Website
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RXPERTUSA
Medication Therapy Management Services
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Charles S. Feucht,PD,FASCP Senior Care Clinical Pharmacist

Patient Profile for: M C

Personal Information

Patient ID:	#05112007
Attending Physician:	J R, MD 3521 Highway, Suite V,
Patient Name:	MTC
Address:	.
City:	
State:	
Zipcode:	
Country:	USA
Phone:	

Medical Information

Diagnosis:
Atrial Fibrillation
Hypertension
CAD with coronary stents
CVA
Hyperlipidemia
GERD
Post-menopausal
Urinary Incontinence NOS
Insomnia NOS

Surgical Hx:
IAH with BSO
Cholecystectomy
Rt. Wrist fracture
Bilateral Knee replacements

General complaints not listed as diagnosis by your doctor:
SOB at times with exertion but not limiting
BP elevated on day of visit 11-8-07 190/78
Wakes at least 2x at night due to urge to urinate also indicates stress incontinence

Possible hypotensive episodes as patient states having dizzy spells and having to sit on the side of the bed on waking or on rising or standing due to dizziness and weakness when changing from lying to sitting or standing position. (No falls within the past year)
c/o buring in her feet a rest "feels like she's walking on fire"
difficulty swallowing at times but no heartburn
coughs on lying down with expectoration.
Joint pain in knees level 4 on Wong-Baker scale unable to kneel anymore
Describes her insomnia as onset and maintenance 2^{o} to waking to urinate
Mild depression symptoms as indicated by Geriatric Deression Rating Scale score of 6 done 11-8-07

Allergies: No known allergies reported

Current Medications:

Medication	Date	Precriber
Hydrocholrothiazide 25mg 1 tablet by mouth every morning.	since 5-07 or earlier	R,J.
Furosemide 20mg 1 tablet by mouth daily	since 5-07 or earlier	R,J.
Fosinopril 40mg 1 tablet by mouth daily	since 5-07 or earlier	R,J.
Tekturna 300mg 1 tablet by mouth daily	9-24-07	K,J.
Sotalol 80mg ½ tablet by mouth twice daily	since 5-07 or earlier	H,C.
Digoxin 0.25mg 1 tablet by mouth daily	since 5-07 or earlier	H,C.
Isosorbide Mononitrate 60mg ½ tablet by mouth daily	since 5-07 or earlier	R,J.
Aspirin 81mg 1 tablet by mouth daily	since 5-07 or earlier	R,J.
Plavix 75mg 1 tab by mouth daily 5-07	since 5-07 or earlier	R,J.
Crestor 10mg 1 tablet by mouth at bedtime	since 5-07 or earlier	R,J.
Zantac 150mg 1 tablet by mouth at bedtime	since 5-07 or earlier	R,J.
Zegerid 40mg 1 capsule by mouth daily in the morning	since 5-07 or earlier	R,J.
Aricept 10mg 1 tablet at bedtime	since 5-07 or earlier	R,J.
Allegra 180mg 1 tablet by mouth daily	since 5-07 or earlier	R,J.
Enablex 7.5mg 1 tablet daily for bladder	8-1-07	H,M.
Ambien 5mg 1 po hs	10-16-07	R, J.

Dosing considerations
78 y/o Female African American
TBW = 210lbs

Gender: Female
DOB: 3/20/1929 Age: 78
Height: 66" (162cm)
Weight: 210lbs (95Kg)
Ideal Body Weight: 112-150lbs (50-60Kg
BMI = 33.9 Obesity Class = Class I Disease risk = Very high
Body Surface Area: $2.04M^2$
Serum Creatinine: 0.9mg/dl Date:11-15-07
Estimated Creatinine Clearance: 56.7ml/min

Laboratory Values:

Comprehensive Metabolic Panel(CMP)		11-15-07 reference range	
Glucose	99	70-110mg/dl	
BUN	18	7-18mg/dl	
Osmolarity	285	273-304	
Creatinine	0.9	0.6-1.3mg/dl	
BUN/Cr	20.0	12-20	
Bilirubin Total	0.35	0.0-1.0mg/dl	
Calcium	8.6	8.8-10.5G/dl	Corrected for albumin this level WNL @ 9.2G/dl
TProtein	6.4	6.4-8.1G/dl	
Glob	3.2	2.1-3.7 G/dl	
Albumin	3.2	3.4-5.0G/dl	
A/G	1.0	1.0-2.5	
Alk Phos	51	50-136	
AST(SGOT)	18	15-37U/L	
ALT(SGPT)	29	30-65U/L	
Sodium	142	136-145mmol/L	
Potassium	3.3	3.5-5.1mmol/L	
Chloride	104	98-107mmol/L	
CO_2	34.9	21-32mmol/L	
AGAP	6.4	7.0-16mmol/L	

Lipids: 11-15-07			
Trig	124	30-200mg/dl	
Chol	126	0-200mg/dl	
LDL	61	80-130mg/dl	
HDL	40	32-96mg/dl	
Non-HDL	65		
Risk	3.2	0.0-4.8	

Lipids: 4-4-07			
Trig	57	30-200mg/dl	
Chol	236	0-200mg/dl	
LDL	163	80-130mg/dl	
HDL	62	32-96mg/dl	
Non-HDL	73		
Risk	3.8	0.0-4.8	

Serum Drug Levels:			
digoxin	0.98	0.9-2.0ng/ml	11-15-07
digoxin	0.05	0.9-2.0ng/ml	4-4-07

Thyroid Function:			
TSH	2.96	0.34-4.82UIU.ml	4-4-07

Renal

Microalbumin UR rand		
Creatinine-UR	53.7	
Microalbumin	33.6	0-37mg/L
Ratio	62	

Complete Blood Count with differential (CBC with diff)

WBC	5.35	4.6-10.2K/UL
RBC	4.11	4.04-6.13M/UL
Hgb	11.2	12.2-18.G/dl
Hct	34.2	37.7-53.7%
MCV	83.2	80-97FL
MCH	27.3	27-31.2PG
MCHC	32.7	31.8-35.4G/dl
RDW	14.1	11.6-14.8%
Platelets CT auto	184	142-424K/UL
MPV	12.2	0.00-99.9FL
Nuetrophils%	45.0	37.0-80.0%
Lymphocytes%	40.2	10.0-50.0%
Monocytes%	12.7	0.0-12.0%
Eosinophils%	1.9	0.0-7.0%
Basophils%	0.2	0.0-2.5%
Nuetrophils#	2.41	2.0-6.9K/UL
Lymphocyte #	2.15	0.60-3.4K/UL
Monocyte#	0.68	0.0-0.9K/UL
Eosinophil#	0.10	0.0-0.7K/UL
Basophil#	0.01	0.0-0.20K/UL
Mandiff	----	----------

Date: 11-29-07

Pharmacology Review and recommendations:

Initial review & assessment:

This 78 year old African American female presents with the above listed diagnosis and pertinent complaints obtained from personal history. The patient's memory (cognition) and functioning skills are intact with MMSE score in normal range of 27 out of 30. A Geriatric Depression Rating Scale was performed the score of 6 on this test indicated possible mild depression but non s/s of such were detected during the interview. The patient has no diagnosis of dementia The patient is currently on Aricept. Drugs with high anticholinergic activity like, Enablex , can negate the effects of the already minimally effective cholinesterase ihibitors. This class of drugs was recently tested for treating pre-dementia and found to be of no benefit.

Her laboratory values are within acceptable ranges for the most part. Lipids are well within the goal of therapy ranges. Calcium levels showed below normal values but when corrected for albumin level fall well within the normal range. Her potassium level was low at 3.3 and she is on both furosemide and hydrochlorothiazide. Since the patient is also receiving digoxin 0.25mg this is of some concern. Serum digoxin levels are within normal levels and pulse rate has been also. However, her current dose of digoxin is no longer recommended for geriatric patients.

The patient is receiving nitrate therapy with isosorbide mononitrate but has no diagnosis of heart failure, angina secondary to CAD, but does have CAD and has had PCI and stent placement. Geriatric patients are very susceptible to nitrate induced orthostatic hypotension in addition to her other combinations of blood pressure medicatons this risk is significantly increased.

The patient is on combination therapy with a proton pump inhibitor Zegerid 40mg daily and a histamine antagonist, Zantac 150mg hs. This combination is warranted in light of patient given history. Administration of both of these agents together is not supported by the fact that the PPIs such as Zegerid act at the final point of acid secretion and, therefore, blocking the histamine receptor with Zantac is unlikely to add benefit and may result in tachyphylaxis instead. Use of a proton pump inhibitor, twice daily is indicated if nocturnal heartburn is a problem rather than this combination therapy. A trial period without either agent may be warranted with the implementation of non-drug therapy recommended below. If GERD reappears then use of only a proton pump inhibitor is recommended with bid dosing if nocturnal heartburn is an issue. Additionally, the time at which the patient takes the proton pump inhibitor is also critical to maximize benefit. The combination of the proton pump inhibitor with bicarbonate only improves the rate of absorption and not the extent. These drugs need to be given before meals in the longest fasting state possible to maximize binding to active proton pump ihibitors. The combination product Zegerid is no exception.

