Patient Profile for Larry Besloft

General Information

ID:	lb07252010
Prescriber:	Washington, Harold M.D.
Name:	Larry Besloft
Address:	27 Tifton Road
City:	Maragold
State:	CA
Zip:	30001
Country:	USA
Phone:	h/310.213.2314 c/310.123.3456

Current Conditions

- aneurysm
- angina
- atrial fibrillation
- benign prostatic hyperplasia (BPH)
- cardiac arrhythmias
- diarrhea
- gastroesophageal reflux disease (GERD)
- hyperlipoproteinemia
- hypertension
- hypokalemia
- myalgia
- nutritional supplementation
- osteoarthritis
- renal impairment
- restless legs syndrome (RLS)
- thrombosis prophylaxis

Current Allergies

- Keflex
- Procardia

Current Medications

• Medication		
• Acetaminophen; Oxycodone	Dosage: 7.5mg / 500mg Acetaminophen (Endocet)	Sig: tab 1 at bedtime for shoulder pain
• Amlodipine	Dosage: 5mg	Sig: tab 1 daily
• Aspirin, ASA	Dosage: 81mg	Sig: tab 1 daily
• Magnesium	Dosage: 200mg	Sig: daily for leg cramps and heart
• Diovan HCT®	Dosage: 320mg/12.5mg	Sig: tab 1 AM and PM
• Endocet®	Dosage: 5mg/325mg	Sig: tab every 4 to 6 hours as needed for moderate pain
• Flomax®	Dosage: 0.4mg	Sig: daily
• Imdur®	Dosage: 30mg	Sig: daily
• Lipitor®	Dosage: 20mg	Sig: tab 1 at bedtime
• Loperamide	Dosage: 2mg	Sig: tab 2 first dose then 1 every 2 hours as needed diarrhea
• Mirapex®	Dosage: 0.25mg	Sig: tab 1 at bedtime RLS
• CoQ10	Dosage: 60mg	Sig: daily
• Piroxicam	Dosage: 20mg	Sig: cap 1 daily
• Plavix®	Dosage: 75mg	Sig: daily

- Potassium Chloride Dosage: 750mg Sig: tab 1 daily
- Protonix® Dosage: 40mg Sig: tab 1 AM
- Super B Complex With Vitamin C Sig: daily
- Toprol XL® Dosage: 50mg Sig: 75mg (1 1/2) tab twice a day AM & PM
- Trental® Dosage: 400ng Sig: twice a day AM and PM
- Tylenol® Arthritis Dosage: 650mg Sig: tab 2 every 8 hours for shoulder pain
- Vitamin C with Rose Hips Dosage: 500mg Sig: AM & PM
- Vitamin E Dosage: 400 U Sig: tab 1 AM & PM

Dosing Parameters

Gender:	Male
Birthdate:	12/19/1923
Weight:	79.55 kgs
Height:	175.26 cm
Ideal Body Weight:	70.65 kgs
Body Surface Area:	1.97 m²
Serum Creatinine:	1.4 mg/dL
Creatinine Clearance:	39.95 mL/min

Notes

Title: Initial Interview & Assessment

Date: 07/24/2007

This 84 year old white male presents with multiple problems of muscle spasms, generalized pain in muscles, severe anemia to the degree that he constantly dozes off while trying to converse, multiple problems with stomach, arthritis, weakness, syncope, fatigue, and persistent problems with coronary disease. He is exceptionally alert and cognitively sound, although his severe anemia makes maintaining a train of thought difficult. He is currently on 22 different medications, many of which are causing most of his problems. Since starting the Statin therapy back in 2002, he has experienced a cascade of health events that has caused him much discomfort, multiple hospitalizations, multiple coronary catheterizations, blood loss, multiple treatments that further caused more deterioration of his health and, in fact, has placed his life in a high degree of risk of a fatal episode. Almost immediately after starting Statin therapy, he experienced more arthritis pain, shoulder pain, cramps in legs and general aches and pain. For this problem he was started on Trental, and Bextra which further exacerbated his GI tract and started slow gastric bleeds. Although some relief of pain was experienced he then started Prednisone along with the Trental and Bextra. Continued therapy for arthritis provided little benefit and soon he was again hospitalized for Angina episodes for which a Nitrate (Imdur) was added to his regimen along with Plavix. During this period of time the patient had bilateral cataract surgery which was very successful and improved his vision dramatically. By this time, November 2003, he was becoming weak, dizzy and nauseated and was hospitalized with a severe GI bleed. Protonix ,a PPI, was added to his regimen and the prednisone removed. Later the Bextra, Imdur and Plavix were removed from his regimen and Toprol, a beta blocker, was added along with an Angiotensin II, ARB, with Hydrochlorthiazide and Ultrasound for his Arthritis and Cramps. By 2004 the patient

explained that the Arthritis was all over his body and he was administered an injection, unknown, in his left shoulder, but no relief was realized. At this time Oxycodone + Acetaminophen both 5mg for pain throughout the day and 7.5mg at bedtime were ordered. Repeated laboratory tests were done to identify the Arthritis diagnosis but no positive results from the test were seen. So the diagnosis changed to Lupus and Effexor XR was prescribed. Again he was admitted to the hospital for an emergency episode which was diagnosed as Atrial Fib that had converted on the way to the hospital. He was placed on Toprol and Clonidine and had an MRI resulting in another diagnosis of Torn Rotator Cuff and discharged. In a few months, he was again admitted to the hospital with dangerously low blood pressure and was again treated for Angina. Another Coronary Catheterization was ordered and another stint was added. Now the cramps in his legs were more severe and resulted in restless leg syndrome. Chest Xrays revealed no problems. Later in 2006 he started with episodes of severe diarrhea and Anemia and more cramps and shoulder pains. The shoulder pains have almost stopped all of his activities and he can't play golf, which he loves to do, and almost anything requiring range of motion. There are more and more hospitalizations, Coronary Catheterizations, EKGs, Xrays, symptomatic heart problems, Angina, erratic blood pressures and no relief.

As I look at his drug therapy throughout this 5 or 6 year ordeal, I keep going back to the beginning and how everyone overlooked the obvious side effects precipitated by the Statin Lipitor that started appearing within a month of starting therapy. A cascade of events occurred due to medications ordered to treat the symptoms of the adverse events from Statin use and the awful problems that these additional drugs have caused and are causing at this time. I am seeing a very alert 84 year old male who is having a very difficult time staying awake long enough to talk to me due to severe anemia. This anemia was identified 7 months ago and no drug changes were made and no attempts to get his dangerously low CBC values up. He may need a few units of blood to hasten his recovery from this serious problem. Since I am working from laboratory tests that are 6 months old, he needs updated CMP and CBC and if his HGB is still 10 or less the blood should be considered. If the HGB has improved then the iron therapy and other vitamin regimens to be suggested should allow for the necessary improvements without the blood. He is on multiple blood thinners, Aspirin, Plavix, Trental and Vitamin E. He is on a Proton Pump Inhibitor that has pushed his gastric acid pH to such a basic state that his potential risk for C. Diff Diarrhea of which he has had episodes along with the loss of Folate and Vitamin B12 due to this drug further inhibits an opportunity to get well. Additionally, he is taking the strongest and potentially fatal NSAID, Piroxicam, which is totally contraindicated in the geriatric patient. All this, combined with previous GI bleeds, means there is the potential risk of a fatal GI hemorrhage at any time. The arthritis, chest pain, myalgia and neuropathic pain are probably all resulting from the use of Lipitor in this patient. Subsequent problems are just exacerbated by the addition of all the drug therapy both concomitantly and free standing. His calculated Creatinine Clearance (CrCl) is 39cc/min which makes many of the drugs currently being used contraindicated and influence many of the serious adverse episodes experienced. He is suffering from the familiar drug non-productive cough consistent with ACE and ARB therapy especially in the very large dosing of

640mg of Diovan. Use of thiazide diuretics in patients with renal impairment in the range of this patient is not recommended due to clearance problems- the amount of the drug that does not clear migrates to the lungs, increasing potential risk for pulmonitis, dry cough and pneumonia. Loop diuretics are the drugs of choice in the geriatric population. Need for Dopamine Agonists (Mirapex) is probably unnecessary after a brief time of removal of the Lipitor. Many of the ups and downs of his blood pressure are due to the many different drug agents used to control his blood pressure as well as the alpha blocker,Flomax, used for his BPH. All of these drugs need to be consolidated to control blood pressure and a different agent utilized for the BPH. His excessive use of Acetaminophen both in the Oxycodone preparations along with intermittent use of Acetaminophen place him at a very high risk for hepatotoxicity due to excess of 3000mg daily. An evaluation of Depression by the Validated Geriatric Depression Scale shows a value of 2 which indicates very little depression. Further discussion shows that although he is not depressed, being the sole caregiver of his wife who suffers from dementia, places him at a very high anxiety level. His devotion and dedication to making sure she is taken care of is paramount in his mind. This high level of anxiety will also have to be resolved as I am sure his recovery from this Polypharmacy war will be accomplished with a little help. I truly believe that if we can remove these drugs and allow the body to heal itself that his playing golf is not an unrealistic goal. I know that consistent with the youthful dexterity he displays, his return to good health is a very strong possibility. In an effort to try and remove some of the critical problems at once I have advised him to stop the Aspirin, Trental, Piroxicam (every other day x 4 days and completely stop) and Lipitor. If he has to use more Oxycodone at present that is OK until other tapering and discontinuing of drugs are achieved with this report. Physician cooperation is required and I am very happy to hear that his new physician is anxious to work with us. His list of allergies includes Procardia and Diltiazem yet he is on another calcium channel blocker for the Procardia (dihydropyridine family) which made me wonder if reactions to some of the other past medications may have been mistaken for the calcium channel blockers. I would like to attempt using the Diltiazem (benzothiazepine) type calcium channel blocker in the total maintenance of his blood pressure needs. Benzothiazepine calcium channel blockers are very geriatric friendly and will allow for monotherapy which reduces potential risks for adverse events.
I will breakdown each drug further in this report and address each of the serious adverse events and how a management program should be developed to return the patient to an appropriate health status.

Title: Drug Therapy Evaluation & Recommendations
Date: 08/06/2007

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

Oxycodone / Acetaminophen (Endocet) - Use of this combination is an excellent analgesic consistent with severe chronic pain. Problems occur when a physical and mental dependence result from long term use. More studies show that patients with true chronic pain are less prone to become addicted than those with moderate or minor pain. In this patient pain is ever present and should subside with the reduction of many of the offending drugs. At that time a slow tapering of Oxycodone will be attempted. I expect an excellent outcome. The problem presently is the amount of Acetaminophen that is ingested which can lead to serious problems with the liver. Our discussion today indicated that about 5000mg of Acetaminophen are taken daily. This has to stop at once.

Amiodipine - a dihydropyridine calcium blocker from the same chemical family at the Procardia and the patient has not had any problems taking this drug. The benzothiazepine group of calcium channel blockers is more geriatric friendly than Amiodipine due to the fact that the half life of the Amiodipine (Norvasc) is extended to over 30 hours causing compounding of dosing leading to edema in the hands and feet. The use of the time release benzothiazepine (Diltiazem) allows for greater activity under the curve (AUC) thereby affording more hypertensive protection. As a rule there is more concern in the white male for vascular causes for hypertension than renal issues treated with ACE and ARB drugs.

Aspirin Low Dose 81mg - Although I advised the patient to stop this drug for now, I will later recommend for it to be used as a stroke prophylactic therapy over the current Plavix 75mg that I wanted him to continue. He was on many NSAID drugs from the Piroxicam to the Aspirin so we must remove all NSAID therapy in an effort to reduce potential for a fatal GI bleed and allow his stomach to heal. Later a slow taper of the PPI (Protonix) will be recommended and the Plavix will be replaced with the Aspirin.

Magnesium - I don't see a need for continued use of the Magnesium at this time. Leg cramps are a very high probability adverse event from the Statin therapy and should subside in a few months. Current use has not proven to be effective.

Diovan HCT - With a calculated Creatinine Clearance of only 39cc/min, use of ARB and thiazide diuretics are questionable and as in this case of twice the recommended geriatric dose places the patient at severe risk for angioedema, myalgia, rhabdomyolysis and respiratory problems with cough and pulmonitis. Many of these symptoms are present at this time. Past treatment for the persistent dry non-productive cough, which is chronic, is surely an adverse event with the ARB since you are currently on such a high dose. Muscle pain and other neuropathic pains are all exacerbated by the use of this drug. Loop diuretics are the drugs of choice in the geriatric population due to filtration impairment in the glomerulra areas of the kidney. The use of long

acting half life torsemide (Demadex), a loop diuretic, will allow for big reductions in dosing thereby sparing more potassium and calcium.

Flomax - an alpha blocker used to treat BPH and works well, but in fact in many older patients on antihypertensive medications will lower the blood pressure even more resulting in fatigue and orthostatic hypotension. Although many patients have had success with the Flomax there have be a statistical amount of patients that had to discontinue the Flomax due to unspecified chest pains, back pains and arthralgia. For this reason I believe a change in therapy is reasonable in an effort to avoid these possible adverse events that could be occurring. A six month trial of Avodart (dutasteride) may help in stopping some of the neuropathic pain.

Imdur - nitrate therapy is contraindicated in patients with severe anemia, which exists in this patient, because the drug causes oxidation of hemoglobin to methemoglobin which could exacerbate the anemia problem. The geriatric patient is more sensitive to the hypotensive effects of nitrates. Nitrate-induced hypotension has resulted in fatalities. This age group is at higher risk of falling due to syncope at normal therapeutic doses of nitrates. This problem occurs due to reduced baroceptor function; severe orthostatic hypotension may occur when vasodilators such as nitrates are used. A consolidation of all antihypertensive/cardio drugs to monotherapy of Diltiazem CD will be recommended. Questioning both the patient and his daughters about problems perceived with the use of Diltiazem in the past seem to point to dosing problems and concomitant use of several antihypertensive drugs.

