heart disease, or other cardiac disease due to the sympathomimetic effects of phenylephrine and anticholinergic effects of chlorpheniramine and phenyltoloxamine. The quinidine-like local anesthetic and anticholinergic effects of H_1-antagonists are responsible for adverse cardiac effects that have been observed with such drugs, including tachycardia, ECG changes, hypotension, and arrhythmias.

Precaution: Norel®SR in constipation
Products containing phenylephrine may exacerbate urinary retention and should be used with extreme caution in patients with this symptomatology. A worsening of symptoms may occur in patients with bladder obstruction, benign prostatic hypertrophy, pre-existing constipation, and GI disease (e.g., ulcerative colitis, GI obstruction or ileus, *pyloric stenosis*, *stenosing* peptic ulcer disease) due to the anticholinergic effects of chlorpheniramine and phenyltoloxamine.

Precaution: Norel®SR in hypertension
Products containing phenylephrine are contraindicated in patients with *acute cardiac arrhythmias* (*tachycardia, ventricular tachycardia, ventricular fibrillation, atrial fibrillation, atrial flutter*), *severe or uncontrolled hypertension*, or *severe coronary artery disease* (including *acute myocardial infarction*, *angina*, or *history of myocardial infarction*). Products containing phenylephrine, chlorpheniramine, and phenyltoloxamine should be used with considerable caution in patients with bradycardia, partial heart block (AV block, bundle-branch block), controlled or mild hypertension, heart failure, cardiomyopathy, ischemic heart disease, or other cardiac disease due to the sympathomimetic effects of phenylephrine and anticholinergic effects of chlorpheniramine and phenyltoloxamine. The quinidine-like local anesthetic and anticholinergic effects of H_1-antagonists are responsible for adverse cardiac effects that have been observed with such drugs, including tachycardia, ECG changes, hypotension, and arrhythmias.

Precaution: Norel®SR in renal impairment
There are no data on the use of acetaminophen; chlorpheniramine; phenylephrine; phenyltoloxamine combinations in patients with renal disease, renal impairment, or renal failure. However, in chronic renal failure patients undergoing hemodialysis, the half-life of chlorpheniramine may be as long as 280-330 hours. Dosage adjustments may be required, as drug accumulation or prolonged duration of action can occur in patients with renal dysfunction. Chronic acetaminophen administration should be avoided in patients with underlying renal disease (see Adverse Reactions); however it may be used for episodic pain.

Precaution: Percocet® in constipation
Due to the effects of opiate agonists on the gastrointestinal tract, acetaminophen-oxycodone should be used cautiously in patients with GI disease including GI obstruction or ileus, ulcerative colitis, or pre-existing constipation. Opiate agonists may obscure the diagnosis or clinical course in patients with acute abdominal conditions. Oxycodone is contraindicated in patients who have or are suspected of having *paralytic ileus*. Patients with acute ulcerative colitis or other inflammatory bowel disease may be more sensitive to the constipating effects of opiate agonists. Although opiate agonists are contraindicated for use in patients with *diarrhea secondary to poisoning or infectious diarrhea*, antimotility agents have been used successfully in these patients. If possible, opiate agonists should not be given until the toxic substance has been eliminated.

Precaution: Percocet® in renal impairment
Acetaminophen-oxycodone should be used cautiously in patients with renal impairment or renal failure; dosage adjustments may be required. Oxycodone can cause urinary retention and oliguria, due to increasing the tension of the detrusor muscle. Patients more prone to these effects include those with prostatic hypertrophy, urethral stricture, bladder obstruction or pelvic tumors. In addition, oxycodone may accumulate in these patients leading to a prolonged duration of action and potential increase in side effects. Chronic acetaminophen administration should be avoided in patients with underlying renal disease; however it may be used for episodic pain.

Precaution: Plavix® in renal impairment
Although no dosage adjustment is recommended in patients with renal impairment, the manufacturer warns that clopidogrel should be used with caution in patients with severe renal impairment. Experience is limited in patients with severe renal disease or renal failure.

Precaution: Rythmol in renal impairment

The pharmacokinetics of propafenone and 5-hydroxypropafenone do not appear to be altered in patients with renal impairment; however, caution is advised by the manufacturer in patients with renal failure or renal disease since 38% of propafenone's metabolites are renally excreted. In addition, the dosage of propafenone should be increased more gradually during initial treatment in elderly patients.

Precaution: Verapamil in constipation
Verapamil is frequently causes constipation. Verapamill should be used cautiously in patients with GI obstruction or ileus, fecal impaction, or pre-existing constipation. Calcium channel blockers should also be used cautiously in patients with gastroesophageal reflux disease (GERD) or hiatal hernia associated with reflux esophagitis. Calcium-channel blockers act to relax the lower esophageal sphincter.