The patient had to be started on Enablex urinary frequency. She is also on Ambien for sleep which is interrupted because of the urinary frequency. Cholinesterase inhibitors induce contraction of the detrusor muscle and decrease bladder capacity and can worsen urinary frequency. The use of both diuretic agents hydrochlorothiazide and furosemide also increase the risk of urinary frequency and incontinence discontinuation of one of these agents preferably the furosemide is recommended. Other agents this patient is receiving which can worsen or induce urinary incontinence include: sotalol

The patient's was seen by her primary physician for a follow up on her blood pressure on 11-13-07. Her BP reading then was well within the goal of therapy at 134/70. She was asked to keep a BP record for the two weeks prior to her return visit to me but when contacted today by phone indicated she had not done so. We have no daily values for comparison. She seems to be very compliant with her medications. Examination of her pharmacy records indicates she regularly refills medications timely. While our BP reading showed elevated systolic levels it may have been related to the fact that she had difficulty finding the office and was running a little late.

The patient has a diagnosis of atrial fibrillation and CVA. Coumadin remains the first line agent recommended by ACC, AHA, 7thAnnual Conference of Chest Physicians for secondary prevention of stroke ,

DVT & PE with INR within a target range of 2-3. The patient is currently on Plavix and aspirin combination. In cases of bare metal stents this combination is recommended for up to 12 months. Randomized controlled clinical trials using the combination of Plavix and aspirin in these cases do not extended beyond this period making clinical evaluation of use beyond this period controversial. No changes in this therapy are recommended at this time. Patient needs to be consulted about warfarin therapy prior to any changes. The patient reports no bleeding or bruising episodes.

The need for both digoxin and sotalol is not clear. The current dose is above the maximum recommended dose for geriatric patients and renal function for this patient. Since the patient has atrial fibrillation the dose of sotalol could be increased to control rate and digoxin therapy discontinued as digoxin is not the drug of choice for rate control. An option which serves as an reliable alternative and address both rate control, reduction of the risk of the orthostatic hypotension issue from nitrate therapy and would allow for removal of digoxin therapy as well is the addition of low dose benzothiazepine calcium channel blocker in controlled release formulation.

Specific Medication change recommendations:

1. **Discontinue Aricept repeat MMSE in 30 days**
   Rationale: This drug has no diagnosis to support use. The patient's MMSE score indicates no dementia problems. Use with Enablex renders this drug which is at best minimally effective for dementia relatively ineffective.
2. **Discontinue furosemide start Demadex 10mg 1 po q day.**
   Rationale: The need for both hydrochlorothiazide and furosemide is questionable. Diuretic therapy for control of BP especially in African Americans is considered first line therapy along with and angiotensin converting enzyme inhibitor which she is receiving. Her renal(kidney) function is still adequate enough to justify the use of the thiazide diuretic, hydrochlorothiazide but seems insufficient with respect to diuresis as the furosemide had to be added. Start Demadex(torsemide) This will produce some frequent urination during its first three days of therapy but will elvel off after that time. It will provide for longer duration of diuresis action since it has a longer half life that furosemide. It also has better antihypertensive activity than furosemide and keeps the diuretic n board to enhance ACEI activity and beta blocker action which is generally less effective in blacks. There is less potassium, calcium and magnesium wasting with torsemide and due to its longer half life reduces the risk of paradoxical antidiuresis seen with furosemide.
3. **Discontinue HCTZ**
   Rationale: See above

4. **Discontinue Imdur start diltiazem CD 60mg 1 po q day**
   & evaluate BPand pulse rate in 30 days. Have the patient keep BP and pulse rate logs during those 30 days twice daily. To aid in compliance she can have BP taken at our office as possible.
   Rationale: The addition of the benzothiazepine calcium channel blocker, diltiazem, allows for several drug changes and the ability to control blood pressure and heart rate. Starting diltiazem CD 60mg q day will allow for discontinuation of Imdur and still provide anginal protection if this is why the Imdur was started (although not specified in the diagnosis). Imdur has a grater propensity to cause orthostatic hypotension in geriatric patients as they have reduced baroreceptor fuction.There is the potential synergistic rate effect with sotalol which is the reason for starting at a low dose and evaluating in 30 days for needed dose change up or down in either of the rate control medications.

5. **Discontinue digoxin 0.25mg q day**
   Rationale: See above. Additionally, this dose of digoxin is not recommended for geriatric patients even those with atrial fibrillation due to reduced kidney function. With the recent low serum potassium tere is an increase risk of digoxin adverse events.

6. **Evaluate for discontinuation of Tekturna in 30 days after diltiazem/sotalol combination results are seen.**
   Rationale: Potential interaction between Tenktura and sotalol resulting in QT interval prolongation.

7. **Discontinue the Allegra 180mg q day change to either Zyrtec 1 po q day as needed for allergy symptoms.**
   Rationale: Allegra dosing needs to be adjusted for reduced renal(kidney) function in most geriatric patients. Doses of 60mg or less should be used in patient with CrCl rates of less than 80m/min. Zyrtec can be utilized at 10mg dose down to clearance rates of 32ml/min and 5mg 1 daily for those with rates of less than 31ml/min. Patient has no diagnosis to support chronic long term use of Allegra. If given for seasonal allergic rhinitis/sinusitis then use only as neededand at reduced dose. I recommend or discontinuing it at this timeand utilizing one of the alternate agents above prn only .

8. **Discontinue Zegerid slowly by decreasing it to qod for 1 week then discontinue it. Reduce Zantac to 75mg hs x 1 month then qod hs x 1 month then DC.**

Rationale: Patient has GERD but indicates she's had no problem for some time. Long term use of PPIs) in the *geriatric may lead to several serious conditions*

- Incidence of C. difficile diarrhea is 3 times higher for patient on long term PPI therapy and twice as high for patients on H2 antagonist long term than control patients on neither.
- Rebound acidity –from the body's attempt to regain the low gastric pH and through more gastric acid secretions exacerbating the GI condition
- Aspiration Pneumonia risk are increased - raising the pH of the gut for long times produce a basic gut that complicates digestion, increase more gas and discomfort, slows down the breakdown of foods and many drugs and increase potential risk for aspiration of this basic fluid into the lungs.

Combination therapy ncrease the risk of rebound acidity.
Nocturnal heartburn is more effectively treated with twice daily dosing of PPIs than combination PPI & H2 antagonist therapy, but every attempt should be made to wean the patient from both due to the above risk.
Implementation of non-drug therapy options can be very effective in controlling nocturnal heartburn. Gradual decrease of the Zegerid is need to avoid a rebound acidity problem. Decreasing the Zegerid to qod for 1 week will help to avoid this problem and lead to successful withdrawal of this medication. Additionally, the non-pharmacological interventions listed below are necessary to enhance tapering away the PPI, Zegerid.

9. **Implement non-drug therapy for GERD**
   - Prohibit spicy and difficult to digest foods after evening meal
   - Have patient consume either 3 oz buttermilk and saltine crackers or a container of plain yogurt daily in the evenings.

10. **Evaluate urinary frequency in 30 days after discontinuation of furosemide, HCTZ and Aricept for possible feasibility of dicontinuing the Enablex if frequency has improved.**

11. **Change Ambien to as needed with a goal to wean her off of it in the next few months**. **Add Effexor XR 37.5mg hs increase to 75mg hs in 1 week.**
Rationale: It is ineffective at this time due to the urinary frequency. The patient continues to awaken twice during the night despite the Ambien use. Adding Effexor XR at hs will address three issues. Insomnia as this drug can induce somnolence within the first two weeks of initiation of therapy and dosage changes. It may help with her c/o of "walking on fire" and will address the issue of mild depression as indicated by her GDRS score of 6 on 11-8-07.

Old Regimen	**New Regimen**	
1. Hydrocholrothiazide	Demadex	1.
2. Furosemide 20mg	----------	
3. Fosinopril 40mg	Fosinopril 40mg	2.
4. Tekturna 300mg	Tekturna 300mg	3.
5. Sotalol 80mg ½	Sotalol 80mg ½	4.
6. Digoxin 0.25mg	Diltiazem CD 60mg	5.
7. Isosorbide Mononitrate 60mg	----------	
8. Aspirin 81mg	Aspirin 81mg	6.
9. Plavix 75mg	Plavix 75mg	7.
10. Crestor 10mg	Crestor 10mg	8.
11. Zantac 150mg	Zantac 75mg daily x 30 then Every other day x 30 then stop	Wean
12. Zegerid 40mg	every other day x 1 week then stop	
13. Aricept 10mg	----------	
14. Allegra 180mg.	Zyrtec only as needed for allergies	PRN
15. Enablex 7.5mg	----------	
16. Ambien 5mg hs	Effexor XR hs	9.