Lipitor - Statin use in the very old is not possible without risk of many serious adverse events that could be fatal. These adverse events manifest themselves in exacerbation of muscle mass loss resulting in arthralgia, myalgia, chest pain, back and shoulder pain, leg cramps and overall body pain, which the patient is experiencing . I advised him to discontinue this drug the day of our interview. In all patients over 65 years of age, the condition of Sarcopenia (loss of muscle mass) occurs and is only exacerbated by the use of statin therapy. Many of the suspected diagnosis Lupus, Arthritis, Restless Leg Syndrome, muscle cramps and multitudes of complaints throughout this patient's medical history seemed to be overlooked as drug induced problems for the use of the statin Lipitor started in 2002. Review of his Lipid profile did not show a need for this therapy. In my practice geriatric patients respond extremely well to lipid lowering with the B Vitamins regimen that I will suggest. Assuming an elevated homosystine level which is common in the geriatric patient and treating to lower this level will allow the Lipids to seek lower acceptable levels for an 84 year old male. Starting therapy is Vitamin B12 Inj., Vitamin B6 200mg daily, Folic Acid 1mg daily. Practice guidelines currently followed are for much younger adults and are not necessary in the geriatric patient.

Loperamide - diarrhea problems are related to the long term use of the PPI (proton pump inhibitor) Protonix. In the geriatric patient, long term use results in the permanent change in the gastric pH from acid to basic (pH about 7) which will not allow for acid sensitive drugs to breakdown and perform. Serious problems with anemia can result due to the B12 and Folate loss. Problems appearing in nursing home facilities from long term use of PPI therapy is C. Diff Diarrhea due to gut remaining basic. This can lead to aspiration pneumonia with the basic fluids

causing bacterial pneumonia, which is normally fatal. Although the PPI is needed in this patient for at least the next 2 or 3 months due to the NSAID therapies, the PPI will help stop the gastric bleeding that I think is ongoing. After that a more natural approach to treating geriatric heartburn with either Buttermilk or Yogurt with as needed supplemental support of an H2 blocker (ranitidine) will be tried. Again, consistent with my findings this works extremely well in the geriatric population with much less potential risk.

Mirapex - use of dopamine agonists in the very old increases potential risks for hallucinations seven fold. Many of the arthralgia or muscle type symptoms can be exacerbated by the use of this drug. Rhabdomyolysis has been reported in the geriatric patient with its use. Increased fatigue and weakness are often seen with its use for RLS.

CoQ10 - the theory is that this drug will supplement enzymes lost with statin therapy guarding against the muscle pain and muscle mass loss. No substantial validated controlled studies have been presented to prove this claim. With the removal of the Statin therapy there is little need for continued use of this drug.

Piroxicam - A very potent NSAID with a serious adverse events profile. Use in the very old is totally contraindicated. With a history of gastric hemorrhage and GI disorders this drug is life threatening. I asked for the patient to take a dose every other day for 4 doses and to totally stop this drug afterwards. Although I don't like to advise stopping medications prior to the physician sanction of my report, I felt that this was vital and should not be continued any longer consistent with his severe anemia and probable blood loss.

Plavix - a platelet inhibitor like Aspirin. This drug works well and is recommended to continue for the next two months while his stomach is healing from the NSAID invasion that has now been stopped. All the current studies show that there is little to no benefit of Plavix over full strength Aspirin in platelet inhibition. As soon as his stomach is allowed to recover then the Plavix can be changed to full strength enteric coated Aspirin with no change in benefits.

Potassium Chloride - with last Serum Potassium of 4, there is no need to continue Potassium supplementation at this time. Stopping this drug will also reduce caustic effects in the gut.

Protonix - the PPI addressed previously in this report. Continued use for the next 2 to 3 months is advised to reestablish a healthy stomach. After about 60 days a gradual taper to twice a day for 30 days and discontinued is advised. Use of Buttermilk 6oz or Yogurt 4oz throughout the day and always at bedtime is requested. If severe heartburn use Ranitidine 75mg twice a day only as needed for the severe episodes.

Super B Complex with C - although this is a good vitamin, I plan to make many changes in his vitamin consumption to improve his Anemic condition, control his lipids and improve his overall problems with fatigue and weakness. This drug should be discontinued.

Toprol XL - a beta blocker also has many problems with muscle disorders, cramps, arthralgia and lupus type symptoms currently present in the patient. Additionally it can cause changes in cognition as well as insomnia and elevated lipids. The goal is to stop all antihypertensive/cardio drugs and use monotherapy of Diltiazem CD in an effort to stop all these adverse events. In an effort to provide optimum support, I like to use the CD (24 hour) dosing form of Diltiazem in a

twice a day dosing. This increases the activity under the curve (AUC) and allows for lower dosing and less potential for any adverse event. As we taper away the other drugs, a starting dose of the Diltiazem CD will be initiated and increased as the other drugs are discontinued. Keep in mind that the response in a 24 hour acting drug is slower in reaching therapeutic levels, so with that in mind, changes made today will not be fully realized until several days later. Removal of all the antihypertensive/cardio drugs will greatly reduce his current problems with side effects.

Trental - an older drug for circulatory problems especially in the legs is very caustic and exacerbates GI bleeds. Its blood thinning effects concomitant with Aspirin and Plavix could have started a GI hemorrhage that may have been fatal. I asked for this drug to be stopped at once.

Tylenol Arthritis Strength - acetaminophen is a very good analgesic, but when given with all the other drugs being taken that contain acetaminophen it becomes hepatotoxic. No more than a once a day use of this drug is allowed with the Endocet dosing that is used. As we stop the pain from the various drug reductions, use of this Arthritis Strength Tylenol with Tramadol will be recommended.

Vitamin C / Rose Hips - Vitamin C is needed and will continue therapy but at greater dosing.

Vitamin E - excellent antioxidant to use but this will be provided in the multivitamin that I will recommend (Centrum Silver or like store brand). Vitamin E should then be discontinued.

Drug Therapy Management

Stop Lipitor
Stop Low Dose Aspirin
Stop Trental
Stop Feldene (piroxicam) every other day x 4 days and Discontinue completely
Stop Amlodipine
Stop Magnesium
Stop Diovan HCT 320/12.5 daily x 4 days, every other day for 4 days and Stop
Stop Flomax 0.4mg every other day x 4 doses and Stop
Stop Imdur 30mg every other day x 6 days and Stop
Stop Mirapex 0.25mg every other night x 30 days and Stop
Stop CoQ10
Stop Plavix 75mg daily x 60 days and stop and start Aspirin EC 325mg daily
Stop Potassium Chloride
Stop Protonix 40mg daily x 60 days every other day x 30 days and Stop
Stop Vitamin B Complex
Stop Toprol XL 75mg daily x 7 days every other day x 7 days and Stop
Stop Vitamin E 400U daily
Stop Endocet 5/325mg

New Drug Therapy

Start
Diltiazem CD 120mg twice a day x 7 days then 180mg AM and 120mg PM x 7 days then 180mg twice a day x 7 days and call with AM & PM blood pressure values to establish need for additional titration of the Diltiazem CD dosing. If blood pressures are over 160/95 two times in a row please call at once.
Avodart 0.5mg daily
Loperamide 2mg continue current dosing
Effexor XR 37.5mg at bedtime x 14 days, then 75mg at bedtime
Aspirin EC 325mg daily (after last dose of Plavix in 60 days)
Tramadol 100mg at bedtime for restless legs and pain relief
Endocet 7.5mg/500mg at night when not relieved by Tramadol within 2 hours
May take Tramadol 50mg + Arthritis Strength Tylenol every 8 hours throughout the day for breakthrough pain.
Vitamin B12 Injection 1000mcg IM weekly x 8 weeks then monthly
Vitamin B6 200mg daily
Folic Acid 1mg daily
Fish Oil 1200mg (CVS brand) tablet 1 twice a day
Demadex (torsemide) 10mg daily
Vitamin C / Rose Hips 1000mg twice a day
Centrum Silver (or like store brand) daily
Ferrous Sulfate 325mg daily
Buttermilk 6oz or Yogurt 4oz throughout the day and at always at bedtime
Ranitidine 75mg twice a day ONLY as needed for severe heartburn (start after Protonix is stopped in 90 days)

Remember that it will take time to see all the changes that the new drug therapy will produce. After completing the titration 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 diltiazem CD dosing may be needed until we reach your dose. Continue to keep your blood pressure and pulse log. This is very important. I really do not know your dose of Diltiazem CD yet because you have so many conflicting drugs being used. When you get the Diltiazem CD prescriptions filled at the pharmacy do not get over a two weeks supply until we find your dose. The Effexor XR dosing will not only make you sleep better but will help control your restless legs and neuropathic pains and afford you much relief from many of those symptoms. I know you have used these in the past but I believe you were not dosed

right and the reaction you had was too soon after starting the drug to make me feel the drug was the cause. Again just get a two week supply until we are sure this is OK for you. I feel confident that it will be. The amount of success I have had in treating diabetic neuropathy, restless leg syndrome and all other neuropathic pains in the geriatric with Effexor XR make me feel very confident that it will do the same for you. You may want to get your physician to write you an order for a 10cc bottle of Vitamin B12 Injection and administer the weekly injections at home. This way it is less trouble and more cost efficient.

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 October or the first of November but would like a progress report weekly by phone until we have all your medication dosages adjusted for you.

Drug Interactions

Acetaminophen; Oxycodone (Endocet®) **and Loperamide**

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.

Concurrent use of loperamide and opiate agonists can lead to severe constipation, obstruction/impaction, or paralytic ileus and possibly additive CNS depression.[6855]

Acetaminophen; Oxycodone (Endocet®) **and Acetaminophen** (Tylenol® Arthritis)

Severity: High

Many prescription and non-prescription medicines contain acetaminophen. Avoid concurrent use of products that contain acetaminophen as the maximum daily dose (i.e., 4 g/day for adults; 75 mg/kg/day for infants and children) may be exceeded leading to an increased risk of hepatotoxicity. Advise patients to carefully read the ingredients of any other medicines they are taking with acetaminophen and oxycodone products.[4925]

Acetaminophen; Oxycodone (Endocet®) **and Pramipexole** (Mirapex®)

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.

The use of ethanol, other parkinson's medications (e.g., entacapone or tolcapone), opiate agonists, buprenorphine, butorphanol, dronabinol, THC, nabilone [9044], nalbuphine, pentazocine, or anxiolytics, sedatives, and hypnotics in combination with pramipexole may increase the risk of clinically significant sedation via a pharmacodynamic interaction.[7757]

Amlodipine and Metoprolol (Toprol XL®)

Severity: Moderate

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.

Metoprolol is an antihypertensive agent, so its effects are additive with other antihypertensive agents.[6714] This interaction is often used advantageously in treating hypertension; however, lower doses of each agent may be necessary. Hypotension can be potentiated when beta-blockers are co-administered with dihydropyridine-type calcium-channel blockers, most notably rapid-release nifedipine. Nicardipine been reported to increase plasma concentrations and oral bioavailability of certain beta-blockers (e.g., metoprolol, propranolol). It is prudent to avoid using beta-blockers with guanethidine, reserpine, or other rauwolfia alkaloids that have a high incidence of orthostatic hypotension due to catecholamine depletion, since beta-blockers will interfere with reflex tachycardia, worsening the orthostasis.[5269]

Amlodipine and Piroxicam

Severity: Moderate

NSAIDs may alter the response to antihypertensive agents due to inhibition of vasodilatory prostaglandins.[805] Among NSAIDs, indomethacin, naproxen, and piroxicam may have the greatest pressor effect, while the effects of sulindac and nabumetone may be significantly less

Nonsteroidal anti-inflammatory drugs (NSAIDs), to varying degrees, have been associated with an elevation in blood pressure (approximately 5 mmHg) when given over a period of weeks. This effect is most significant in patients receiving concurrent antihypertensive agents and long-term NSAID therapy. NSAIDs may decrease the effect of antihypertensive agents through various mechanisms, including renal and peripheral vasoactive pathways.[805] NSAIDs have been shown to attenuate the effects of diuretics, beta-blockers, angiotensin-converting enzyme inhibitors (ACEIs), vasodilators, central alpha-2 agonists, peripheral alpha-1 blockers, and angiotensin II blockers. Doses of antihypertensive medications may require adjustment in patients receiving concurrent NSAIDs.[4087] Concomitant volume depletion caused by diuretics and prostaglandin inhibition caused by piroxicam may increase the risk of renal failure due to inadequate kidney perfusion. Elderly patients may be at increased risk of adverse effects from combined long-term NSAID therapy and antihypertensive agents, especially diuretics, due to age-related decreases in renal function and an increased risk of stroke and coronary artery disease.[3154]

Amlodipine and Tamsulosin (Flomax®)

Severity: Moderate

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.

No pharmacokinetic interaction occurred when tamsulosin was co-administered with either digoxin, furosemide, or theophylline. In addition, tamsulosin did not potentiate the hypotensive effects of atenolol, enalapril, furosemide, or nifedipine.[6419] However, since the symptoms of orthostasis (e.g., postural hypotension, dizziness and vertigo) are reported more frequently in tamsulosin-treated vs. placebo patients, there is a potential risk of enhanced hypotensive effects when co-administered with antihypertensive agents.[6419] Tamsulosin should not be used with other alpha-blockers.[6419]

Amlodipine and Hydrochlorothiazide, HCTZ; Valsartan (Diovan HCT®)

Severity: Moderate

NOTE: The enzyme(s) responsible for valsartan metabolism have not been identified; however, it appears that valsartan is primarily eliminated as unchanged drug via biliary excretion.[4178] One study has demonstrated no significant affinity of valsartan for CYP2C9 or CYP2C19 isoenzymes.[4179] No clinically significant drug interactions were observed when valsartan was administered concomitantly with amlodipine, atenolol, cimetidine, digoxin, furosemide, glyburide, or indomethacin. The concomitant administration of valsartan and warfarin did not change the pharmacokinetics of valsartan or the time-course of the anticoagulant properties of warfarin.

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.

The antihypertensive effects of valsartan can be additive with other antihypertensive agents, including other diuretics. This additive effect can be desirable, but dosages must be adjusted accordingly. Valsartan tends to reverse the potassium loss, but not the serum uric acid rise associated with hydrochlorothiazide monotherapy. No pharmacokinetic drug interaction was observed between hydrochlorothiazide and valsartan.

Amlodipine and Calcium Salts (found in Chelated Calcium Magnesium 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.