Precaution: Verapamil in renal impairment
The elderly, patients with renal disease, or patients with hepatic disease, such as cirrhosis or hepatic failure, can experience a delayed clearance of verapamil and its metabolites. Drug accumulation may increase the risk of adverse effects. The elimination half-life of verapamil may be prolonged in the elderly. In general, lower initial doses of verapamil may be warranted in elderly patients. About 70% of an administered dose of verapamil is excreted as metabolites in the urine. Until further data are available, verapamil should be administered cautiously to patients with renal impairment or renal failure; these patients should be carefully monitored for abnormal prolongation of the PR interval or other signs of excessive dosage. The half-life of verapamil may be increased up to 14-16 hours in patients with hepatic impairment; plasma clearance may be reduced by 30%. Dosage adjustments may be necessary in patients with hepatic impairment.

Precaution: Xopenex® in hypertension
Levalbuterol should be used with caution in patients with cardiovascular disorders including ischemic cardiac disease (coronary artery disease), hypertension, cardiac arrhythmias, tachycardia, or QT prolongation. In addition, beta-agonists should be avoided in patients with suspected or known congenital long QT syndrome due to the risk for torsade de pointes.[4951] Significant changes in systolic and diastolic blood pressures and heart rate could be expected to occur in some patients after use of any beta-adrenergic bronchodilator. As with other beta-adrenergic agonist medications, levalbuterol may produce significant hypokalemia in some patients, possibly through intracellular shunting, which has the potential to produce adverse cardiovascular effects. The decrease is usually transient, not requiring supplementation. Correct pre-existing hypokalemia prior to beta-agonist administration.

Precaution: Xopenex® in renal impairment
Racemic albuterol is substantially excreted by the kidney, and the risk of toxic reactions may be greater in patients with renal impairment including renal failure. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function. In addition, elderly patients may be more sensitive to the side effects of beta-agonists, especially tremor and tachycardia; this risk is higher in patients with preexisting coronary artery disease. Although not clearly established, airway responsiveness to beta-agonist medications may also change with age.

Precaution: Zantac 150™ in renal impairment
Ranitidine should be used cautiously in those patients with renal disease, specifically in those with renal impairment or renal failure. Accumulation of ranitidine can occur. Ranitidine dosage should be reduced in patients with creatinine clearances of less than 50 ml/min (see Dosage). No special precautions have been advised for the elderly, but some older patients may exhibit decreased renal function. Accumulation of ranitidine can occur. Dosage adjustments may be necessary in some older individuals based on renal function. Critically ill, elderly patients have been noted in some uncontrolled studies to be more likely to exhibit central nervous system (CNS) reactions to the H_2-blockers.

Allergy Alerts

No warnings noted

Therapeutic Duplications

- Albuterol, Codimal® DH, Combivent®, Foradil® Aerolizer, Norel®SR, and Xopenex® are Adrenergic agonists.
- Albuterol, Combivent®, Foradil® Aerolizer, and Xopenex® are Beta-agonists.
- Atrovent®, Combivent®, and Donnatal® are Anticholinergics.
- Atrovent®, Combivent®, and Donnatal® are Antimuscarinics.
- Atrovent® and Combivent® are Antimuscarinics.
- Cafergot® and Fiorinal® with Codeine are Psychostimulants.
- Codimal® DH, Diphenhydramine, Histex™ I/E, Norel®SR, and Unisom® Sleeptabs™ are H_1-blockers.
- Codimal® DH, Diphenhydramine, Histex™ I/E, Norel®SR, and Unisom® Sleeptabs™ are Sedating H_1-blockers.

• Codimal® DH and Norel®SR are Sympathomimetics.
• Codimal® DH and Norel®SR are Adrenergic agonists.
• Codimal® DH and Norel®SR are Decongestants.
• Cyanocobalamin, Vitamin B12 and Vitamin D are Vitamins.
• Digitek™, Rythmol, and Verapamil are Antiarrhythmics.
• Diphenhydramine, Donnatal®, Fiorinal® with Codeine, Klonopin®, and Unisom® Sleeptabs™ are Anxiolytics.
• Diphenhydramine, Donnatal®, Fiorinal® with Codeine, Klonopin®, and Unisom® Sleeptabs™ are Sedatives.
• Diphenhydramine, Donnatal®, Fiorinal® with Codeine, Klonopin®, and Unisom® Sleeptabs™ are and Hypnotics.
• Donnatal® and Fiorinal® with Codeine are Barbiturates.
• Fiorinal® with Codeine and Percocet® are Opiate Agonists.
• Fosamax® and Vitamin D are Calcium Modifiers.
• Fosamax® and Vitamin D are Bone Resorption Inhibitors.
• Norvasc® and Verapamil are Antianginals.
• Norvasc® and Verapamil are Calcium-channel blockers.
• Norvasc® and Verapamil are Antihypertensive Agents.

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