Please remember it will take sometime for the medication changes to produce beneficial results. Both the titrations to decrease some medications and to add a new one will not show immediate results but over time should begin to alleviate some of the problems you are now having.

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. Once your physician makes these changes schedule a return visit with me to review your new medication orders. We will then see you for a follow-up visit in the next 30 days or so to evaluate your response to your new medication regimen.

Thank You,

Charles S. Feucht, PD, FASCP

Drug Interactions Report

Drug Interactions report for the following 17 medications:
• **Aliskiren** (Tekturna®)
• **Aspirin, ASA** (Acuprin® 81 | Ascriptin® Enteric | Aspergum® | Aspir-Low® | Aspirtab® | Aspir-trin® | Bayer® | Bayer® Childrens | Bayer® Low Strength | Bayer® Migraine Pain | Bayer® Plus | Bayer® Therapy | Bayer® Womens | Bufferin® Extra Strength | Bufferin® Tablet | Easprin® | Ecotrin® | Empirin® | Entercote® | Genacote® | Gennin® FC | Genprin® | Halfprin® | Litecoat® Aspirin | Minitabs® | Norwich® Aspirin | Ridiprin® | St. Joseph® Aspirin | St. Joseph® Aspirin Adult Chewable | St. Joseph® Aspirin Adult EC | Stanback® | Uni-Tren® | Zero Order™ Aspirin | ZORprin®)
• **Clopidogrel** (Plavix®)
• **Darifenacin** (Enablex®)
• **Digoxin** (Digitek™ | Lanoxicaps® | Lanoxin®)
• **Donepezil** (Aricept® | Aricept® ODT)
• **Fexofenadine** (Allegra®)
• **Fosinopril** (Monopril®)
• **Furosemide** (Delone™ | Furosemide | Lasix®)
• **Hydrochlorothiazide, HCTZ** (Esidrix® | Ezide™ | HCT 50™ | HydroDIURIL® | HydroKraft™ | Microzide® | Oretic® | Zide™)
• **Isosorbide Mononitrate** (Imdur® | Ismo® | Monoket®)
• **Omeprazole; Sodium Bicarbonate** (Zegerid®)
• **Ranitidine** (Wal-Zan | Zantac®)
• **Rosuvastatin** (Crestor®)
• **Sotalol** (Betapace AF™ | Betapace® | Sorine™)
• **Caffeine** (.44 Magnum™ | 357 HR Magnum® | Alert® | Alertness AL® | Awake | Cafcit® | Enerjets® | Fastlene® | Keep Alert® | Keep Going® | Lucidex™ | Molie® | NoDoz® | NoDoz® Maximum Strength | Overtime® | Revive® | Stay Awake | Stay Awake® | Ultra Pep-Back® | Valentine® | Verv® | Vivarin® | Wakespan® | Waykup®)
• **Ethanol**

include the following in the drug interactions report:
• **Caffeine • Ethanol / Alcohol • Enteral Feedings • Food • Grapefruit Juice • Tobacco**

The following drug-drug interactions are found:

- Aliskiren and Ethanol/Alcohol
- Fosinopril and Ethanol/Alcohol
- Hydrochlorothiazide, HCTZ and Ethanol/Alcohol
- Aliskiren and Hydrochlorothiazide, HCTZ
- Darifenacin and Donepezil
- Fosinopril and Hydrochlorothiazide, HCTZ
- Sotalol and Aspirin, ASA
- Fosinopril and Isosorbide Mononitrate
- Ethanol/Alcohol and Sotalol
- Hydrochlorothiazide, HCTZ and Darifenacin
- Ranitidine and Ethanol/Alcohol
- Omeprazole; Sodium Bicarbonate and Fosinopril
- Furosemide and Darifenacin
- Darifenacin and Caffeine
- Omeprazole; Sodium Bicarbonate and Aspirin, ASA
- Ethanol/Alcohol and Darifenacin

• Aspirin, ASA and **Clopidogrel**

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.

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.

• Omeprazole; Sodium Bicarbonate and **Sotalol**

Severity: High

Coadministration of antacids with sotalol reduces the Cmax and AUC of sotalol by 26% and 20%, respectively. This interaction results in a 25% reduction in the bradycardic effect of sotalol (measured at rest).[5558] Antacid administration two hours after the sotalol dose does not alter sotalol pharmacokinetics or pharmacodynamics.[5558] Patients should be instructed to avoid using antacids containing aluminum hydroxide or magnesium hydroxide within 2 hours of taking sotalol.[5558]

• Omeprazole; Sodium Bicarbonate and **Rosuvastatin**

Severity: High

Coadministration of rosuvastatin with antacids (aluminum hydroxide; magnesium hydroxide combination) has reduced rosuvastatin plasma concentrations by 54%. When the antacid is given 2 hours after rosuvastatin, no significant change in rosuvastatin plasma concentrations is observed.[4705]

• Omeprazole; Sodium Bicarbonate and **Fexofenadine**

Severity: High

Coadministration with antacids (containing aluminum or magnesium) within 15 minutes decreases the AUC and Cmax of fexofenadine by 41% and 43%, respectively.[6196] Separate administration is recommended.

• Furosemide and **Sotalol**

Severity: High

Bepridil has been associated with QT prolongation and concomitant use with sotalol should be avoided where possible. Use sotalol with considerable caution along with other calcium-channel blockers with additional AV nodal-blocking activity such as verapamil and diltiazem. Sotalol should generally be administered with caution in conjunction with calcium-channel blocks, due to possible additive effects on AV conduction or ventricular function.[5558] Additionally, concomitant use of sotalol and calcium-channel blockers or other antihypertensive agents may have additive effects on blood pressure, possibly leading to hypotension.[5558] Patients treated with catecholamine-depleting agents, such as reserpine, other rauwolfia alkaloids, or guanethidine, together with sotalol should be carefully monitored because excessive reductions in resting sympathetic tone can produce hypotension or bradycardia, precipitating a syncopal episode.[5558]

Diuretics should be used cautiously with sotalol and should be accompanied by close monitoring of electrolyte balance because hypokalemia and hypomagnesemia have been associated with an increased risk of proarrhythmia.[5558] Sotalol is contraindicated in patients with uncorrected hypokalemia (< 4 mEq/ml). No pharmacokinetic interaction has been observed between sotalol and hydrochlorothiazide.[5558]

• Aspirin, ASA and **Ethanol / Alcohol**

Severity: High

Ethanol can cause an increased risk of gastric irritation and GI mucosal bleeding when given with aspirin, as both ethanol and aspirin are mucosal irritants and aspirin decreases platelet aggregation. Patients that consume 3 or more alcoholic drinks every day should be counseled about the bleeding risks involved with chronic, heavy alcohol use while taking aspirin.[5717] Administration of aspirin should be limited or avoided altogether in patients with alcoholism or who consume ethanol regularly. Chronic alcoholism is often associated with hypoprothrombinemia, which increases the risk of aspirin-induced bleeding.

Concomitant ingestion of ethanol with NSAIDs or salicylates, especially aspirin, ASA, increases the risk of developing gastric irritation and GI mucosal bleeding.[7181] Ethanol and salicylates are mucosal irritants and NSAIDs and aspirin decrease platelet aggregation. Routine ingestion of ethanol and aspirin or NSAIDs can cause significant GI bleeding, which may or may not be overt. Even occasional concomitant use of NSAIDs or salicylates and ethanol should be avoided. Chronic alcoholism is often associated with hypoprothrombinemia and this condition increases the risk of salicylate-induced bleeding. Patients should be warned regarding for potential increased risk of GI bleeding if alcohol-containing beverages are taken concurrently with salicylates or NSAIDs.

• Digoxin and **Omeprazole; Sodium Bicarbonate**

Severity: High

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

The oral absorption of digoxin can be decreased if given concomitantly with sodium bicarbonate. On the other hand, gastric acid pump-inhibitors may increase digoxin bioavailability. The clinical significance of the interactions of digoxin with omeprazole; sodium bicarbonate are not known. Omeprazole increases the AUC of digoxin by about 10%.[6108] When rabeprazole is coadministered with digoxin, the AUC and Cmax for digoxin increases approximately 19% and 29%, respectively.[5515] Patients with digoxin serum concentrations at the upper end of the therapeutic range may need to be monitored for potential increases in serum digoxin concentrations when omeprazole; sodium bicarbonate is coadministered.