Aspirin, ASA and Metoprolol (Toprol XL®)

Severity: Moderate

The efficacy of selected antihypertensive agents needs to be carefully assessed during aspirin usage. During antihypertensive therapy with beta-blockers, high concentrations of vasodilatory prostaglandins are produced in response to reflex-mediated pressor mechanisms (e.g., sympathetic tone). Concurrent use of beta-blockers with aspirin may result in loss of antihypertensive activity due to inhibition of renal prostaglandins and thus, salt and water retention and decreased renal blood flow.[5717] Aspirin can increase the risk of renal insufficiency in patients receiving diuretics, secondary to the effects of aspirin on renal blood flow. Aspirin inhibits renal prostaglandin production, which causes salt and water retention and decreased renal blood flow. Thus, the effectiveness of diuretics in patients with underlying renal or cardiovascular disease may be diminished by the concomitant administration of aspirin.[5717] Aspirin may decrease the hyperuricemic effect of thiazide diuretics (e.g., hydrochlorothiazide) or loop diuretics like furosemide. Concomitant use of aspirin and potassium-sparing diuretics, such as triamterene or spironolactone, may cause hyperkalemia.[5717] The hyponatremic and hypotensive effects of angiotensin-converting enzyme (ACE) inhibitors may be diminished by concurrent use of aspirin; the inhibition of cyclooxygenase by aspirin prevents the formation of vasodilatory prostaglandins.[5717] Furthermore, reduced renal blood flow is expected from the decreased pressure gradient created in the glomeruli when aspirin is used with an ACE inhibitor.[5718] Low-dose aspirin (e.g., 81 mg/day) may be less likely to attenuate the antihypertensive or cardioprotective effects of ACE inhibitors; however, the dose-related effect is controversial.[6439] The established benefits of using low-dose aspirin in combination with an ACE inhibitor in patients with ischemic heart disease and left ventricular dysfunction generally outweigh concerns, especially with appropriate renal function and serum potassium monitoring.[5718] [6060] [6439] Monitor the patient's blood pressure, renal function, and clinical status for the desired responses and adjust therapy accordingly.

During antihypertensive therapy with beta-blockers, high concentrations of vasodilatory prostaglandins are produced in response to reflex-mediated pressor mechanisms (e.g., sympathetic tone). Concurrent use of beta-blockers with aspirin and other salicylates may result in loss of antihypertensive activity due to inhibition of renal prostaglandins and thus, salt and water retention and decreased renal blood flow.[5717]

Aspirin, ASA and Piroxicam

Severity: High

Since the use of NSAIDs and aspirin, ASA, is associated with GI irritation, exercise caution when administering these agents with risedronate due to the potential for additive GI toxicity. During clinical trials for osteoporosis, most patients took either NSAIDs or aspirin, and the incidence of adverse upper GI reactions was similar between risedronate-treated (24.5%) and placebo-treated patients (24.8%).[6090] Patients using risedronate and piroxicam concurrently should be monitored closely for gastrointestinal adverse effects including signs and symptoms of bleeding.

The concurrent use of aspirin with other nonsteroidal anti-inflammatory drugs (NSAIDs) should be avoided because this may increase bleeding or lead to decreased renal function.[5717] The use of aspirin together with nonsalicylate NSAIDs (e.g., indomethacin) can lead to additive GI toxicity.[5232] Due to competition for plasma protein binding sites and/or reduced renal clearance, aspirin may enhance the toxicity of naproxen.[7827] Avoid concurrent use of NSAIDs and aspirin. Concurrent use of chronic ibuprofen therapy (800 mg three times daily) seems to antagonize the inhibition of platelet cyclooxygenase (COX)-1 activity and impairment of platelet aggregation by low-dose aspirin (81 mg once daily) per an ex vivo analysis.[4062] Interestingly in this study, diclofenac or rofecoxib therapy, agents with less activity at COX-1 than ibuprofen, did not affect inhibition of platelet aggregation by aspirin.[4062] An in vitro study has shown that the antagonism of aspirin platelet inhibition probably involves competition at platelet-derived COX-1 and is related to the NSAIDs' ability to inhibit COX-1 mediated thromboxane B_2 production in platelets.[4063] Clinically, the interaction may be more dramatic with regular as compared with intermittent ibuprofen usage. Quantification of the risk was determined by the

analysis of retrospective data, which may be inaccurate and incomplete. However, a trend towards a greater risk of a second myocardial infarction in the year after the initial event among adults taking daily aspirin was associated with a greater length of ibuprofen exposure.[9029] The FDA issued an advisory that 400 mg of ibuprofen can interfere with the antiplatelet effects of low dose aspirin (81 mg per day). Routine use of ibuprofen is likely to have the most significant effect. The FDA recommends administering ibuprofen 8 hours before or 30 minutes after aspirin if concurrent therapy is needed. Whether or not antagonism of aspirin's platelet activity occurs with NSAIDs other than ibuprofen and naproxen (see naproxen monograph) has not been determined.

Increased adverse gastrointestinal effects are possible if piroxicam is used with salicylates (e.g., aspirin).[6354] Plasma concentrations of piroxicam are decreased by 20% during concurrent administration with aspirin 3900 mg daily due to competition at the binding sites.[6354] Concomitant aspirin and piroxicam use is not recommended. Because piroxicam can cause GI bleeding, inhibit platelet aggregation, and prolong bleeding time, additive effects may be seen in patients receiving platelet inhibitors (e.g., aspirin), anticoagulants, or thrombolytic agents. Patients treated with anticoagulants may have an increased risk of gastrointestinal (GI) bleeding with nonsteroidal anti-inflammatory drug usage.[7254] A prolongation of prothrombin time has been reported with concurrent administration of warfarin and NSAIDs.[6354] Both piroxicam and warfarin are highly protein bound. Therefore, close monitoring of the INR is recommended during and shortly after concurrent use of piroxicam and warfarin.[6354] Patients receiving any anticoagulant or thrombolytic agent and piroxicam concurrently should be monitored closely for bleeding.

Aspirin, ASA and Clopidogrel (Plavix®)

Severity: High

Use caution in combining aspirin therapy with other platelet inhibitors due to the potential for additive effects; patients should be monitored for an increased risk of bleeding when aspirin is combined with other platelet inhibitors. Some combinations are therapeutic. For example, the results of the CHARISMA trial, a study that enrolled > 15,000 patients and randomized patients to either clopidogrel plus low-dose aspirin or low-dose aspirin alone, indicate that combination antiplatelet therapy, in patients with established cardiovascular disease, significantly reduces the 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, combination antiplatelet therapy is associated with a nonsignificant trend towards an increased risk of adverse outcomes (n=3284; 20% increased relative risk for combination therapy, p=0.22). Specifically, in this subgroup of patients, there is an increase in cardiovascular mortality as well as a nonsignificant increase in bleeding. The risk of bleeding is not increased with the use of combination therapy in those patients with established cardiovascular disease.[8833] Until more data are available, it may be prudent to avoid using clopidogrel and aspirin combination therapy in patients that do not have established cardiovascular disease. Also, aspirin should not be used in combination with ticlopidine for > 30 days, as safety and efficacy have not been established.

Theoretically feverfew, Tanacetum parthenium may enhance the effects of the platelet inhibitors (including aspirin, ASA) via inhibition of platelet aggregation or via antithrombotic activity.[2913] [2914] [2915] Feverfew also inhibits the secretion of various substances (e.g., arachidonic acid, and serotonin) from the platelet.[1797] In theory, concurrent use may increase the risk of bleeding. Clinical interactions have not yet been reported; however, avoidance of the use of feverfew during antiplatelet therapy seems prudent.[5314]

Because clopidogrel inhibits platelet aggregation, a potential additive risk for bleeding exists if clopidogrel is given in combination with other drugs that affect hemostasis such as platelet inhibitors.[5164] Ticlopidine and clopidogrel inhibit platelets via the same mechanism [5165] [5166]; combination therapy would therefore be illogical. Because clopidogrel and cilostazol cause platelet inhibition through different mechanisms [5165] [5167], clinical evaluation may reveal that the combined use of these two drugs is both safe and effective; currently such evidence is lacking and combination therapy should be used with caution, if at all, as the magnitude of increased risk of bleeding is unknown. The manufacturers of cilostazol have indicated that studies are planned to determine the pharmacodynamic effects of clopidogrel and cilostazol combination therapy. Dipyridamole and clopidogrel also cause platelet inhibition via different mechanisms [5168]; however, their combined use has not been formally evaluated in clinical trials. The increased risk of bleeding is not known at this time and combined use should be avoided until data supporting safety and efficacy are known.

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.

Aspirin, ASA and Hydrochlorothiazide, HCTZ; Valsartan (Diovan HCT®)

Severity: Moderate

The efficacy of selected antihypertensive agents needs to be carefully assessed during aspirin usage. During antihypertensive therapy with beta-blockers, high concentrations of vasodilatory prostaglandins are produced in response to reflex-mediated pressor mechanisms (e.g., sympathetic tone). Concurrent use of beta-blockers with aspirin may result in loss of antihypertensive activity due to inhibition of renal prostaglandins and thus, salt and water retention and decreased renal blood flow.[5717] Aspirin can increase the risk of renal insufficiency in patients receiving diuretics, secondary to the effects of aspirin on renal blood flow. Aspirin inhibits renal prostaglandin production, which causes salt and water retention and decreased renal blood flow. Thus, the effectiveness of diuretics in patients with underlying renal or cardiovascular disease may be diminished by the concomitant administration of aspirin.[5717] Aspirin may decrease the hyperuricemic effect of thiazide diuretics (e.g., hydrochlorothiazide) or loop diuretics like furosemide. Concomitant use of aspirin and potassium-sparing diuretics, such as triamterene or spironolactone, may cause hyperkalemia.[5717] The hyponatremic and hypotensive effects of angiotensin-converting enzyme (ACE) inhibitors may be diminished by concurrent use of aspirin; the inhibition of cyclooxygenase by aspirin prevents the formation of vasodilatory prostaglandins.[5717] Furthermore, reduced renal blood flow is expected from the decreased pressure gradient created in the glomeruli when aspirin is used with an ACE inhibitor.[5718] Low-dose aspirin (e.g., 81 mg/day) may be less likely to attenuate the antihypertensive or cardioprotective effects of ACE inhibitors; however, the dose-related effect is controversial.[6439] The established benefits of using low-dose aspirin in combination with an ACE inhibitor in patients with ischemic heart disease and left ventricular dysfunction generally outweigh concerns, especially with appropriate renal function and serum potassium monitoring.[5718] [6060] [6439] Monitor the patient's blood pressure, renal function, and clinical status for the desired responses and adjust therapy accordingly.

Salicylates can increase the risk of renal toxicity in patients receiving diuretics because salicylates inhibit renal prostaglandin synthesis, which can lead to fluid retention and increased peripheral vascular resistance. Salicylates may decrease the hyperuricemic effect of hydrochlorothiazide.

Aspirin, ASA and Acetaminophen (Tylenol® Arthritis)

Severity: Moderate

Prolonged concurrent use of acetaminophen and salicylates 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 and Ascorbic Acid, Vitamin C (found in Super B Complex With Vitamin C, Vitamin C with Rose Hips)

Severity: Low

Agents that acidify the urine should be avoided in patients receiving high-dose salicylates. Urinary pH changes can have a significant effect on salicylate excretion.[6859] Urine acidifying agents (e.g., ammonium chloride, ascorbic acid, vitamin C, potassium chloride, or phosphate salts) may increase renal tubular reabsorption of salicylic acid and possibly increase salicylic acid levels. However, if the urine is acidic prior to administration of an acidifying agent, the increase in salicylic acid concentrations should be minimal. Increases in salicylic acid levels are more likely in patients receiving acidifying agents with a baseline urinary pH > 6.5.

Acidification of the urine by ascorbic acid, vitamin C will alter the excretion of certain other drugs administered concurrently.[5449] Agents that acidify the urine should be avoided in patients receiving high-dose salicylates. Urine acidifying agents may increase renal tubular reabsorption of salicylic acid and possibly increase salicylic acid levels. However, if the urine is acidic prior to administration of an acidifying agent, the increase in salicylic acid concentrations should be minimal. Increases in salicylic acid levels are more likely in patients with a urinary pH > 6.5.

Calcium Salts (found in Chelated Calcium Magnesium Tablets) **and Hydrochlorothiazide, HCTZ; Valsartan** (Diovan HCT®)

Severity: Moderate

The simultaneous administration of thiazide diuretics and calcium carbonate may lead to hypercalcemia. Thiazides cause a decrease in renal tubular excretion of calcium as well as increase in distal tubular reabsorption. Moderate increases in serum calcium have been seen during the treatment with thiazides; if calcium salts are used concomitantly, careful monitoring of serum calcium in recommended.[5917]

Prolonged use of calcium salts with thiazide diuretics can lead to the milk-alkali syndrome.[4689] Exogenous calcium and thiazide diuretics each can cause hypercalcemia, and thiazide diuretics may cause metabolic alkalosis. These are pharmacodynamic interactions. While the use of a thiazide diuretic does not preclude administration of calcium salts, these two agents should not be administered together for prolonged periods without monitoring serum calcium and other serum electrolytes.

Magnesium Salts (found in Chelated Calcium Magnesium Tablets) **and Acetaminophen; Oxycodone** (Endocet®)

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 Chelated Calcium Magnesium Tablets) **and Hydrochlorothiazide, HCTZ; Valsartan** (Diovan HCT®)

Severity: Moderate

Diuretics may interfere with the kidneys ability to regulate magnesium concentrations. Long-term use of loop diuretics or thiazide diuretics may impair the magnesium-conserving ability of the kidneys and lead to hypomagnesemia.[7114] Conversely, long-term use of potassium-sparing diuretics has been found to increase renal tubular reabsorption of magnesium which may cause hypermagnesemia in patients also receiving magnesium supplements, especially in patients with renal insufficiency.

Hydrochlorothiazide, HCTZ; Valsartan (Diovan HCT®) **and Metoprolol** (Toprol XL®)

Severity: Moderate

The antihypertensive effects of valsartan can be additive with other antihypertensive agents, including other diuretics. This additive effect can be desirable, but dosages must be adjusted accordingly. Valsartan tends to reverse the potassium loss, but not the serum uric acid rise associated with hydrochlorothiazide monotherapy. No pharmacokinetic drug interaction was observed between hydrochlorothiazide and valsartan.