• Hydrochlorothiazide, HCTZ and **Sotalol**

Severity: High

Bepridil has been associated with QT prolongation and concomitant use with sotalol should be avoided where possible. Use sotalol with considerable caution along with other calcium-channel blockers with additional AV nodal-blocking activity such as verapamil and diltiazem. Sotalol should generally be administered with caution in conjunction with calcium-channel blocks, due to possible additive effects on AV conduction or ventricular function.[5558] Additionally, concomitant use of sotalol and calcium-channel blockers or other antihypertensive agents may have additive effects on blood pressure, possibly leading to hypotension.[5558] Patients treated with catecholamine-depleting agents, such as reserpine, other rauwolfia alkaloids, or guanethidine, together with sotalol should be carefully monitored because excessive reductions in resting sympathetic tone can produce hypotension or bradycardia, precipitating a syncopal episode.[5558]

Diuretics should be used cautiously with sotalol and should be accompanied by close monitoring of electrolyte balance because hypokalemia and hypomagnesemia have been associated with an increased risk of proarrhythmia.[5558] Sotalol is contraindicated in patients with uncorrected hypokalemia (< 4 mEq/ml). No pharmacokinetic interaction has been observed between sotalol and hydrochlorothiazide.[5558]

• Ranitidine and **Omeprazole; Sodium Bicarbonate**

Severity: High

The American College of Gastroenterology states that the effectiveness of proton pump inhibitors (PPIs) may be decreased if given with other antisecretory agents (e.g., antimuscarinics, octreotide, H_2-blockers, or misoprostol).[1569] Proton pump inhibitors (PPIs) inhibit only actively secreting H+-pumps.

• Aliskiren and **Sotalol**

Severity: Moderate

Bepridil has been associated with QT prolongation and concomitant use with sotalol should be avoided where possible. Use sotalol with considerable caution along with other calcium-channel blockers with additional AV nodal-blocking activity such as verapamil and diltiazem. Sotalol should generally be administered with caution in conjunction with calcium-channel blocks, due to possible additive effects on AV conduction or ventricular function.[5558] Additionally, concomitant use of sotalol and calcium-channel blockers or other antihypertensive agents may have additive effects on blood pressure, possibly leading to hypotension.[5558] Patients treated with catecholamine-depleting agents, such as reserpine, other rauwolfia alkaloids, or guanethidine, together with sotalol should be carefully monitored because excessive reductions in resting sympathetic tone can produce hypotension or bradycardia, precipitating a syncopal episode.[5558]

• Darifenacin and **Omeprazole; Sodium Bicarbonate**

Severity: Moderate

The American College of Gastroenterology states that the effectiveness of proton pump inhibitors (PPIs) may be decreased if given with other antisecretory agents (e.g., antimuscarinics, octreotide, H_2-blockers, or misoprostol).[1569] Proton pump inhibitors (PPIs) inhibit only actively secreting H+-pumps.

• Aspirin, ASA and **Furosemide**

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 may decrease the diuretic, natriuretic, and antihypertensive actions of diuretics, possibly through inhibition of renal prostaglandin synthesis.[6136] Patients receiving furosemide and salicylates should be monitored for changes in the effectiveness of their diuretic therapy.[5159]

• Ethanol/Alcohol and **Isosorbide Mononitrate**

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]

• Aliskiren and **Furosemide**

Severity: Moderate

Aliskiren can enhance the effects of antihypertensive agents and diuretics on blood pressure if given concomitantly.[10048] This additive effect may be desirable, but dosages must be adjusted accordingly. Patients with hyponatremia or hypovolemia may

become hypotensive and/or develop reversible renal insufficiency when given aliskiren and diuretics concomitantly. When aliskiren is administered in combination with furosemide, the AUC and Cmax of furosemide are reduced by approximately 30% and 50%, respectively; the pharmacokinetics of aliskiren are not affected.[10048] Patients should be monitored for loss of effect of furosemide when aliskiren is initiated. In addition, multiple doses of coadministered irbesartan and aliskiren reduces the Cmax of aliskiren by up to 50%.[10048] Therefore, blood pressure should be closley monitored in patients taking both of these medications. Combining aliskiren with antihypertensive agents that increase serum potassium such as angiotensin-converting enzyme inhibitors (ACE inhibitors) and angiotensin receptor antagonists (ARBs), may also increase the likelihood of inducing hyperkalemia. During clinical trials, when aliskiren was used in combination with an ACE inhibitor in patients with diabetes, the incidence of hyperkalemia was 5.5% compared to an incidence of 0.9% in patients not using a concomitant ACE inhibitor. Electrolytes should be routinely monitored in patients receiving aliskiren.[10048]

Additive hypotension is possible if furosemide used in combination with any other antihypertensive agents,[5159] including drugs such as nitroglycerin. Hyponatremia or hypovolemia predisposes patients to acute hypotensive episodes following initiation of ACE inhibitor therapy. While ACE inhibitors and loop diuretics are routinely administered together in the treatment of heart failure, if an ACE inhibitor is to be administered to a patient receiving furosemide, initial doses should be conservative.

• Digoxin and **Donepezil**

Severity: Moderate

The increase in vagal tone induced by some cholinesterase inhibitors may produce bradycardia, hypotension, or syncope.[7719] The vagotonic effect of these drugs may theoretically be increased when given with other medications known to cause bradycardia such as digoxin. These interactions are pharmacodynamic in nature rather than pharmacokinetic.

The increase in vagal tone induced by some cholinesterase inhibitors may produce bradycardia, hypotension, or syncope.[7719] The vagotonic effect of these drugs may theoretically be increased when given with other medications known to cause bradycardia such as digoxin. In vitro tests indicate that donepezil is not likely to interfere with the protein binding of digoxin. The metabolism of donepezil is not significantly affected by digoxin.[6382]

• Furosemide and **Hydrochlorothiazide, HCTZ**

Severity: Moderate

Additive hypotension is possible if furosemide used in combination with any other antihypertensive agents,[5159] including drugs such as nitroglycerin. Hyponatremia or hypovolemia predisposes patients to acute hypotensive episodes following initiation of ACE inhibitor therapy. While ACE inhibitors and loop diuretics are routinely administered together in the treatment of heart failure, if an ACE inhibitor is to be administered to a patient receiving furosemide, initial doses should be conservative.

Hydrochlorothiazide can have additive effects when administered with other antihypertensive agents or diuretics.[5917] In some patients, these effects may be desirable, but orthostatic hypotension is possible. Dosages must be adjusted accordingly. In addition, potassium-sparing diuretics (amiloride hydrochloride, spironolactone, and triamterene) can reduce the risk of developing hypokalemia because of their potassium-sparing effects; these agents have been used as therapeutic alternatives to potassium supplements.

• Digoxin and **Furosemide**

Severity: Moderate

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

Electrolyte disturbances (e.g., hypokalemia, hypomagnesemia, hypercalcemia) may occur with administration of loop diuretics, including furosemide.[5159] Hypokalemia increases the potential for proarrhythmic effects (e.g., torsade de pointes) due to arsenic trioxide, cardiac glycosides, dofetilide [4947], or levomethadyl. Potassium levels should be within the normal range prior and during administration of these agents. In the absence of electrolyte imbalances, furosemide and these agents can be used together safely.

• Furosemide and **Ethanol/Alcohol**

Severity: Moderate

Ethanol interacts with antihypertensive agents by potentiating their hypotensive effect.[5944] Ethanol, since it also possesses diuretic properties, should be taken in small quantities in patients receiving loop diuretics. The diuretic properties may be additive, leading to dehydration in some patients.

Ethanol interacts with antihypertensive agents by potentiating their hypotensive effect.[5944]

• Digoxin and **Hydrochlorothiazide, HCTZ**

Severity: Moderate

Since electrolyte disorders modify the actions of digoxin, drugs that can affect electrolyte balance potentially can affect the

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

Electrolyte disturbances (e.g., hypokalemia, hypomagnesemia, hypercalcemia) may occur with administration of thiazide diuretics,[3085] [5917] increasing the potential for proarrhythmic effects (e.g., torsade de pointes) of arsenic trioxide [4951], cardiac glycosides [4999] [5219], dofetilide [4947], or levomethadyl [4951]. Potassium levels should be within the normal range prior and during administration of these agents. In the absence of electrolyte imbalances, these agents can be used together safely. In a population pharmacokinetic analysis of plasma dofetilide concentrations, the mean dofetilide clearance of dofetilide was 16% lower in patients on thiazide diuretics.