Metoprolol is an antihypertensive agent, so its effects are additive with other antihypertensive agents.[6714] This interaction is often used advantageously in treating hypertension; however, lower doses of each agent may be necessary. Hypotension can be potentiated when beta-blockers are co-administered with dihydropyridine-type calcium-channel blockers, most notably rapid-release nifedipine. Nicardipine been reported to increase plasma concentrations and oral bioavailability of certain beta-blockers (e.g., metoprolol, propranolol). It is prudent to avoid using beta-blockers with guanethidine, reserpine, or other rauwolfia alkaloids that have a high incidence of orthostatic hypotension due to catecholamine depletion, since beta-blockers will interfere with reflex tachycardia, worsening the orthostasis.[5269]

Hydrochlorothiazide, HCTZ; Valsartan (Diovan HCT®) **and Piroxicam**

Severity: Moderate

NSAIDs can cause sodium and fluid retention as well as increase peripheral vascular resistance. By inhibiting renal prostaglandin synthesis and inducing sodium/water retention, NSAIDs can reduce the antihypertensive effects of valsartan and hydrochlorothiazide. In some patients with compromised renal function who are being treated with NSAIDs, coadministration of angiotensin II receptor antagonists may result in further deterioration of renal function. These effects are usually reversible. Reports suggest that NSAIDs (including selective COX-2 inhibitors) may diminish the antihypertensive effect of angiotensin II receptor antagonists. This interaction should be given consideration in patients taking NSAIDs concomitantly with angiotensin II receptor antagonists.[5339] Therefore, blood pressure and renal function should be monitored when an NSAID is administered to a patient taking hydrochlorothiazide; valsartan.

Nonsteroidal anti-inflammatory drugs (NSAIDs), to varying degrees, have been associated with an elevation in blood pressure (approximately 5 mmHg) when given over a period of weeks. This effect is most significant in patients receiving concurrent antihypertensive agents and long-term NSAID therapy. NSAIDs may decrease the effect of antihypertensive agents through various mechanisms, including renal and peripheral vasoactive pathways.[805] NSAIDs have been shown to attenuate the effects of diuretics, beta-blockers, angiotensin-converting enzyme inhibitors (ACEIs), vasodilators, central alpha-2 agonists, peripheral alpha-1 blockers, and angiotensin II blockers. Doses of antihypertensive medications may require adjustment in patients receiving concurrent NSAIDs.[4087] Concomitant volume depletion caused by diuretics and prostaglandin inhibition caused by piroxicam may increase the risk of renal failure due to inadequate kidney perfusion. Elderly patients may be at increased risk of adverse effects from combined

long-term NSAID therapy and antihypertensive agents, especially diuretics, due to age-related decreases in renal function and an increased risk of stroke and coronary artery disease.[3154]

Hydrochlorothiazide, HCTZ; Valsartan (Diovan HCT®) **and Acetaminophen; Oxycodone** (Endocet®)

Severity: Moderate

Ethanol, barbiturates, or opiate agonists may potentiate orthostatic hypotension when used concurrently with hydrochlorothiazide.

Hydrochlorothiazide, HCTZ; Valsartan (Diovan HCT®) **and Potassium Salts** (Potassium Chloride)

Severity: Moderate

As with other drugs that block angiotensin II or its effects, concomitant use of valsartan with potassium-sparing diuretics, potassium salts, or salt substitutes containing potassium may lead to increases in serum potassium. Valsartan attenuates diuretic-induced potassium loss (e.g. loop or thiazide diuretics). Use of potassium-sparing diuretics (e.g., spironolactone, triamterene, or amiloride), potassium supplements, or potassium salts may lead to significant increases in serum potassium concentrations. Therefore, if concomitant use of these agents with valsartan-hydrochlorothiazide is indicated because of documented hypokalemia, they should be used with caution and with frequent monitoring of serum potassium.

Potassium salts [7025] should be used with caution in patients taking drugs that may increase serum potassium levels such as ACE inhibitors [5365]; angiotensin II receptor antagonists [5339]; cyclosporine [5134]; eplerenone [4707]; potassium-sparing diuretics (amiloride [5873], spironolactone [5751], or triamterene [5898]); high-doses of IV potassium penicillin G [6826]; trimethoprim (especially high dose) [5073]; or heparin [2173]. Concurrent use can cause hyperkalemia, especially in elderly patients or patients with impaired renal function. Conversely, potassium supplements should be discontinued when hypokalemia-causing agents are discontinued or re-evaluated to avoid the possibility of developing hyperkalemia. Examples of hypokalemia-causing agents include: thiazide diuretics and loop diuretics; amphotericin B; high-dose beta-agonists; and high doses of extended-spectrum penicillins (carbenicillin, mezlocillin, piperacillin, and ticarcillin).

Tamsulosin (Flomax®) **and Metoprolol** (Toprol XL®)

Severity: Low

No pharmacokinetic interaction occurred when tamsulosin was co-administered with either digoxin, furosemide, or theophylline. In addition, tamsulosin did not potentiate the hypotensive effects of atenolol, enalapril, furosemide, or nifedipine.[6419] However, since the symptoms of orthostasis (e.g., postural hypotension, dizziness and vertigo) are reported more frequently in tamsulosin-treated vs. placebo patients, there is a potential risk of enhanced hypotensive effects when co-administered with antihypertensive agents.[6419] Tamsulosin should not be used with other alpha-blockers.[6419]

Tamsulosin (Flomax®) **and Hydrochlorothiazide, HCTZ; Valsartan** (Diovan HCT®)

Severity: Low

No pharmacokinetic interaction occurred when tamsulosin was co-administered with either digoxin, furosemide, or theophylline. In addition, tamsulosin did not potentiate the hypotensive effects of atenolol, enalapril, furosemide, or nifedipine.[6419] However, since the symptoms of orthostasis (e.g., postural hypotension, dizziness and vertigo) are reported more frequently in tamsulosin-treated vs. placebo patients, there is a potential risk of enhanced hypotensive effects when co-administered with antihypertensive agents.[6419] Tamsulosin should not be used with other alpha-blockers.[6419]

Isosorbide Mononitrate (Imdur®) **and Amlodipine**

Severity: Moderate

Concomitant use of isosorbide mononitrate with other antihypertensive agents, peripheral vasodilators, beta-blockers, opiate agonists, phenothiazines, or ethanol (moderate or excessive amounts) [5944] can cause additive hypotensive effects.[6288] Marked orthostatic hypotension has been reported following the concomitant administration of calcium-channel blockers and organic nitrates, and dosage adjustments may be necessary.[6288]

Isosorbide Mononitrate (Imdur®) **and Metoprolol** (Toprol XL®)

Severity: Moderate

Concomitant use of isosorbide mononitrate with other antihypertensive agents, peripheral vasodilators, beta-blockers, opiate agonists, phenothiazines, or ethanol (moderate or excessive amounts) [5944] can cause additive hypotensive effects.[6288] Marked orthostatic hypotension has been reported following the concomitant administration of calcium-channel blockers and organic nitrates, and dosage adjustments may be necessary.[6288]

Isosorbide Mononitrate (Imdur®) **and Hydrochlorothiazide, HCTZ; Valsartan** (Diovan HCT®)

Severity: Moderate

Concomitant use of isosorbide mononitrate with other antihypertensive agents, peripheral vasodilators, beta-blockers, opiate agonists, phenothiazines, or ethanol (moderate or excessive amounts) [5944] can cause additive hypotensive effects.[6288] Marked orthostatic hypotension has been reported following the concomitant administration of calcium-channel blockers and organic nitrates, and dosage adjustments may be necessary.[6288]

Atorvastatin (Lipitor®) **and Clopidogrel** (Plavix®)

Severity: Low

Atorvastatin has been reported to attenuate the antiplatelet activity of clopidogrel potentially by inhibiting CYP3A4 metabolism to its active metabolite;[5163] [5477] however, conflicting data exists.[5398] The clinical significance of this theoretical interaction is not known. Patients should be monitored for therapeutic effectiveness when clopidogrel is administered with atorvastatin or other HMG CoA reductase inhibitors metabolized by the CYP 3A4 isozyme (i.e., lovastatin, simvastatin, and cerivastatin).

Atorvastatin has been reported to attenuate the antiplatelet activity of clopidogrel potentially by inhibiting CYP3A4 metabolism to its active metabolite;[5163] [5477] however, conflicting data exists.[5398] The clinical significance of this theoretical interaction is not known. Patients should be monitored for therapeutic effectiveness when clopidogrel is administered with atorvastatin or other HMG Co-A reductase inhibitors metabolized by the CYP 3A4 isozyme (i.e., lovastatin, simvastatin, and cerivastatin).

Atorvastatin (Lipitor®) **and Niacin, Niacinamide** (found in Super B Complex With Vitamin C)

Severity: Moderate

The risk of myopathy increases when HMG-CoA reductase inhibitors are administered concurrently with fibric acid derivatives (e.g., gemfibrozil, fenofibrate, clofibrate) or antilipemic doses of niacin (i.e., vitamin B_3 as nicotinic acid).[5460] [5506] When possible, avoid concurrent use of HMG-reductase inhibitors with drugs known to increase the risk of developing rhabdomyolysis or acute renal failure. The serious risk of myopathy or rhabdomyolysis should be weighed carefully versus the benefits of combined 'statin' and fibrate therapy; there is no assurance that periodic monitoring of CK will prevent the occurrence of severe myopathy and renal damage.[5460] Additionally, gemfibrozil has been reported to increase plasma concentrations of atorvastatin and its metabolites.[8879]

Rare cases of rhabdomyolysis have been reported in patients taking niacin (nicotinic acid) in lipid-altering doses (i.e., >=1 g/day) and HMG-CoA reductase inhibitors (Statins) concurrently.[5506] Patients undergoing combined therapy should be carefully monitored for myopathy or rhabdomyolysis, particularly in the early months of treatment or during periods of upward dose titration of either drug. Since compounds in red yeast rice are pharmacologically similar to the HMG-CoA reductase inhibitors,[5911] clinicians and patients should use this dietary supplement cautiously in combination with niacin, particularly in non-prescription use.

Piroxicam and Metoprolol (Toprol XL®)

Severity: Moderate

During antihypertensive therapy with beta-blockers, high concentrations of vasodilatory prostaglandins are produced in response to reflex-mediated pressor mechanisms (e.g., sympathetic tone). NSAIDs may decrease the antihypertensive activity of beta-blockers through various mechanisms, including renal and peripheral vasoactive pathways and inhibition of vasodilatory prostaglandins.[4087] Importantly, blood pressure control should be monitored more closely after the introduction of NSAIDs in a patient taking a beta-blocker; the dose of beta-blocker may need to be adjusted. Among NSAIDs, indomethacin, naproxen, and piroxicam may have the greatest pressor effect, while the effects of sulindac and nabumetone may be significantly less.

Nonsteroidal anti-inflammatory drugs (NSAIDs), to varying degrees, have been associated with an elevation in blood pressure (approximately 5 mmHg) when given over a period of weeks. This effect is most significant in patients receiving concurrent antihypertensive agents and long-term NSAID therapy. NSAIDs may decrease the effect of antihypertensive agents through various mechanisms, including renal and peripheral vasoactive pathways.[805] NSAIDs have been shown to attenuate the effects of diuretics, beta-blockers, angiotensin-converting enzyme inhibitors (ACEIs), vasodilators, central alpha-2 agonists, peripheral alpha-1 blockers, and angiotensin II blockers. Doses of antihypertensive medications may require adjustment in patients receiving concurrent NSAIDs.[4087] Concomitant volume depletion caused by diuretics and prostaglandin inhibition caused by piroxicam may increase the risk of renal failure due to inadequate kidney perfusion. Elderly patients may be at increased risk of adverse effects from combined long-term NSAID therapy and antihypertensive agents, especially diuretics, due to age-related decreases in renal function and an increased risk of stroke and coronary artery disease.[3154]

Piroxicam and Clopidogrel (Plavix®)

Severity: Moderate

Increased adverse gastrointestinal effects are possible if piroxicam is used with salicylates (e.g., aspirin).[6354] Plasma concentrations of piroxicam are decreased by 20% during concurrent administration with aspirin 3900 mg daily due to competition at the binding sites.[6354] Concomitant aspirin and piroxicam use is not recommended. Because piroxicam can cause GI bleeding, inhibit platelet aggregation, and prolong bleeding time, additive effects may be seen in patients receiving platelet inhibitors (e.g., aspirin), anticoagulants, or thrombolytic agents. Patients treated with anticoagulants may have an increased risk of gastrointestinal (GI) bleeding with nonsteroidal anti-inflammatory drug usage.[7254] A prolongation of prothrombin time has been reported with concurrent administration of warfarin and NSAIDs.[6354] Both piroxicam and warfarin are highly protein bound. Therefore, close monitoring of the INR is recommended during and shortly after concurrent use of piroxicam and warfarin.[6354] Patients receiving any anticoagulant or thrombolytic agent and piroxicam concurrently should be monitored closely for bleeding.

In healthy volunteers, an increase in occult GI blood loss occurred when clopidogrel was administered concomitantly with naproxen.[5165] Thus, if combination therapy with NSAIDs and clopidogrel is deemed necessary, caution is advised.[5165]

Clopidogrel (Plavix®) **and Pentoxifylline** (Trental®)

Severity: Moderate

Because clopidogrel inhibits platelet aggregation, a potential additive risk for bleeding exists if clopidogrel is given in combination with other agents that affect hemostasis such as thrombolytic agents, rheologic agents (i.e., pentoxifylline [6316]), or anticoagulants.[5164] Although the risk of bleeding is increased when clopidogrel is used concomitantly with thrombolytic agents [5171], it is common to see patients receive these drugs simultaneously. In healthy volunteers receiving heparin, clopidogrel does not alter the effect of heparin on coagulation parameters or require adjustment of the heparin dose. In addition, heparin has no effect on inhibition of platelet aggregation induced by clopidogrel.[5165] Nevertheless, the safety of this combination has not been established and concomitant administration of clopidogrel with heparin should be undertaken with caution. Because of increased bleeding risk, coadministration of clopidogrel with warfarin should be undertaken with caution.[5165]

The concomitant administration of cilostazol or other platelet inhibitors (e.g., clopidogrel, ticlopidine) with rheologic agents (i.e., pentoxifylline) in the treatment of intermittent claudication has not been evaluated and should be approached with caution, due to the potential for synergistic effects.[6316]

Potassium Salts (Potassium Chloride) **and Loperamide**

Severity: Low

Drugs that decrease GI motility may increase the risk of GI irritation from sustained-release solid oral dosage forms of potassium salts.[7025] Examples of drugs that significantly decrease GI motility include antimuscarinics [6338], diphenoxylate and loperamide.