• Darifenacin and **Digoxin**

Severity: Moderate

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

• Hydrochlorothiazide, HCTZ and **Isosorbide Mononitrate**

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]

• Digoxin and **Sotalol**

Severity: Moderate

Digoxin used concomitantly with sotalol can increase the possibility of proarrhythmia. Sotalol does not appear to interfere substantially with digoxin serum levels. Proarrhythmic events were more common in sotalol-treated patients also receiving digoxin; it is not clear whether this represents an interaction or is related to the presence of CHF, a known risk factor for proarrhythmia, in the patients receiving digoxin.[5558] Despite potential for interactions, digoxin sometimes is intentionally used in combination with sotalol. Nevertheless, these combinations should be used cautiously, and therapy dosages may need adjustment in some patients.

• Aliskiren and **Isosorbide Mononitrate**

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]

• Aliskiren and **Fosinopril**

Severity: Moderate

Aliskiren can enhance the effects of antihypertensive agents and diuretics on blood pressure if given concomitantly.[10048] This additive effect may be desirable, but dosages must be adjusted accordingly. Patients with hyponatremia or hypovolemia may become hypotensive and/or develop reversible renal insufficiency when given aliskiren and diuretics concomitantly. When aliskiren is administered in combination with furosemide, the AUC and Cmax of furosemide are reduced by approximately 30% and 50%, respectively; the pharmacokinetics of aliskiren are not affected.[10048] Patients should be monitored for loss of effect of furosemide when aliskiren is initiated. In addition, multiple doses of coadministered irbesartan and aliskiren reduces the Cmax of aliskiren by up to 50%.[10048] Therefore, blood pressure should be closley monitored in patients taking both of these medications. Combining aliskiren with antihypertensive agents that increase serum potassium such as angiotensin-converting enzyme inhibitors (ACE inhibitors) and angiotensin receptor antagonists (ARBs), may also increase the likelihood of inducing hyperkalemia. During clinical trials, when aliskiren was used in combination with an ACE inhibitor in patients with diabetes, the incidence of hyperkalemia was 5.5% compared to an incidence of 0.9% in patients not using a concomitant ACE inhibitor. Electrolytes should be routinely monitored in patients receiving aliskiren.[10048]

Fosinopril can enhance the hypotensive effects of antihypertensive agents or diuretics if given concomitantly.[5894] This additive

effect can be desirable, but dosages must be adjusted accordingly. Patients with hyponatremia or hypovolemia are more susceptible to developing reversible renal insufficiency when given fosinopril and diuretic therapy concomitantly.

• Furosemide and **Isosorbide Mononitrate**

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]

• Aspirin, ASA and **Fosinopril**

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.

Aspirin, ASA may reduce the vasodilatory efficacy of ACE inhibitors by inhibiting the synthesis of vasodilatory prostaglandins. This interaction has been documented primarily in heart failure patients. However, the established benefits of using aspirin in combination with an ACE inhibitor in patients with ischemic heart disease and left ventricular dysfunction generally outweigh this concern.[5718] [6060] Patients receiving concurrent salicylates and ACE inhibitor therapy should be monitored for antihypertensive or vasodilatory efficacy; the dose of the ACE inhibitor can be adjusted if indicated based on clinical evaluation.

• Fosinopril and **Furosemide**

Severity: Moderate

Fosinopril causes a decrease in aldosterone secretion, leading to small increases in serum potassium levels.[5894] Due to the risk of developing hyperkalemia, drugs that increase serum potassium concentration, such as potassium-sparing diuretics, potassium salts, and heparin, should be given cautiously to patients receiving fosinopril.

Additive hypotension is possible if furosemide used in combination with any other antihypertensive agents,[5159] including drugs such as nitroglycerin. Hyponatremia or hypovolemia predisposes patients to acute hypotensive episodes following initiation of ACE inhibitor therapy. While ACE inhibitors and loop diuretics are routinely administered together in the treatment of heart failure, if an ACE inhibitor is to be administered to a patient receiving furosemide, initial doses should be conservative.

• Aspirin, ASA and **Hydrochlorothiazide, HCTZ**

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.[6136] Salicylates inhibit renal prostaglandin synthesis, which can lead to fluid retention and increased peripheral vascular resistance. Salicylates may decrease the hyperuricemic effect of hydrochlorothiazide.

• Fosinopril and **Sotalol**

Severity: Moderate

Bepridil has been associated with QT prolongation and concomitant use with sotalol should be avoided where possible. Use sotalol with considerable caution along with other calcium-channel blockers with additional AV nodal-blocking activity such as verapamil and diltiazem. Sotalol should generally be administered with caution in conjunction with calcium-channel blocks, due to possible additive effects on AV conduction or ventricular function.[5558] Additionally, concomitant use of sotalol and calcium-channel blockers or other antihypertensive agents may have additive effects on blood pressure, possibly leading to hypotension.[5558] Patients treated with catecholamine-depleting agents, such as reserpine, other rauwolfia alkaloids, or guanethidine, together with sotalol should be carefully monitored because excessive reductions in resting sympathetic tone can produce hypotension or bradycardia, precipitating a syncopal episode.[5558]

• Aliskiren and **Ethanol / Alcohol**

Severity: Moderate

Ethanol interacts with antihypertensive agents by potentiating their hypotensive effect.[5944]

• Fosinopril and **Ethanol / Alcohol**

Severity: Moderate

Ethanol interacts with antihypertensive agents by potentiating their hypotensive effect.[5944]

• Hydrochlorothiazide, HCTZ and **Ethanol / Alcohol**

Severity: Moderate

Ethanol, barbiturates, or opiate agonists may potentiate orthostatic hypotension when used concurrently with hydrochlorothiazide.[5917]

Ethanol interacts with antihypertensive agents by potentiating their hypotensive effect.[5944]

• Aliskiren and **Hydrochlorothiazide, HCTZ**

Severity: Moderate

Aliskiren can enhance the effects of antihypertensive agents and diuretics on blood pressure if given concomitantly.[10048] This additive effect may be desirable, but dosages must be adjusted accordingly. Patients with hyponatremia or hypovolemia may become hypotensive and/or develop reversible renal insufficiency when given aliskiren and diuretics concomitantly. When aliskiren is administered in combination with furosemide, the AUC and Cmax of furosemide are reduced by approximately 30% and 50%, respectively; the pharmacokinetics of aliskiren are not affected.[10048] Patients should be monitored for loss of effect of furosemide when aliskiren is initiated. In addition, multiple doses of coadministered irbesartan and aliskiren reduces the Cmax of aliskiren by up to 50%.[10048] Therefore, blood pressure should be closley monitored in patients taking both of these medications. Combining aliskiren with antihypertensive agents that increase serum potassium such as angiotensin-converting enzyme inhibitors (ACE inhibitors) and angiotensin receptor antagonists (ARBs), may also increase the likelihood of inducing hyperkalemia. During clinical trials, when aliskiren was used in combination with an ACE inhibitor in patients with diabetes, the incidence of hyperkalemia was 5.5% compared to an incidence of 0.9% in patients not using a concomitant ACE inhibitor. Electrolytes should be routinely monitored in patients receiving aliskiren.[10048]

Hydrochlorothiazide can have additive effects when administered with other antihypertensive agents or diuretics.[5917] In some patients, these effects may be desirable, but orthostatic hypotension is possible. Dosages must be adjusted accordingly. In addition, potassium-sparing diuretics (amiloride hydrochloride, spironolactone, and triamterene) can reduce the risk of developing hypokalemia because of their potassium-sparing effects; these agents have been used as therapeutic alternatives to potassium supplements.

• Darifenacin and **Donepezil**

Severity: Moderate

Pharmacologically, parasympathomimetic drugs enhance muscarinic/cholinergic function. Because darifenacin is an antimuscarinic,[7474] the muscarinic actions of parasympathomimetics, including both direct cholinergic receptor agonists and cholinesterase inhibitors could be antagonized when used concomitantly with darifenacin. However, successful treatment of both dementia with donepezil 10 mg/day and urinary incontinence with tolterodine 6 mg/day has been reported.[5975] In addition, preliminary evidence indicates that chronic anticholinergic use in patients with Alzheimer's Disease may possibly have an adverse effect on cognitive function. Therefore, the effectiveness of drugs used in the treatment of Alzheimer's such as memantine, may be adversely affected by chronic antimuscarinic therapy.[5976] Furthermore, the adverse effects of antimuscarinic drugs such as dry mouth, urinary hesitancy, or blurred vision, may be enhanced with the use of memantine; dosage adjustments of darifenacin may be required when memantine is coadministered.[6137]

The therapeutic benefits of donepezil may be diminished when co-administered with the antimuscarinics [6338], the functional

antagonists of the cholinesterase inhibitors [6002]. Atropine has been used to offset bradycardia in cholinesterase inhibitor overdose. Other drugs known to exhibit anticholinergic properties that could potentially interfere with the cholinesterase inhibitor activity include: amantadine, amoxapine, clozapine, cyclobenzaprine, disopyramide, sedating H_1-blockers, maprotiline, olanzapine, orphenadrine, the antipsychotic phenothiazines, and tricyclic antidepressants. When concurrent use cannot be avoided, monitor the patient for reduced donepezil efficacy. In addition to anticholinergic effects, desipramine may potentially inhibit the metabolism of donepezil by inhibiting the hepatic CYP2D6 isoenzyme.[4718]

• Fosinopril and **Hydrochlorothiazide, HCTZ**

Severity: Moderate

Fosinopril causes a decrease in aldosterone secretion, leading to small increases in serum potassium levels.[5894] Due to the risk of developing hyperkalemia, drugs that increase serum potassium concentration, such as potassium-sparing diuretics, potassium salts, and heparin, should be given cautiously to patients receiving fosinopril.

Hydrochlorothiazide can have additive effects when administered with other antihypertensive agents or diuretics.[5917] In some patients, these effects may be desirable, but orthostatic hypotension is possible. Dosages must be adjusted accordingly. In addition, potassium-sparing diuretics (amiloride hydrochloride, spironolactone, and triamterene) can reduce the risk of developing hypokalemia because of their potassium-sparing effects; these agents have been used as therapeutic alternatives to potassium supplements.

• Sotalol and **Aspirin, ASA**

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.

• Fosinopril and **Isosorbide Mononitrate**

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]

• Ethanol/Alcohol and **Sotalol**

Severity: Moderate

Acute alcohol consumption lowers blood pressure; ethanol may interact with antihypertensive agents by potentiating their hypotensive effect.[5944]

• Hydrochlorothiazide, HCTZ and **Darifenacin**

Severity: Low

Diuretics can increase urinary frequency, which may aggravate bladder symptoms.[5985]

• Ranitidine and **Ethanol/Alcohol**

Severity: Low

Although some studies have suggested that H_2-receptor antagonists inhibit gastric alcohol dehydrogenase and thus decrease the first pass metabolism of ethanol [5305], a small study of patients receiving treatment for duodenal ulcer with either famotidine or ranitidine did not demonstrate altered ethanol pharmacokinetics.[135] A meta-analysis evaluating the effects of H_2-blockers on blood ethanol concentrations reported that only cimetidine and ranitidine, but not other H_2-blockers, caused small elevations in serum ethanol levels. However, it was reported that larger studies were less likely to show an effect and that these elevations were not likely to be clinically relevant.[5305]

The interaction between ethanol and H_2-blockers is unclear. Various studies have documented conflicting effects of H_2-blockers on ethanol pharmacokinetics. One drug interaction reference suggests that this interaction is most likely when modest amounts of ethanol are administered in the morning to non-fasting male subjects. A meta-analysis evaluating the effects of H_2-blockers on blood ethanol concentrations reported that only cimetidine and ranitidine, but not other H_2-blockers, caused small elevations in serum ethanol levels. However, it was reported that larger studies were less likely to show an effect and that these elevations were not likely to be clinically relevant.[5305]

• Omeprazole; Sodium Bicarbonate and **Fosinopril**

Severity: Low

Coadministration of an antacid (aluminum hydroxide, magnesium hydroxide, and simethicone) with fosinopril reduced serum levels and urinary excretion of fosinoprilat, suggesting that antacids may impair absorption of fosinopril.[5894] Therefore, if concomitant administration of these agents is indicated, dosing should be separated by 2 hours.

• Furosemide and **Darifenacin**

Severity: Low

Diuretics can increase urinary frequency, which may aggravate bladder symptoms.[5985]

• Darifenacin and **Caffeine**

Severity: Low

Consuming > 400 mg/day caffeine has been associated with the development of urinary incontinence. Although conflicting data exists, daily consumption of alcohol may also be a risk factor for incontinence. Both caffeine and ethanol may aggravate bladder symptoms and counteract the effectiveness of darifenacin to some degree. Patients may wish to limit their intake of caffeinated drugs, dietary supplements (e.g., guarana), or beverages (e.g., green tea, other teas, coffee, colas) and alcoholic beverages.[5985]

Consuming > 400 mg/day caffeine has been associated with the development of urinary incontinence. Caffeine may aggravate bladder symptoms and counteract the effectiveness of drugs used to treat overactive bladder (i.e., darifenacin, oxybutynin, trospium, or tolterodine) to some degree. Patients with overactive bladder may wish to limit their intake of caffeine including caffeine from drugs, dietary supplements (i.e., guarana), beverages (i.e., teas, coffee, colas), or foods (i.e., chocolate).[5985]

• Omeprazole; Sodium Bicarbonate and **Aspirin, ASA**

Severity: Low

Concurrent administration of high doses of antacids (e.g., sodium bicarbonate 4 g or aluminum and magnesium hydroxide 60-120 ml) or other urinary alkalinizing agents [7648] (e.g., sodium bicarbonate) may increase urine pH and decrease serum salicylate levels by decreasing renal tubular reabsorption of salicylic acid. Antacids do not appear to affect the bioavailability of aspirin, but may cause earlier release of aspirin from enteric-coated products.

• Ethanol/Alcohol and **Darifenacin**

Severity: Low

Consuming > 400 mg/day caffeine has been associated with the development of urinary incontinence. Although conflicting data exists, daily consumption of alcohol may also be a risk factor for incontinence. Both caffeine and ethanol may aggravate bladder symptoms and counteract the effectiveness of darifenacin to some degree. Patients may wish to limit their intake of caffeinated drugs, dietary supplements (e.g., guarana), or beverages (e.g., green tea, other teas, coffee, colas) and alcoholic beverages.[5985]

The following drug-food interactions are found:

• Fexofenadine (Allegra®) and food interactions
• Omeprazole; Sodium Bicarbonate (Zegerid®) and food interactions
• Caffeine (.44 Magnum™ | 357 HR Magnum® | Alert® | Alertness AL® | Awake | Cafcit® | Enerjets® | Fastlene® | Keep Alert® | Keep Going® | Lucidex™ | Molie® | NoDoz® | NoDoz® Maximum Strength | Overtime® | Revive® | Stay Awake | Stay Awake® | Ultra Pep-Back® | Valentine® | Verv® | Vivarin® | Wakespan® | Waykup®) and food interactions

• Fexofenadine (Allegra®) and **food** interactions

Severity: Moderate

Most food does not interact significantly with fexofenadine; the drug may be administered with or without food.[6196] However, some fruit juices appear to impair the absorption of fexofenadine. Apple juice, orange juice, and grapefruit juice have been reported to decrease the AUC and Cmax of fexofenadine by roughly 60-70%, but individual variability in the changes have been noted in various studies.[6328] According to the manufacturer, the bioavailability of fexofenadine is estimated to be reduced by 36% during coadministration with grapefruit or orange juice.[6196] The mechanism of the interaction is proposed to be an inhibition of intestinal P-glycoprotein transport systems by the juices, resulting in decreased systemic drug absorption. Histamine-induced skin evaluations indicate that the size of wheal and flare reactions are significantly greater when fexofenadine is coadministered with either grapefruit or orange juice compared to water.[6196] The clinical significance of these observations is unknown. To maximize

the effects of fexofenadine, the manufacturer recommends that fexofenadine be taken with water (see Dosage).[6196] Since fexofenadine effectiveness may be reduced, it is prudent for patients to avoid coadministration with grapefruit, orange, or apple juices.

• Omeprazole; Sodium Bicarbonate (Zegerid®) and **food** interactions

Severity: Moderate

Food or drugs with a high sodium content (e.g., tomato juice) could increase the risk of complications of sodium excess when given with omeprazole; sodium bicarbonate. The Zegerid® brand of omeprazole; sodium bicarbonate contains 460 mg sodium in each packet of powder for oral suspension and 300 mg sodium in each capsule. This should be taken into consideration for patients on a sodium-restricted diet.[8851]

• Caffeine (.44 Magnum™ | 357 HR Magnum® | Alert® | Alertness AL® | Awake | Cafcit® | Enerjets® | Fastlene® | Keep Alert® | Keep Going® | Lucidex™ | Molie® | NoDoz® | NoDoz® Maximum Strength | Overtime® | Revive® | Stay Awake | Stay Awake® | Ultra Pep-Back® | Valentine® | Verv® | Vivarin® | Wakespan® | Waykup®) and **food** interactions

Severity: Moderate

Clinicians should be aware that grapefruit juice contains a compound that can inhibit cytochrome P-450 isozymes in the gut wall. Data are limited, and conflicting, as to whether grapefruit juice alters the serum concentrations and/or AUC of caffeine.[4676] [4677] This interaction might potentiate the clinical effects and duration of action of caffeine. Other food-drug interactions involve foods that contain high amounts of caffeine or theobromine (a related methylxanthine). To avoid additive methylxanthine effects, like nausea or tremors, limit coffee, teas (including caffeinated green tea [6531]), caffeinated colas, and chocolate. Charbroiled foods induce the hepatic CYP1A2 isoenzyme and thus increase the metabolism of caffeine and other methylxanthines.