Cyanocobalamin, Vitamin B12 (found in Super B Complex With Vitamin C) **and Pantoprazole** (Protonix®)

Severity: Low

In a study of 10 healthy male volunteers, omeprazole, in doses of 20 mg-40 mg per day, caused a significant decrease in the oral absorption of cyanocobalamin, vitamin B_{12}.[162] Theoretically this interaction is possible with other proton pump inhibitors (PPIs), although specific clinical data are lacking. Patients receiving long-term therapy with omeprazole or other proton pump inhibitors (PPIs) should be monitored for signs of B_{12} deficiency.

Niacin, Niacinamide (found in Super B Complex With Vitamin C) **and Amlodipine**

Severity: Moderate

Clonidine has been shown to inhibit niacin-induced flushing.[7631] This interaction is harmless unless niacin augments the hypotensive actions of clonidine. Finally, clinicians should keep in mind that cutaneous vasodilation induced by niacin may become problematic if high-dose niacin is used concomitantly with other antihypertensive agents,[5932] especially peripheral vasodilators such as epoprostenol, nitrates, calcium-channel blockers, or others, particularly in the setting of acute myocardial infarction, unstable angina, or other acute hemodynamic compromise.

Niacin, Niacinamide (found in Super B Complex With Vitamin C) **and Metoprolol** (Toprol XL®)

Severity: Moderate

Clonidine has been shown to inhibit niacin-induced flushing.[7631] This interaction is harmless unless niacin augments the hypotensive actions of clonidine. Finally, clinicians should keep in mind that cutaneous vasodilation induced by niacin may become problematic if high-dose niacin is used concomitantly with other antihypertensive agents,[5932] especially peripheral vasodilators such as epoprostenol, nitrates, calcium-channel blockers, or others, particularly in the setting of acute myocardial infarction, unstable angina, or other acute hemodynamic compromise.

Niacin, Niacinamide (found in Super B Complex With Vitamin C) **and Hydrochlorothiazide, HCTZ; Valsartan** (Diovan HCT®)

Severity: Moderate

Clonidine has been shown to inhibit niacin-induced flushing.[7631] This interaction is harmless unless niacin augments the hypotensive actions of clonidine. Finally, clinicians should keep in mind that cutaneous vasodilation induced by niacin may become problematic if high-dose niacin is used concomitantly with other antihypertensive agents,[5932] especially peripheral vasodilators such as epoprostenol, nitrates, calcium-channel blockers, or others, particularly in the setting of acute myocardial infarction, unstable angina, or other acute hemodynamic compromise.

Pentoxifylline (Trental®) **and Amlodipine**

Severity: Moderate

Pentoxifylline has been used concurrently with antihypertensive drugs, beta blockers, digitalis, diuretics, and antiarrhythmics without observed problems. Small decreases in blood pressure have been observed in some patients treated with pentoxifylline; periodic systemic blood pressure monitoring is recommended for patients receiving concomitant antihypertensives. If indicated, dosage of the antihypertensive agents should be reduced.[6316]

Pentoxifylline (Trental®) **and Aspirin, ASA**

Severity: Moderate

The concomitant administration of cilostazol or other platelet inhibitors (e.g., clopidogrel, ticlopidine) with rheologic agents (i.e., pentoxifylline) in the treatment of intermittent claudication has not been evaluated and should be approached with caution, due to the potential for synergistic effects.[6316]

Pentoxifylline (Trental®) **and Metoprolol** (Toprol XL®)

Severity: Moderate

Pentoxifylline has been used concurrently with antihypertensive drugs, beta blockers, digitalis, diuretics, and antiarrhythmics without observed problems. Small decreases in blood pressure have been observed in some patients treated with pentoxifylline; periodic systemic blood pressure monitoring is recommended for patients receiving concomitant antihypertensives. If indicated, dosage of the antihypertensive agents should be reduced.[6316]

Pentoxifylline (Trental®) **and Hydrochlorothiazide, HCTZ; Valsartan** (Diovan HCT®)

Severity: Moderate

Pentoxifylline has been used concurrently with antihypertensive drugs, beta blockers, digitalis, diuretics, and antiarrhythmics without observed problems. Small decreases in blood pressure have been observed in some patients treated with pentoxifylline; periodic systemic blood pressure monitoring is recommended for patients receiving concomitant antihypertensives. If indicated, dosage of the antihypertensive agents should be reduced.[6316]

Adverse Reactions

• abdominal pain (Tylenol® Arthritis | Amlodipine | Aspirin, ASA | Loperamide | Toprol XL® | Piroxicam | Potassium Chloride | Lipitor® | Plavix® | Acetaminophen; Oxycodone | Protonix® | Diovan HCT®)
• acute generalized exanthematous pustulosis (AGEP) (Tylenol® Arthritis | Aspirin, ASA | Acetaminophen; Oxycodone)
• agranulocytosis (Tylenol® Arthritis | Aspirin, ASA | Toprol XL® | Piroxicam | Plavix® | Acetaminophen; Oxycodone | Diovan HCT®)
• akathisia (Piroxicam)
• alopecia (Toprol XL® | Piroxicam | Lipitor® | Protonix® | Diovan HCT®)
• aluminum toxicity (Potassium Chloride)
• amblyopia (Flomax®)
• amnesia (Toprol XL®)
• anaphylactic shock (Tylenol® Arthritis | Loperamide | Piroxicam | Acetaminophen; Oxycodone)

• anaphylactoid reactions (Tylenol® Arthritis | Aspirin, ASA | Loperamide | Piroxicam | Lipitor® | Plavix® | Acetaminophen; Oxycodone | Protonix® | Diovan HCT®)
• anemia (Tylenol® Arthritis | Vitamin C with Rose Hips | Piroxicam | Protonix® | Diovan HCT®)
• angina (Amlodipine)
• angioedema (Tylenol® Arthritis | Amlodipine | Aspirin, ASA | Loperamide | Piroxicam | Lipitor® | Plavix® | Acetaminophen; Oxycodone | Flomax® | Protonix® | Diovan HCT®)
• anorexia (Tylenol® Arthritis | Amlodipine | Piroxicam | Acetaminophen; Oxycodone)
• anxiety (Piroxicam)
• aplastic anemia (Aspirin, ASA | Piroxicam | Plavix® | Diovan HCT®)
• arthralgia (Toprol XL® | Piroxicam | Lipitor®)
• aseptic meningitis (Piroxicam)
• asthenia (Amlodipine | Piroxicam | Lipitor® | Mirapex® | Flomax®)
• AV block (Toprol XL® | Potassium Chloride)
• azotemia (Aspirin, ASA | Diovan HCT®)
• back pain (Vitamin C with Rose Hips | Lipitor® | Flomax®)
• bleeding (Aspirin, ASA | Vitamin E | Plavix® | Acetaminophen; Oxycodone)
• blurred vision (Amlodipine | Toprol XL® | Piroxicam | Vitamin E | Diovan HCT®)
• bradycardia (Amlodipine | Toprol XL® | Acetaminophen; Oxycodone)
• bronchospasm (Aspirin, ASA | Toprol XL® | Plavix®)
• bullous rash (Loperamide | Piroxicam | Lipitor®)
• cardiac arrest (Potassium Chloride | Acetaminophen; Oxycodone)
• chest pain (unspecified) (Toprol XL® | Flomax® | Protonix®)
• chills (Lipitor®)
• cholecystitis (Protonix®)
• cholelithiasis (Protonix®)
• cholestasis (Lipitor®)
• cirrhosis (Lipitor®)
• colitis (Plavix®)
• confusion (Aspirin, ASA | Toprol XL® | Piroxicam | Potassium Chloride | Plavix® | Mirapex® | Acetaminophen; Oxycodone)
• constipation (Amlodipine | Aspirin, ASA | Loperamide | Toprol XL® | Piroxicam | Lipitor® | Mirapex® | Acetaminophen; Oxycodone | Protonix®)
• contact dermatitis (Tylenol® Arthritis | Vitamin E | Acetaminophen; Oxycodone | Protonix®)
• costovertebral pain (Vitamin C with Rose Hips)
• cough (Diovan HCT®)
• cyanosis (Imdur®)
• cystitis (Piroxicam)
• dehydration (Aspirin, ASA)
• dental caries (Vitamin C with Rose Hips)
• depression (Toprol XL® | Piroxicam)
• diabetes mellitus (Toprol XL®)
• diaphoresis (Aspirin, ASA | Imdur® | Piroxicam)
• diarrhea (Amlodipine | Vitamin C with Rose Hips | Aspirin, ASA | Toprol XL® | Piroxicam | Vitamin E | Lipitor® | Plavix® | Mirapex® | Flomax® | Protonix® | Diovan HCT®)
• disseminated intravascular coagulation (DIC) (Aspirin, ASA)
• dizziness (Amlodipine | Vitamin C with Rose Hips | Aspirin, ASA | Imdur® | Loperamide | Toprol XL® | Trental® | Piroxicam | Mirapex® | Acetaminophen; Oxycodone | Flomax® | Protonix® | Diovan HCT®)
• drowsiness (Amlodipine | Aspirin, ASA | Loperamide | Toprol XL® | Piroxicam | Lipitor® | Mirapex® | Acetaminophen; Oxycodone | Flomax®)
• dysgeusia (Flomax®)
• dyskinesia (Mirapex®)
• dyspepsia (Aspirin, ASA | Loperamide | Trental® | Lipitor® | Plavix® | Flomax® | Protonix®)
• dysphagia (Amlodipine | Aspirin, ASA | Piroxicam | Potassium Chloride)
• dyspnea (Toprol XL® | Piroxicam | Lipitor®)
• dysuria (Piroxicam)
• ecchymosis (Piroxicam | Protonix®)
• edema (Tylenol® Arthritis | Amlodipine | Piroxicam | Lipitor® | Acetaminophen; Oxycodone)
• ejaculation dysfunction (Flomax®)
• elevated hepatic enzymes (Tylenol® Arthritis | Amlodipine | Aspirin, ASA | Toprol XL® | Piroxicam | Lipitor® | Plavix® | Acetaminophen; Oxycodone | Protonix® | Diovan HCT®)
• encephalopathy (Tylenol® Arthritis | Aspirin, ASA | Acetaminophen; Oxycodone)
• enterocolitis (Vitamin E)
• eosinophilia (Piroxicam | Lipitor®)

• epistaxis (Amlodipine | Piroxicam)
• eructation (Piroxicam | Protonix®)
• erythema (Tylenol® Arthritis | Piroxicam | Lipitor® | Acetaminophen; Oxycodone)
• erythema multiforme (Amlodipine | Piroxicam | Lipitor® | Plavix® | Protonix®)
• erythema nodosum (Aspirin, ASA)
• esophageal stricture (Aspirin, ASA | Potassium Chloride)
• esophageal ulceration (Aspirin, ASA | Potassium Chloride)
• esophagitis (Aspirin, ASA | Piroxicam | Potassium Chloride)
• exfoliative dermatitis (Tylenol® Arthritis | Toprol XL® | Piroxicam | Acetaminophen; Oxycodone | Diovan HCT®)
• fatigue (Amlodipine | Loperamide | Toprol XL® | Piroxicam | Vitamin E | Lipitor® | Mirapex® | Diovan HCT®)
• fever (Tylenol® Arthritis | Aspirin, ASA | Piroxicam | Lipitor® | Plavix® | Acetaminophen; Oxycodone | Diovan HCT®)
• flatulence (Amlodipine | Loperamide | Toprol XL® | Piroxicam | Lipitor® | Protonix®)
• flushing (Amlodipine | Vitamin C with Rose Hips | Imdur® | Lipitor®)
• gastritis (Aspirin, ASA | Piroxicam | Plavix®)
• GI bleeding (Aspirin, ASA | Piroxicam | Potassium Chloride | Plavix®)
• GI obstruction (Potassium Chloride)
• GI perforation (Aspirin, ASA | Piroxicam | Potassium Chloride)
• gingival hyperplasia (Amlodipine)
• glomerulonephritis (Plavix®)
• glossitis (Piroxicam)
• gout (Diovan HCT®)
• gynecomastia (Amlodipine)
• hallucinations (Aspirin, ASA | Toprol XL® | Piroxicam | Plavix® | Mirapex® | Acetaminophen; Oxycodone)
• headache (Tylenol® Arthritis | Amlodipine | Vitamin C with Rose Hips | Aspirin, ASA | Imdur® | Loperamide | Toprol XL® | Trental® | Piroxicam | Vitamin E | Lipitor® | Mirapex® | Acetaminophen; Oxycodone | Flomax® | Protonix® | Diovan HCT®)
• hearing loss (Aspirin, ASA | Piroxicam)
• heart failure (Toprol XL® | Piroxicam | Vitamin E)
• hematemesis (Piroxicam)
• hematuria (Piroxicam)
• hemolysis (Tylenol® Arthritis | Vitamin C with Rose Hips | Acetaminophen; Oxycodone | Diovan HCT®)
• hemolytic anemia (Tylenol® Arthritis | Vitamin C with Rose Hips | Aspirin, ASA | Piroxicam | Lipitor® | Acetaminophen; Oxycodone)
• hemorrhoids (Aspirin, ASA)
• hepatic failure (Piroxicam | Lipitor® | Plavix® | Protonix®)
• hepatic necrosis (Tylenol® Arthritis | Aspirin, ASA | Lipitor® | Acetaminophen; Oxycodone)
• hepatitis (Amlodipine | Aspirin, ASA | Toprol XL® | Piroxicam | Lipitor® | Plavix® | Protonix® | Diovan HCT®)
• hyperbilirubinemia (Aspirin, ASA | Protonix® | Diovan HCT®)
• hypercalcemia (Diovan HCT®)
• hypercholesterolemia (Diovan HCT®)
• hyperglycemia (Aspirin, ASA | Toprol XL® | Protonix® | Diovan HCT®)
• hyperkalemia (Piroxicam | Potassium Chloride | Diovan HCT®)
• hypernatremia (Aspirin, ASA)
• hyperoxaluria (Vitamin C with Rose Hips)
• hypertension (Piroxicam)
• hypertriglyceridemia (Toprol XL® | Diovan HCT®)
• hyperuricemia (Aspirin, ASA | Diovan HCT®)
• hyperventilation (Aspirin, ASA)
• hypoglycemia (Aspirin, ASA | Toprol XL®)
• hypokalemia (Aspirin, ASA)
• hypomagnesemia (Diovan HCT®)
• hypoprothrombinemia (Tylenol® Arthritis | Aspirin, ASA | Acetaminophen; Oxycodone)
• hypotension (Amlodipine | Imdur® | Toprol XL® | Potassium Chloride | Plavix® | Mirapex® | Acetaminophen; Oxycodone | Flomax® | Diovan HCT®)
• hypovolemia (Diovan HCT®)
• ileus (Loperamide)
• impotence (erectile dysfunction) (Toprol XL® | Flomax® | Diovan HCT®)
• infection (Lipitor® | Flomax®)
• influenza (Mirapex®)
• injection site reaction (Potassium Chloride | Protonix®)
• insomnia (Toprol XL® | Piroxicam | Mirapex® | Flomax® | Protonix®)
• interstitial nephritis (Tylenol® Arthritis | Aspirin, ASA | Piroxicam | Acetaminophen; Oxycodone | Protonix®)
• intracranial bleeding (Aspirin, ASA | Plavix®)