The following drug-grapefruit juice interactions are found:

• Fexofenadine (Zegerid®) and grapefruit juice interactions
• Caffeine (.44 Magnum™ | 357 HR Magnum® | Alert® | Alertness AL® | Awake | Cafcit® | Enerjets® | Fastlene® | Keep Alert® | Keep Going® | Lucidex™ | Molie® | NoDoz® | NoDoz® Maximum Strength | Overtime® | Revive® | Stay Awake | Stay Awake® | Ultra Pep-Back® | Valentine® | Verv® | Vivarin® | Wakespan® | Waykup®) and grapefruit juice interactions
• Darifenacin (Allegra®) and grapefruit juice interactions

• Fexofenadine (Zegerid®) and **grapefruit juice** interactions

Severity: Moderate

Most food does not interact significantly with fexofenadine; the drug may be administered with or without food.[6196] However, some fruit juices appear to impair the absorption of fexofenadine. Apple juice, orange juice, and grapefruit juice have been reported to decrease the AUC and Cmax of fexofenadine by roughly 60-70%, but individual variability in the changes have been noted in various studies.[6328] According to the manufacturer, the bioavailability of fexofenadine is estimated to be reduced by 36% during coadministration with grapefruit or orange juice.[6196] The mechanism of the interaction is proposed to be an inhibition of intestinal P-glycoprotein transport systems by the juices, resulting in decreased systemic drug absorption. Histamine-induced skin evaluations indicate that the size of wheal and flare reactions are significantly greater when fexofenadine is coadministered with either grapefruit or orange juice compared to water.[6196] The clinical significance of these observations is unknown. To maximize the effects of fexofenadine, the manufacturer recommends that fexofenadine be taken with water (see Dosage).[6196] Since fexofenadine effectiveness may be reduced, it is prudent for patients to avoid coadministration with grapefruit, orange, or apple juices.

• Caffeine (.44 Magnum™ | 357 HR Magnum® | Alert® | Alertness AL® | Awake | Cafcit® | Enerjets® | Fastlene® | Keep Alert® | Keep Going® | Lucidex™ | Molie® | NoDoz® | NoDoz® Maximum Strength | Overtime® | Revive® | Stay Awake | Stay Awake® | Ultra Pep-Back® | Valentine® | Verv® | Vivarin® | Wakespan® | Waykup®) and **grapefruit juice** interactions

Severity: Moderate

Clinicians should be aware that grapefruit juice contains a compound that can inhibit cytochrome P-450 isozymes in the gut wall. Data are limited, and conflicting, as to whether grapefruit juice alters the serum concentrations and/or AUC of caffeine.[4676] [4677] This interaction might potentiate the clinical effects and duration of action of caffeine. Other food-drug interactions involve foods that contain high amounts of caffeine or theobromine (a related methylxanthine). To avoid additive methylxanthine effects, like nausea or tremors, limit coffee, teas (including caffeinated green tea [6531]), caffeinated colas, and chocolate. Charbroiled foods induce the hepatic CYP1A2 isoenzyme and thus increase the metabolism of caffeine and other methylxanthines.

• Darifenacin (Allegra®) and **grapefruit juice** interactions

Severity: Low

Per the manufacturer of darifenacin, the daily dose of darifenacin should not exceed 7.5 mg when coadministered with the following potent CYP3A4 inhibitors: clarithromycin, erythromycin, itraconazole, ketoconazole, lopinavir; ritonavir, nefazodone, nelfinavir, and ritonavir.[7474] The manufacturer does not necessitate a dosage adjustment when darifenacin is coadministered with less potent CYP3A4 inhibitors including erythromycin, fluconazole, diltiazem, and verapamil.[7474] Other examples of CYP3A4 inhibitors include amiodarone [5629], other antiretroviral protease inhibitors[4718] [5747], aprepitant [7438], conivaptan [8569], dalfopristin; quinupristin [5221], delavirdine [4718], efavirenz (inducer or inhibitor) [5172], fluoxetine [4718], fluvoxamine [4718], grapefruit juice [5822], mifepristone, RU-486 [4718], norfloxacin [6789], other systemic azole antifungals (miconazole, and voriconazole) [4718], troleandomycin [4718], zafirlukast [4948], and zileuton [5415]. This list is not inclusive of all CYP3A4 inhibitors. Patients should be monitored for increased adverse anticholinergic effects of darifenacin when drugs that inhibit CYP3A4 are coadministered; the dosage of darifenacin should be adjusted if warranted.

No clinically significant interactions are expected between these drugs and enteral feedings._____
_____

The following drug-tobacco interactions are found:
• Caffeine (Allegra®) and tobacco interactions

• Caffeine (Allegra®) and **tobacco** interactions

Severity: Moderate
Inducers of the hepatic CYP450 isoenzyme CYP1A2 may induce the hepatic oxidative metabolism of caffeine.[4666] Tobacco smoke contains hydrocarbons that induce hepatic CYP450 microsomal enzymes (e.g., CYP1A1, CYP1A2, CYP2E1).[5056] The increased clearance of caffeine by smokers may contribute to the higher consumption of caffeinated beverages reported to occur in this group. Because the effect on hepatic microsomal enzymes is not related to the nicotine component of tobacco, the sudden cessation of tobacco smoking may result in a reduced clearance of caffeine, despite the initiation of a nicotine replacement product. Following several days of abstinence from chronic tobacco smoking, caffeine clearance may decrease by roughly 40%, leading to the possible occurrence of caffeine-related side effects like nausea, nervousness, irritability, tremors, or insomnia, if caffeine use remains the same.

Therapeutic duplication found.
• Digoxin, Sotalol are Antiarrhythmics.• Fosinopril, Furosemide, Hydrochlorothiazide, HCTZ, Aliskiren are Antihypertensive Agents.• Ranitidine, Omeprazole; Sodium Bicarbonate are Antiulcer Agents.• Furosemide, Hydrochlorothiazide, HCTZ are Diuretics.• Aspirin, ASA, Clopidogrel are Platelet Inhibitors.

Specific Drug Information:

Hydrochlorothiazide, HCTZ
Esidrix® | Ezide™ | HCT 50™ | HydroDIURIL® | HydroKraft™ | Microzide® | Oretic®
Classification:
- Cardiovascular Agents
  - Antihypertensive Agents
    - Diuretics
- Electrolytic and Renal Agents
  - Diuretics
    - Thiazide diuretics

Description, Mechanism of Action, Pharmacokinetics

Description: Hydrochlorothiazide (HCTZ) is a thiazide diuretic used in the management of edema and hypertension. In hypertension, thiazide diuretics are often used as initial therapy, either alone or in combination with other agents. Unlike the loop diuretics, their efficacy is diminished in patients with renal insufficiency. Hydrochlorothiazide also has been used to treat diabetes insipidus and hypercalciuria, although these are not FDA-approved indications. Hydrochlorothiazide was approved by the FDA in 1959.