• jaundice (Tylenol® Arthritis | Amlodipine | Aspirin, ASA | Toprol XL® | Piroxicam | Lipitor® | Acetaminophen; Oxycodone | Protonix® | Diovan HCT®)
• laryngeal edema (Aspirin, ASA)
• leukocytosis (Aspirin, ASA)
• leukopenia (Amlodipine | Aspirin, ASA | Piroxicam | Lipitor® | Protonix® | Diovan HCT®)
• libido decrease (Toprol XL® | Flomax®)
• lupus-like symptoms (Lipitor®)
• lymphadenopathy (Piroxicam)
• maculopapular rash (Tylenol® Arthritis | Aspirin, ASA | Plavix® | Acetaminophen; Oxycodone | Protonix®)
• malaise (Piroxicam | Lipitor®)
• melena (Aspirin, ASA | Piroxicam)
• metabolic acidosis (Aspirin, ASA)
• methemoglobinemia (Tylenol® Arthritis | Imdur® | Acetaminophen; Oxycodone)
• miosis (Acetaminophen; Oxycodone)
• muscle cramps (Diovan HCT®)
• musculoskeletal pain (Toprol XL®)
• myalgia (Lipitor® | Plavix®)
• myasthenia (Lipitor®)
• myocarditis (Tylenol® Arthritis)
• myoglobinuria (Lipitor®)
• myopathy (Lipitor®)
• nausea/vomiting (Tylenol® Arthritis | Amlodipine | Vitamin C with Rose Hips | Aspirin, ASA | Imdur® | Loperamide | Toprol XL® | Trental® | Piroxicam | Potassium Chloride | Vitamin E | Lipitor® | Mirapex® | Acetaminophen; Oxycodone | Flomax® | Protonix® | Diovan HCT®)
• neonatal abstinence syndrome (Acetaminophen; Oxycodone)
• nephrolithiasis (Vitamin C with Rose Hips | Diovan HCT®)
• nephrotic syndrome (Piroxicam)
• neutropenia (Tylenol® Arthritis | Plavix® | Acetaminophen; Oxycodone)
• ocular hemorrhage (Plavix®)
• odynophagia (Aspirin, ASA | Potassium Chloride)
• oliguria (Piroxicam)
• onycholysis (Piroxicam)
• orthostatic hypotension (Amlodipine | Imdur® | Mirapex® | Acetaminophen; Oxycodone | Flomax® | Diovan HCT®)
• palpitations (Amlodipine | Toprol XL® | Piroxicam | Acetaminophen; Oxycodone)
• pancreatitis (Amlodipine | Piroxicam | Lipitor® | Plavix® | Protonix® | Diovan HCT®)
• pancytopenia (Tylenol® Arthritis | Aspirin, ASA | Piroxicam | Plavix® | Acetaminophen; Oxycodone | Protonix® | Diovan HCT®)
• paresthesias (Amlodipine | Piroxicam | Potassium Chloride)
• peptic ulcer (Aspirin, ASA | Piroxicam | Potassium Chloride | Plavix®)
• peripheral edema (Amlodipine | Toprol XL® | Piroxicam | Lipitor®)
• peripheral neuropathy (Lipitor®)
• peripheral vasoconstriction (Toprol XL®)
• peripheral vasodilation (Amlodipine)
• pernicious anemia (Protonix®)
• petechiae (Piroxicam)
• pharyngitis (Lipitor® | Flomax®)
• phlebitis (Potassium Chloride | Protonix®)
• photophobia (Piroxicam)
• photosensitivity (Toprol XL® | Piroxicam | Lipitor® | Diovan HCT®)
• physiological dependence (Acetaminophen; Oxycodone)
• platelet dysfunction (Aspirin, ASA | Piroxicam | Plavix®)
• pneumonitis (Plavix®)
• polyuria (Piroxicam | Mirapex®)
• priapism (Flomax®)
• prolonged bleeding time (Aspirin, ASA | Plavix®)
• proteinuria (Piroxicam)
• pruritus (Tylenol® Arthritis | Loperamide | Toprol XL® | Piroxicam | Lipitor® | Plavix® | Acetaminophen; Oxycodone | Flomax® | Protonix®)
• psoriasis (Toprol XL®)
• psychosis (Toprol XL®)
• pulmonary edema (Aspirin, ASA)
• purpura (Tylenol® Arthritis | Aspirin, ASA | Piroxicam | Lipitor® | Plavix® | Acetaminophen; Oxycodone)
• pyrosis (heartburn) (Toprol XL® | Piroxicam)

• rash (unspecified) (Tylenol® Arthritis | Toprol XL® | Piroxicam | Potassium Chloride | Lipitor® | Plavix® | Acetaminophen; Oxycodone | Flomax® | Protonix®)
• renal failure (unspecified) (Tylenol® Arthritis | Aspirin, ASA | Piroxicam | Acetaminophen; Oxycodone)
• renal papillary necrosis (Tylenol® Arthritis | Aspirin, ASA | Piroxicam | Acetaminophen; Oxycodone)
• renal tubular necrosis (Tylenol® Arthritis | Aspirin, ASA | Acetaminophen; Oxycodone)
• renal tubular obstruction (Vitamin C with Rose Hips | Lipitor®)
• respiratory depression (Aspirin, ASA | Acetaminophen; Oxycodone)
• restlessness (Acetaminophen; Oxycodone)
• retinal hemorrhage (Plavix®)
• retroperitoneal bleeding (Plavix®)
• Reye's syndrome (Aspirin, ASA)
• rhabdomyolysis (Lipitor® | Mirapex® | Protonix® | Diovan HCT®)
• rhinitis (Aspirin, ASA | Toprol XL® | Flomax®)
• seizures (Aspirin, ASA)
• serum sickness (Piroxicam | Plavix®)
• sialadenitis (Diovan HCT®)
• sickle-cell crisis (Vitamin C with Rose Hips)
• sinus tachycardia (Amlodipine | Imdur®)
• sinusitis (Lipitor® | Flomax®)
• skin hyperpigmentation (Toprol XL®)
• skin irritation (Vitamin E)
• Stevens-Johnson syndrome (Aspirin, ASA | Piroxicam | Lipitor® | Plavix® | Protonix® | Diovan HCT®)
• stomatitis (Piroxicam | Plavix®)
• syncope (Amlodipine | Imdur® | Toprol XL® | Acetaminophen; Oxycodone | Flomax® | Diovan HCT®)
• teratogenesis (Diovan HCT®)
• thrombocytopenia (Tylenol® Arthritis | Amlodipine | Aspirin, ASA | Toprol XL® | Piroxicam | Lipitor® | Acetaminophen; Oxycodone | Protonix® | Diovan HCT®)
• thrombocytosis (Tylenol® Arthritis | Acetaminophen; Oxycodone)
• thrombotic thrombocytopenic purpura (TTP) (Plavix®)
• tinnitus (Aspirin, ASA | Toprol XL® | Piroxicam)
• tolerance (Imdur® | Acetaminophen; Oxycodone)
• toxic epidermal necrolysis (Tylenol® Arthritis | Aspirin, ASA | Loperamide | Piroxicam | Lipitor® | Plavix® | Acetaminophen; Oxycodone | Protonix® | Diovan HCT®)
• toxic megacolon (Loperamide)
• tremor (Amlodipine | Piroxicam)
• urinary retention (Loperamide)
• urticaria (Tylenol® Arthritis | Aspirin, ASA | Loperamide | Toprol XL® | Piroxicam | Lipitor® | Acetaminophen; Oxycodone | Flomax® | Protonix® | Diovan HCT®)
• vasculitis (Piroxicam | Lipitor® | Plavix®)
• vertigo (Amlodipine | Piroxicam | Flomax®)
• visual impairment (Aspirin, ASA | Piroxicam)
• vitamin B_{12} deficiency (Protonix®)
• weakness (Potassium Chloride | Vitamin E | Lipitor®)
• wheezing (Aspirin, ASA | Toprol XL®)
• withdrawal (Acetaminophen; Oxycodone)
• xanthopsia (Diovan HCT®)
• xerosis (Toprol XL® | Protonix®)
• xerostomia (Loperamide | Piroxicam | Mirapex®)

Precautions

Precaution: Acetaminophen; Oxycodone in cardiac arrhythmias
Opiate agonists, such as oxycodone, produce cholinergic side effects (by stimulating medullary vagal nuclei) causing bradycardia and vasovagal syncope, and induce the release of histamine, causing peripheral vasodilatation and orthostatic hypotension. These effects can cause problems in patients with cardiac disease. Acetaminophen-oxycodone should be used with caution in patients with cardiac arrhythmias, hypotension, or hypovolemia.

Precaution: Acetaminophen; Oxycodone in diarrhea
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: Acetaminophen; Oxycodone 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: Amlodipine in gastroesophageal reflux disease (GERD)
Calcium channel blockers should be used cautiously in patients with gastroesophageal reflux disease (GERD) or hiatal hernia associated with reflux esophagitis. The drugs relax the lower esophageal sphincter.

Precaution: Aspirin, ASA in hypertension
Sodium-restricted patients or patients with hypovolemic states (e.g., ascites, dehydration, heart failure, hypertension, or hypovolemia) may be more susceptible to adverse renal effects of salicylate therapy. Buffered aspirin contains a high sodium content. In patients with carditis, high doses of salicylates may precipitate congestive heart failure or pulmonary edema.

Precaution: Aspirin, ASA in renal impairment
Salicylates should be used with caution in patients with renal impairment and with extreme caution, if at all, in patients with advanced, chronic renal failure since salicylic acid and its metabolites are excreted in the urine. In addition, these patients may be at increased risk of developing salicylate-induced nephrotoxicity. In a case-controlled study of patients with early renal failure, the regular use of aspirin (without acetaminophen) was associated with a risk of chronic renal failure that was 2.5-times as high as that for non-aspirin users.[4064] The risk increased significantly with increasing cumulative lifetime dose and increasing average dose during periods of regular use; duration of therapy was not associated with increased risk. When aspirin was given regularly in analgesic doses (> 500 g per year during periods of regular use) the odds ratio for chronic renal failure was 3.5 (95% confidence interval 1.4 to 8). Low-dose aspirin use for cardiovascular prophylaxis was not significantly associated with the development of renal failure. In this study, it appears that pre-existing renal disease or systemic disease is a required precursor to the development of analgesic-induced renal failure; patients without preexisting renal disease who used analgesics had only a small risk of developing end-stage renal disease. Renal function should be monitored periodically in patients receiving prolonged or high-dose salicylate therapy. Salicylates should 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.

Precaution: Chelated Calcium Magnesium Tablets in cardiac arrhythmias
Parenteral calcium salts should not be used in patients with *digitalis toxicity* because of an increased risk of developing arrhythmias. Cardiac glycosides and calcium salts both increase intracellular calcium, so calcium salts can worsen digitalis toxicity. Cardiac glycoside therapy, however, does not preclude the use of calcium salts (see Drug Interactions). Calcium salts should be used cautiously in patients with preexisting cardiac arrhythmias. Calcium salts are no longer recommended for ACLS algorithms for pulseless electrical activity or asystole during cardiopulmonary resuscitation except when indications exist to counterbalance electrolyte disturbances.[2999] Parenteral calcium salts also should not be used during ventricular fibrillation. In the past, IV calcium salts were routinely administered during cardiac resuscitation; now, however, IV calcium salts are used more conservatively because of the known relationship between calcium ions and myocardial ischemia.[2999]

Precaution: Chelated Calcium Magnesium Tablets in diarrhea
Calcium supplements should be used with caution in patients with diarrhea or malabsorption because fecal excretion can be increased.

Precaution: Chelated Calcium Magnesium 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: Diovan HCT® in hypokalemia
Valsartan and hydrochlorothiazide should be considered an FDA pregnancy risk category D medication when used in combination. Valsartan should not be used during the second or third trimester of pregnancy (FDA category D), unless the benefits appear to outweigh the potential risks. Drugs which affect the renin-angiotensin system have been associated with fetal and neonatal injury.

These effects include hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure and death. Oligohydramnios has also been reported; it is attributed to decreased fetal renal function and results in fetal limb contractures, craniofacial deformation, and hypoplastic lung development. These adverse effects do not appear to occur during drug exposure during the first trimester, and valsartan is classified as FDA category C during this time. However, based on the results from one large study, first trimester use of thiazide and related diuretics may increase the risk for congenital defects (pregnancy category D). In addition to malformations, other fetal risks associated with thiazide use during pregnancy include hypoglycemia, thrombocytopenia, hyponatremia, hypokalemia, and death from maternal complications. Therefore, once pregnancy is detected, every effort should be made to discontinue valsartan; hydrochlorothiazide unless this drug combination is considered life-saving for the mother.

Precaution: Diovan HCT® in renal impairment
Valsartan; hydrochlorothiazide is contraindicated in patients with *renal failure* or *anuria* since thiazide diuretics are considered ineffective when the creatinine clearance is less than 30 ml/minute. Hydrochlorothiazide should be used cautiously in patients with renal disease resulting in severe renal impairment because the drug decreases the glomerular filtration rate and may precipitate azotemia in these patients. Valsartan should be used with caution in patients whose renal function is critically dependent on the activity of the renin-angiotensin-aldosterone system (RAS) (e.g., patients with heart failure). Angiotensin converting enzyme inhibitors (ACEIs) and angiotensin II receptor antagonists affect the RAS system and have caused increases in serum creatinine in susceptible individuals. Although serum creatinine returns to baseline or stabilizes in most patients with continued use, oliguria, progressive azotemia, and rarely, acute renal failure have occurred. In addition, ACEIs have been associated with azotemia in patients with unilateral or bilateral renal artery stenosis. Although valsartan has not been studied in renal artery stenosis, similar effects to the ACEIs might be anticipated due to valsartan's pharmacology. Renal function should be monitored in patients receiving valsartan; hydrochlorothiazide.

Precaution: Endocet® in cardiac arrhythmias
Opiate agonists, such as oxycodone, produce cholinergic side effects (by stimulating medullary vagal nuclei) causing bradycardia and vasovagal syncope, and induce the release of histamine, causing peripheral vasodilatation and orthostatic hypotension. These effects can cause problems in patients with cardiac disease. Acetaminophen-oxycodone should be used with caution in patients with cardiac arrhythmias, hypotension, or hypovolemia.

Precaution: Endocet® in diarrhea
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: Endocet® 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: Flomax® in renal impairment
Tamsulosin should be used cautiously in patients with orthostatic hypotension, vertigo, or syncope. The signs and symptoms of orthostasis (postural hypotension, dizziness, and vertigo) were more frequently reported in tamsulosin-treated patients than those receiving placebo. As with other alpha-adrenergic blocking agents, there is a potential risk of syncope and patients should be cautioned to avoid situations where injury could result should syncope occur. Patients with renal impairment, renal failure or other renal disease and the elderly should also be monitored carefully for exaggerated hypotensive effects (e.g., first dose effect).

Precaution: Lipitor® in renal impairment
Other HMG-CoA reductase inhibitors have been associated with toxicity to the skeletal muscle system. Myopathy, defined as muscle aches or muscle weakness in conjunction with increases in creatine phosphokinase (CPK) values > 10 times upper limit of normal (ULN), should be considered in any patient with diffuse myalgias, muscle tenderness or weakness, and/or marked elevation of CPK. Any evidence of myalgia, muscle weakness, or elevated CPK values may indicate myopathy, particularly if symptoms include fever or malaise. Clinicians should note that *rhabdomyolysis* and renal failure have been associated with HMG-CoA reductase inhibitor therapy. The risk of developing myopathy appears to be increased when HMG-CoA reductase inhibitors are used in combination with other drugs (see Drug Interactions). Atorvastatin should be discontinued immediately in any patient who develops myopathy or elevations in CPK. In addition, atorvastatin may be contraindicated in conditions that can cause decreased renal perfusion because renal failure is possible if atorvastatin-induced rhabdomyolysis occurs. Predisposing conditions include renal disease or renal

impairment, hypotension, acute infection, endocrine disease, electrolyte imbalance, uncontrolled seizure disorder, major surgery, and trauma. Atorvastatin should be used with caution in organ transplant patients receiving immunosuppressant therapy such as cyclosporine because of an increased risk of rhabdomyolysis and renal failure (see Drug Interactions). Renal disease has no influence on atorvastatin plasma concentrations or LDL cholesterol reductions; dosage adjustments are not needed in patients with renal impairment.

Precaution: Mirapex® in renal impairment
Urinary excretion is the major route of pramipexole elimination, with 90% of a dose excreted unchanged in urine. Clearance of pramipexole is 60-70% lower in patients with moderate-severe renal impairment (CrCl <= 40 ml/min) than in patients with normal renal function. Dosages should be adjusted in patients with a CrCl <= 60 ml/min (see Dosage). Use of pramipexole has not been adequately studied in patients with a CrCl <= 15 ml/min or in patients undergoing hemodialysis (a negligible amount of pramipexole is removed by dialysis). In general, pramipexole should be used with caution in patients with renal impairment.

Precaution: Piroxicam in angina
Piroxicam, like all NSAIDs, may exacerbate hypertension and congestive heart failure (see Adverse Reactions) and may cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. The risk may increase with duration of use, and patients with cardiovascular disease or risk factors for cardiovascular disease (e.g., high blood pressure) may be at greater risk. Caution is recommended when administering piroxicam to patients with cardiac disease, cardiomyopathy, cardiac arrhythmias (e.g., tachycardia), significant coronary artery disease (including acute myocardial infarction, angina, or history of myocardial infarction), peripheral vascular disease, cerebrovascular disease (e.g., stroke, transient ischemic attack), hypertension, pre-existing renal disease, fluid retention, or edema. Congestive heart failure, hypertension, syncope, and tachycardia have been reported with piroxicam administration. Use the lowest effective dose for the shortest duration possible to minimize the potential risk for an adverse cardiovascular event.

Precaution: Piroxicam in cardiac arrhythmias
Piroxicam, like all NSAIDs, may exacerbate hypertension and congestive heart failure (see Adverse Reactions) and may cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. The risk may increase with duration of use, and patients with cardiovascular disease or risk factors for cardiovascular disease (e.g., high blood pressure) may be at greater risk. Caution is recommended when administering piroxicam to patients with cardiac disease, cardiomyopathy, cardiac arrhythmias (e.g., tachycardia), significant coronary artery disease (including acute myocardial infarction, angina, or history of myocardial infarction), peripheral vascular disease, cerebrovascular disease (e.g., stroke, transient ischemic attack), hypertension, pre-existing renal disease, fluid retention, or edema. Congestive heart failure, hypertension, syncope, and tachycardia have been reported with piroxicam administration. Use the lowest effective dose for the shortest duration possible to minimize the potential risk for an adverse cardiovascular event.

Precaution: Piroxicam in hypertension
Piroxicam causes a dose-dependent decrease in prostaglandin synthesis and thus, renal blood flow in patients that utilize prostaglandins to support renal blood flow. Due to the role of prostaglandins in renal function and hemodynamics, patients with renal disease should be closely observed during therapy with piroxicam due to an increased risk for reduced renal blood flow or volume. Piroxicam is not recommended for use by patients with *advanced renal disease*.[6354] Piroxicam and its metabolites are renally excreted. Accumulation of parent drug and metabolites can occur in patients with renal disease, renal impairment or renal failure, increasing the risk of potential toxicity. Close monitoring of renal function is recommended; dosage adjustment may be necessary (see Dosage). Conditions such as congestive heart failure, edema, or hypertension can be exacerbated by the fluid retention cause by suboptimal renal perfusion. Piroxicam should be used cautiously in patients with any of these conditions or other diseases that predispose to fluid retention. Meta-analysis have demonstrated that the effect of NSAIDs on blood pressure is the greatest in hypertensive individuals receiving antihypertensive medication. In addition, normotensive patients receiving antihypertensive therapy had higher increases in blood pressure than subjects with uncontrolled hypertension or normotensive subjects receiving no hypertensive therapy.[4087] Patients with renal impairment, renal failure, hepatic disease, diabetes mellitus, systemic lupus erythematosus (SLE), or congestive heart failure, rheumatoid arthritis, edema, extracellular volume depletion (i.e., hypovolemia or dehydration), sepsis; those taking diuretics or nephrotoxic drugs; and the elderly are at the highest risk for developing complications related to suboptimal renal perfusion.

Precaution: Piroxicam in renal impairment
Piroxicam causes a dose-dependent decrease in prostaglandin synthesis and thus, renal blood flow in patients that utilize prostaglandins to support renal blood flow. Due to the role of prostaglandins in renal function and hemodynamics, patients with renal disease should be closely observed during therapy with piroxicam due to an increased risk for reduced renal blood flow or volume. Piroxicam is not recommended for use by patients with *advanced renal disease*.[6354] Piroxicam and its metabolites are renally excreted. Accumulation of parent drug and metabolites can occur in patients with renal disease, renal impairment or renal failure, increasing the risk of potential toxicity. Close monitoring of renal function is recommended; dosage adjustment may be necessary (see Dosage). Conditions such as congestive heart failure, edema, or hypertension can be exacerbated by the fluid retention cause by suboptimal renal perfusion. Piroxicam should be used cautiously in patients with any of these conditions or other diseases that predispose to fluid retention. Meta-analysis have demonstrated that the effect of NSAIDs on blood pressure is the greatest in

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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: Potassium Chloride in atrial fibrillation
Potassium supplements should be monitored closely in patients with cardiac arrhythmias (e.g., atrial fibrillation, atrial flutter, digitalis toxicity (except due to documented hypokalemia), and ventricular arrhythmias including ventricular fibrillation and ventricular tachycardia), including patients receiving digoxin or other antiarrhythmic therapy. Based on a multidisciplinary review of literature and clinical practice trends, the National Council on Potassium in Clinical Practice recommends that serum potassium concentrations >= 4 mEq/L be achieved and maintained in patients with hypertension, heart failure, and cardiac arrhythmias to minimize complications of potassium depletion.[3085] In addition, the Council recommends potassium supplementation for patients at risk for developing hypokalemia and associated complications. Potassium supplementation is specifically recommended for patients with potential for diuretic-induced potassium loss (e.g., receiving thiazide or loop diuretics), patients with high sodium intake (unwilling to reduce salt intake), and patients with reduced GI intake (e.g., GI disturbances, laxative abuse).[3085]

Precaution: Potassium Chloride in cardiac arrhythmias
Potassium supplements should be monitored closely in patients with cardiac arrhythmias (e.g., atrial fibrillation, atrial flutter, digitalis toxicity (except due to documented hypokalemia), and ventricular arrhythmias including ventricular fibrillation and ventricular tachycardia), including patients receiving digoxin or other antiarrhythmic therapy. Based on a multidisciplinary review of literature and clinical practice trends, the National Council on Potassium in Clinical Practice recommends that serum potassium concentrations >= 4 mEq/L be achieved and maintained in patients with hypertension, heart failure, and cardiac arrhythmias to minimize complications of potassium depletion.[3085] In addition, the Council recommends potassium supplementation for patients at risk for developing hypokalemia and associated complications. Potassium supplementation is specifically recommended for patients with potential for diuretic-induced potassium loss (e.g., receiving thiazide or loop diuretics), patients with high sodium intake (unwilling to reduce salt intake), and patients with reduced GI intake (e.g., GI disturbances, laxative abuse).[3085]

Precaution: Potassium Chloride in diarrhea
Potassium supplements are contraindicated in patients with *hyperkalemia* since a further increase in serum potassium concentration in such patients can produce cardiac arrest. Due to the risk of developing hyperkalemia, potassium supplementation should be used with caution in patients with adrenal insufficiency (untreated Addison's disease); acute dehydration; systemic metabolic acidosis such as diabetic ketoacidosis; diarrhea; strenuous physical exercise (especially unconditioned persons); in patients receiving salt substitutes, potassium-sparing diuretics (e.g., amiloride, spironolactone, triamterene), ACE inhibitors, or angiotensin II antagonists; or in patients with renal disease, renal failure, or renal impairment. Potassium supplements should also be used cautiously in patients with severe burns because these patients are prone to hyperkalemia secondary to tissue breakdown and renal insufficiency. Serum potassium levels and renal function should be monitored closely in patients at risk for hyperkalemia. Because elderly patients are more likely to have decreased renal function, potassium salts should be dosed cautiously based on an assessment of renal function and therapeutic goals. NOTE: Potassium acetate injection contains aluminum (<= 200 mcg/L). Thus, aluminum may reach toxic levels with prolonged administration in patients with renal impairment. Premature neonates are at particular risk for aluminum toxicity following administration of aluminum-containing injectables. Since premature neonates have immature kidneys, they may require large amounts of calcium and phosphate solutions, which contain aluminum. 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: Potassium Chloride in hypertension
Potassium supplements should be monitored closely in patients with cardiac arrhythmias (e.g., atrial fibrillation, atrial flutter, digitalis toxicity (except due to documented hypokalemia), and ventricular arrhythmias including ventricular fibrillation and ventricular tachycardia), including patients receiving digoxin or other antiarrhythmic therapy. Based on a multidisciplinary review of literature and clinical practice trends, the National Council on Potassium in Clinical Practice recommends that serum potassium concentrations >= 4 mEq/L be achieved and maintained in patients with hypertension, heart failure, and cardiac arrhythmias to minimize complications of potassium depletion.[3085] In addition, the Council recommends potassium supplementation for patients at risk for developing hypokalemia and associated complications. Potassium supplementation is specifically recommended for patients with potential for diuretic-induced potassium loss (e.g., receiving thiazide or loop diuretics), patients with high sodium intake (unwilling to reduce salt intake), and patients with reduced GI intake (e.g., GI disturbances, laxative abuse).[3085]

Precaution: Potassium Chloride in renal impairment
Potassium supplements are contraindicated in patients with *hyperkalemia* since a further increase in serum potassium concentration in such patients can produce cardiac arrest. Due to the risk of developing hyperkalemia, potassium supplementation should be used with caution in patients with adrenal insufficiency (untreated Addison's disease); acute dehydration; systemic metabolic acidosis such as diabetic ketoacidosis; diarrhea; strenuous physical exercise (especially unconditioned persons); in patients receiving salt substitutes, potassium-sparing diuretics (e.g., amiloride, spironolactone, triamterene), ACE inhibitors, or angiotensin II antagonists; or in patients with renal disease, renal failure, or renal impairment. Potassium supplements should also be used cautiously in patients with severe burns because these patients are prone to hyperkalemia secondary to tissue breakdown and renal insufficiency. Serum potassium levels and renal function should be monitored closely in patients at risk for hyperkalemia. Because elderly patients are more likely to have decreased renal function, potassium salts should be dosed cautiously based on an assessment of renal function and therapeutic goals. NOTE: Potassium acetate injection contains aluminum (<= 200 mcg/L). Thus, aluminum may reach toxic levels with prolonged administration in patients with renal impairment. Premature neonates are at particular risk for aluminum toxicity following administration of aluminum-containing injectables. Since premature neonates have immature kidneys, they may require large amounts of calcium and phosphate solutions, which contain aluminum. 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: Super B Complex With Vitamin C in renal impairment
Parenteral pyridoxine solutions contain varying concentrations of aluminum. Patients with renal impairment, especially as seen with neonatal prematurity, are at risk of aluminum accumulation which may result in toxicity. Limit intravenous pyridoxine therapy and consider the cumulative aluminum content among all therapies under administration in patients with renal impairment. It is noted that 4-5 mcg/kg/day of IV aluminum leads to accumulation at concentrations associated with CNS and bone toxicity; further, aluminum tissue loading is possible at lesser, but undefined, daily administration rates.[9771] Aluminum concentration in parenteral solutions can be obtained by direct manufacturer inquiry.

Precaution: Super B Complex With Vitamin C in angina
Due to its vasodilatory action, nicotinic acid (niacin) should be used with caution in those patients with uncorrected hypotension (or predisposition to orthostatic hypotension), acute myocardial infarction, or unstable angina, particularly when vasodilator medications such as nitrates, calcium channel blockers, or adrenergic blocking agents are coadministered (see Drug Interactions). Because the vasodilatory response to niacin may be more dramatic at the initiation of treatment, activities requiring mental alertness (e.g., driving or operating machinery) should not be undertaken until the response to niacin is known.

Precaution: Super B Complex With Vitamin C in renal impairment
Use niacin with caution in patients with renal disease (renal failure or severe renal impairment) since niacin metabolites are excreted through the kidneys. It appears that no special precautions are needed when administering niacin to meet the recommended nutritional daily allowance (RDA). Use caution when administering higher dosages.

Precaution: Trental® in renal impairment
Pentoxifylline and its active metabolites can accumulate in patients with renal impairment; such patients should be monitored carefully for adverse effects. Dosage adjustments are recommended in patients with renal impairment (CrCl < 50 ml/min) or renal failure (see Dosage). Additionally, dosage adjustments are recommended in patients who do not tolerate pentoxifylline (i.e., experience GI or CNS adverse effects) at usual prescribed dosages.

References

162. Marcuard SP, Albernaz L, Khazanie PG. Omeprazole therapy causes malabsorption of cyanocobalamin (vitamin B_{12}). Ann Intern Med 1994;120:211-5.

805. The sixth report of the Joint National Committee on detection, evaluation, and treatment of high blood pressure. National Institute of Health publication No. 99-4080. 1997:1-64.

1797. Robbers JE, Tyler VE. *Tyler's Herbs of Choice: the Therapeutic Use of Phytomedicinals*. Binghamton NY: Haworth Herbal Press, Inc.; 1999.

2173. Lechey D, Gantt C, Lim V. Heparin-induced hypoaldosteronism. JAMA 1981;246:2189-90.

2913. Heptinstall S, Groenewegen WA, Spangenberg P, et al. Inhibition of platelet behaviour by feverfew: a mechanism of action involving sulphydryl groups. Folia Haematol Int Mag Klin Morphol Blutforsch 1988;115:447-9.

2914. Loesche W, Mazurov AV, Voyno-Vasenetskaya TA, et al. Feverfew-an antithrombotic drug? Folia Haematol Int Mag Klin Morphol Blutforsch 1988;115:181-4.

2915. Biggs MJ, Johnson ES, Pesaud NP, et al. Platelet aggregation in patients using feverfew for migraine (letter). Lancet 1982;2:776.

2999. Guidelines 2000 for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Part 6: advanced cardiovascular life support. Circulation 2000;102(8 Suppl):112-165.

3085. Cohn JN, Kowey PR, Whelton PK, Prisant LM. New guidelines for potassium replacement in clinical practice: a contemporary review by the National Council on Potassium in Clinical Practice. Arch Intern Med 2000;160:2429-36.

3154. Johnson AG. NSAIDs and increased blood pressure. What is the clinical significance? Drug Safety 1997;17:277-89.

4062. Catella-Lason F, Reilly MP, Kapoor SC, et al. Cyclooxygenase inhibitors and the antiplatelet effects of aspirin. *N Engl J Med* 2001;345:1809-17.

4063. Ouellet M, Riendeau D, Percival MD. A high level of cyclooxygenase-2 inhibitor selectivity is assocated with a reduced interference of platelet cyclooxygenase-1 inactivation by aspirin. *Proc Natl Acad Sci U S A* 2001;4:14583-8.

4064. Fored CM, Ejerblad E, Lindblad P, et al. Acetaminophen, aspirin, and chronic renal failure. *N Engl J Med* 2001;345:1801-8.

4087. Frishman WH. Effects of nonsteroidal anti-inflammatory drug therapy on blood pressure and peripheral edema. *Am J Cardiol* 2002;89(suppl):18D-25D.

4178. Taavitsainen P, Kiukaanniemi K, Pelkonen O. In vitro inhibition screening of human hepatic P450 enzymes by five angiotensin-II receptor antagonists. *Eur J Clin Pharmacol* 2000;56:135-40.

4179. Brookman LJ, Rolan PE, Benjamin IS, et al. Pharmacokinetics of valsartan in patients with liver disease. *Clin Pharmacol Ther* 1997;62:272-8.

4689. Gora M, Seth S, Bay W, et al. Milk-alkali syndrome associated with use of chlorothiazide and calcium carbonate. *Clin Pharm* 1989;8:227-9.

4707. Inspra™ (eplerenone) package insert. New York, NY: G.D. Searle LLC; 2003 Oct.

4925. Kurtovic J, Riordan SM. Paracetamol-induced hepatotoxicity at recommended dosage. *J Intern Med* 2003;253:240-3.

5073. Sulfamethoxazole and Trimethoprim package insert. Irvine, CA: Gensia Sicor Pharmaceuticals, Inc.; 1999 March.

5134. Neoral® (cyclosporine) package insert. East Hanover, NJ: Novartis Pharmaceuticals Corporation; 2002 Aug.

5163. Clarke TA, Waskell LA. The metabolism of clopidogrel is catalyzed by human cytochrome P450 3A and is inhibited by atorvastatin. *Drug Metab Dispos* 2003;31:53-9.

5164. Wodlinger AM, Pieper JA. The role of clopidogrel in the management of acute coronary syndromes. *Clin Ther* 2003;25:2155-81.

5165. Plavix® (clopidogrel) package insert. New York, NY: Sanofi-Synthelabo; 2004 Oct.

5166. Ticlid® (ticlopidine) package insert. Nutley, NJ: Roche Laboratories, Inc.; 2001 Mar.

5167. Pletal® (cilostazol) package insert. Tokushima, Japan: Otsuka Pharmaceutical Co., Ltd.; 2004 Feb.

5168. Persantine® (dipyridamole) package insert. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc.; 2003 May.

5170. Hayes, AH. Therapeutic implications of drug interactions with acetaminophen and aspirin. *Arch Intern Med* 1981;141:301-4.

5171. Harder S, Klinkhardt U. Thrombolytics: drug interactions of clinical significance. *Drug Saf* 2000;23:391-9.

5232. Fiorinal® (butalbital; aspirin; caffeine) package insert. East Hanover, NJ: Novartis Pharmaceuticals Corporation; 1998 Sep.

5269. Toprol-XL® (metoprolol succinate) package insert. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2006 Mar.

5314. Miller LG. Herbal medicinals: selected clinical considerations focusing on known or potential drug-herb interactions. *Arch Intern Med* 1998;158:2200-11.

5339. Cozaar® (losartan potassium) package insert. Whitehouse Station, NJ: Merck & CO.,INC.; 2005 Apr.

5365. Zestril® (lisinopril) package insert. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2003 July.

5398. Saw J, Steinhubl SR, Berger PB, et al. Lack of adverse clopidogrel-atorvastatin clinical interaction from secondary analysis of a randomized, placebo-controlled clopidogrel trial. *Circulation* 2003;108:921-4.

5449. Cenolate® (ascorbic acid, vitamin C injection) package insert. North Chicago, IL: Abbott Laboratories; 2002 Sept.

5460. Lipitor® (atorvastation calcium) package insert. New York, NY; Parke-Davis; 2005 Sept.

5477. Lau WC, Waskell LA, Walkins PB, et al. Atorvastatin reduces the ability of clopidogrel to inhibit platelet aggregation: a new drug-drug interaction. *Circulation* 2003;107:32-7.

5506. Williams D, Feely J. Pharmacokinetic-pharmacodynamic drug interactions with HMG-CoA reductase inhibitors. *Clin Pharmacokinet* 2002;41:343-370.

5717. U.S. Department of Health and Human Services (DHHS), FDA, 21 CFR Part 343 (Docket No. 77N-094A). Internal analgesic, antipyretic, and antirheumatic drug products for over-the-counter human use; final rule for professional labeling of aspirin, buffered aspirin, and aspirin in combination with antacid drug products. Retrieved May 6, 2004. Published October 23, 1998 on the World Wide Web at: http://www.fda.gov.

5718. Bouvy ML, Heerdink ER, Hoes AW, et al. Effects of NSAIDs on the incidence of hospitalisations for renal dysfunction in users of ACE inhibitors. *Drug Saf* 2003;26:983-9.

5751. Aldactone® (spironolactone) package insert. Chicago, IL: G.D. Searle LLC; 2003 July.

5801. Salhanick SD, Shannon MW. Management of calcium channel antagonist overdose. *Drug Safety* 2003;26:65-79.

5825. Norvasc® (amlodipine) package insert. New York, NY: Pfizer Labs; 2005 Mar.

5873. Midamor® (amiloride) package insert. Whitehouse Station, NJ: Merck & Co., Inc.; 2002 Nov.

5898. Dyrenium(R) (triamterene) package insert. Neptune, NJ: Wellspring Pharmaceuticals; 2001 Jun.

5911. Wang JJ, Lee CL, Pan TM. Improvement of monacolin K, gama-aminobutyric acid and citrinin production ratio as a function of environmental conditions of Monascus purpureus NTU 601. *J Ind Microbiol Biotechnol* 2003;30:669-76.

5917. HydroDIURIL® (hydrochlorothiazide) package insert. Whitehouse Station, NJ: Merck & Co., Inc.; 1998 Jun.

5932. Niaspan® (niacin extended-release tablets) Miami, FL: Kos Pharmaceuticals, Inc; 2003 July.

5944. Johnson RH, Eisenhofer G, Lambie DG. The effects of acute and chronic ingestion of ethanol on the autonomic nervous system. *Drug Alcohol Depend* 1986;18:319-28.

6060. Takkouche B, Etminan M, Caamano F, et al. Interaction between aspirin and ACE inhibitors: resolving discrepancies using a meta-analysis. *Drug Safety* 2002;25:373-8.

6090. Actonel® (risedronate) package insert. Cincinnati, OH: Procter & Gamble Pharmaceuticals; 2003 Mar.

6288. Imdur® (isosorbide mononitrate) package insert. Kenilworth, NJ: Key Pharmaceuticals: 2002 Jul.

6316. Trental® (pentoxifylline) package insert. Bridgewater, NJ: Aventis Pharmaceuticals Inc.; 2004 Apr.

6338. Hoffman BB, Lefkowitz RJ. Atropine, scopolamine, and related antimuscarinic drugs. Gilman AG, Rall TW, Nies AS, Taylor P, (eds.) In: Goodman and Gilman's Pharmacological Basis of Therapeutics. 8th ed., New York, Pergamon Press. 1990. 150-61.

6354. Feldene® (piroxicam) package insert. New York, NY: Pfizer Labs; 2003 May.

6419. Flomax® (tamsulosin) package insert. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc.; 2005 Oct.

6439. Guazzi M, Brambilla R, Reina G, et al. Aspirin-angiotensin-converting enzyme inhibitor coadministration and mortality in patients with heart failure: a dose-related adverse effect of aspirin. *Arch Intern Med* 2003;163:1574-9.

6714. Lam YWF, Shepherd AMM. Drug interactions in hypertensive patients: pharmacokinetic, pharmacodynamic, and genetic considerations. *Clin Pharmacokinet* 1990;18:295-317.

6826. Pfizerpen® (penicillin G potassium injection) package insert. New York, NY: Pfizer Roerig; 2003 Sep.

6855. Imodium A-D Liquid and Caplets® (loperamide HCL) package insert. Fort Washington, PA: McNeil Consumer; 2005 Jun.

6859. Insel PA. Analgesic-antipyretic and antiinflammatory agents and drugs employed in the treatment of gout. In: Hardman JG, Limbird LE, Molinoff PB, et al., eds. *Goodman and Gilman's the pharmacological basis of therapeutics*, 9th edn. New York: McGraw Hill, 1996;617-657.

7025. Potassium Chloride Extended-release Tablets package insert. Fort Lauderdale, FL: Andrx Pharmaceutials Inc.; 2001 Apr.

7114. Jackson EK. Diuretics. Gilman AG, Hardman JG, Limbird LE, (eds.) In: *Goodman and Gilman's The Pharmacological Basis of Therapeutics*. 10th ed., New York, McGraw-Hill Companies. 2001:757-87.

7197. Fawcett WJ, Haxby EJ, Male DA. Magnesium: physiology and pharmacology. *Br J Anaesth* 1999;83:302-20.

7254. Lodine® XL (etodolac extended-release tablets) package insert. Philadelphia, PA: Wyeth Pharmaceuticals Inc.; 2003 Oct.

7631. Sigroth K. Letter: Effect of clonidine on nicotinic-acid flushing. *Lancet* 1974;2:58.

7757. Mirapex® (pramipexole dihydrochloride) package insert. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc.; 2006 Feb.

7827. Salsalate tablets package insert. Little Falls, NJ: Amide Pharmaceuticals, Inc.; 2003 Jun.

8833. Bristol-Myers Squibb Company Press Release, March 12, 2006. New study furthers understanding of the role of dual antiplatelet therapy in the prevention of atherothrombotic events, including heart attack, stroke or cardiovascular death in broad population. Certain subgroups may benefit from dual therapy, for others it should be avoided.

8879. Backman JT, Luurila H, Neuvonen M, et al. Rifampin markedly decreases and gemfibrozil increases the plasma concentrations of atorvastatin and its metabolites. *Clin Pharmacol Ther* 2005;78:154-67.

9029. Hudson M, Baron M, Rahme E, et al. Ibuprofen may abrogate the benefits of aspirin when used for secondary prevention of myocardial infarction. *J Rheumatol* 2005;32:1589-93.

9044. Cesamet™ (nabilone) package insert. Costa Mesa, CA: Valeant Pharmaceuticals International; 2006 May.

9771. Pyridoxine hydrochloride injection, USP package insert. Schaumburg, IL: American Pharmaceutical Partners; 2005 Jun.