Mechanism of Action: Thiazide diuretics increase the excretion of sodium, chloride, and water by inhibiting sodium ion transport across the renal tubular epithelium. Although thiazides may have more than one action, the major mechanism responsible for diuresis is to inhibit active chloride reabsorption at the distal portion of the ascending limb or, more likely, the early part of the distal tubule (i.e., the cortical diluting segment). Exactly how chloride transport is impaired is unknown. Thiazides also increase the excretion of potassium and bicarbonate, and they decrease the urinary excretion of calcium and uric acid. Hydrochlorothiazide may be used to reduce hypercalciuria and prevent the recurrence of calcium-containing renal calculi. By increasing the sodium load at the distal renal tubule, hydrochlorothiazide indirectly increases potassium excretion via the sodium-potassium exchange mechanism. Hypochloremia and hypokalemia can cause mild metabolic alkalosis. The diuretic efficacy of hydrochlorothiazide is not affected by the acid-base balance of the patient. Hydrochlorothiazide is not an aldosterone antagonist, and its main action is independent of carbonic anhydrase inhibition.
The antihypertensive mechanism of hydrochlorothiazide is unknown. It usually does not affect normal blood pressure. Initially, diuretics lower blood pressure by decreasing cardiac output and reducing plasma and extracellular fluid volume. Cardiac output eventually returns to normal, plasma and extracellular fluid values return to slightly less than normal, but peripheral vascular resistance is reduced, resulting in lower blood pressure. These diuretics also decrease the glomerular filtration rate, which contributes to the drug's lower efficacy in patients with renal impairment. The changes in plasma volume induce an elevation in plasma renin activity, and aldosterone secretion is increased, contributing to the potassium loss associated with thiazide diuretic therapy. In general, diuretics worsen LVH and glucose tolerance, and exert detrimental effects on the lipid profile.
Pharmacokinetics: Hydrochlorothiazide is administered orally. The onset of action of the drug is 2 hours following oral administration, with peak effects occurring at 4 hours. The duration of action ranges from 6—12 hours. Hydrochlorothiazide absorption from the GI tract varies depending on the formulation and dose. Bioavailability is approximately 50—60%. The drug crosses the placenta but not the blood-brain barrier and is distributed in breast milk. Hydrochlorothiazide is not significantly metabolized and is excreted unchanged in the urine. The elimination half-life of hydrochlorothiazide was originally reported to range from 5.6—14.8 hours when plasma levels were followed for at least 24 hours. A more recent study reports a mean elimination half-life of 2.5 hours in patients with normal renal function. The elimination half-life is estimated to increase to 12—20 hours in patients with severe renal disease (e.g. CrCl < 10 ml/min).

Description, Mechanism of Action, Pharmacokinetics last revised 12/29/2002 10:14:00 AM

Indications

- ascites
- diabetes insipidus†
- edema
- heart failure
- hypercalciuria†
- hypertension
- nephrolithiasis†
- nephrotic syndrome
- premenstrual syndrome (PMS)†
- renal calculus†

† non-FDA-approved indication

Dosage
For the treatment of hypertension:
Oral dosage:
Adults and Adolescents: Initially, 12.5—25 mg PO once daily. Dosage may be increased, if necessary, up to 50 mg/day PO given in 1—2 divided doses. Although the manufacturer's recommended maintenance dosage is 25—100 mg PO per day, expert panels on the treatment of hypertension recommend the addition of another antihypertensive agent if blood pressure is not controlled with 25—50 mg/day of hydrochlorothiazide.[805] In a double-blind randomized study, the effects of 25 mg/day vs. 50 mg/day of hydrochlorothiazide were evaluated in elderly patients (n=51) with isolated systolic hypertension. Both dosages were associated with similar reductions in blood pressure; however, the higher dose (50 mg/day) caused a greater decline in serum potassium concentration.[1656]
Elderly: See adult dosage. Elderly patients may be more sensitive to the effects of the usual adult dosage.

Children and infants > 6 months: 2 mg/kg/day PO, given in 2 divided doses is the usual dosage recommended by one pediatric dosage source; however, 3 mg/kg/day PO is the highest dosage recommended by the manufacturer.
Infants < 6 months and neonates: 2—4 mg/kg/day PO, given in 2 divided doses is the usual dosage recommended by one pediatric dosage source; however, 3 mg/kg/day PO is the highest dosage recommended by the manufacturer.
For use as an adjunctive agent to treat peripheral edema associated with congestive heart failure, hepatic cirrhosis (ascites), corticosteroid therapy, or estrogen therapy; or to treat edema associated with renal dysfunction† including nephrotic syndrome, acute glomerulonephritis†, and chronic renal failure†:
Oral dosage:
Adults and Adolescents: 25—100 mg/day PO, given in single or divided doses. Many patients with edema respond to intermittent therapy (e.g., every other day or 3—5 days each week).
Elderly: See adult dosage. Elderly patients may be more sensitive to the effects of the usual adult dosage.
Children and infants > 6 months: 2 mg/kg/day PO, given in 2 divided doses is the usual dosage recommended by one pediatric dosage source; however, 3 mg/kg/day PO is the highest dosage recommended by the manufacturer.
Infants < 6 months and neonates: 2—4 mg/kg/day PO, given in 2 divided doses is the usual dosage recommended by one pediatric dosage source; however, 3 mg/kg/day PO is the highest dosage recommended by the manufacturer.
For the treatment of nephrogenic or central diabetes insipidus†:
Oral dosage:
Adults: 50—100 mg/day PO has been used.
Elderly: See adult dosage. Elderly patients may be more sensitive to the effects of the usual adult dosage.
For the prevention of nephrolithiasis† (calcium-containing renal calculus†) due to hypercalciuria†:
Oral dosage:
Adults: 50 mg PO, given 1—2 times per day, has been used.
Elderly: See adult dosage. Elderly patients may be more sensitive to the effects of the usual adult dosage.
For the treatment of symptoms of bloating and weight gain associated with premenstrual syndrome (PMS)†:
Oral dosage:
Adults: 25—50 mg PO, given once daily or twice daily. Diuretic use should be limited to patients who demonstrate a premenstrual weight gain of > 1.4 kg. Dosages should be individually titrated to achieve desired diuresis and decreased weight gain.[734]
Maximum Dosage Limits:
•*Adults and Adolescents:* 50 mg/day PO for hypertension; 200 mg/day PO for edema.
•*Elderly:* 50 mg/day PO for hypertension; 200 mg/day PO for edema.
•*Children 2—12 years:* 2 mg/kg/day PO or 100 mg/day PO.
•*Infants > 6 months—2 years:* 2 mg/kg/day PO or 37.5 mg/day PO.
•*Infants < 6 months and Neonates:* up to 4 mg/kg/day PO is recommended by one pediatric dosage source; 3 mg/kg/day PO is the highest dosage recommended by the manufacturer.
Patients with hepatic impairment:
No specific dosage adjustment is needed; see dosage for the treatment of ascites. In general, diuretics should be used with caution in patients with hepatic disease since minor alterations of fluid and electrolyte balance may precipitate hepatic coma.
Patients with renal impairment:
CrCl >= 30 ml/min: no dosage adjustment needed.
CrCl < 30 ml/min: do not use, generally not effective.
†non-FDA-approved indication

Indications...Dosage last revised 7/30/2004 11:29:00 AM

Administration Guidelines

Oral Administration
•Administer in the morning to prevent disruption of sleep cycle.
•To minimize GI irritation, administer with food or milk.
•For patients with difficulty swallowing, the tablets may be crushed and mixed with fluid.

Administration last revised 8/1/2006 3:38:00 PM

Contraindications/Precautions

- *anuria*
- *sulfonamide hypersensitivity*
- *thiazide diuretic hypersensitivity*
- acid/base imbalance
- breast-feeding
- diabetes mellitus
- elderly
- electrolyte imbalance
- gout
- hepatic disease
- hypercalcemia
- hyperglycemia
- hyperuricemia
- hypotension
- hypovolemia
- jaundice
- metabolic alkalosis
- neonates
- orthostatic hypotension
- pancreatitis
- preeclampsia
- pregnancy
- renal disease
- renal failure
- renal impairment
- sunlight (UV) exposure

- hypochloremia
- hypokalemia
- hypomagnesemia
- hyponatremia
- sympathectomy
- syncope
- systemic lupus erythematosus (SLE)

• *Absolute contraindications are in italics.*

Thiazide diuretics are contraindicated in patients with known *thiazide diuretic hypersensitivity*. According to the manufacturer, hydrochlorothiazide is specifically contraindicated in patients with *sulfonamide hypersensitivity*. Although thiazide diuretics are sulfonamide derivatives, sulfonamide cross-sensitivity has been rarely documented.[53] [3600] [9205] Until further data are available, thiazide diuretics should be used with caution in patients with sulfonamide hypersensitivity. Thiazide diuretics do not contain the N4-aromatic amine or the N1-substituent which are present in sulfonamide antibiotics.[9204] Non-arylamine sulfonamide derivatives, such as thiazide diuretics, have been proposed to have a lower risk of allergic reactions in patients with sulfonamide allergy, presumably due to lack of an arylamine group at the N4 position (a proposed structural site of action for sulfonamide allergy).[9204] [9205] One large retrospective cohort study has reported that in patients with the presence of an allergic reaction after exposure to a sulfonamide antibiotic, 9.9% had an allergic reaction after receiving a non-antibiotic sulfonamide derivative, while in patients who lacked an allergic reaction after sulfonamide antibiotic exposure, 1.6% had an allergic reaction after administration of a non-antibiotic sulfonamide derivative (adjusted odds ratio 2.8; 95% CI, 2.1—3.7).[9206] A causal relationship between sulfonamide hypersensitivity and allergic reactions with non-arylamine sulfonamide derivatives has not been definitively established and remains controversial.[53] [3600] [9204] [9205] In general, patients with a documented sulfonamide allergy are considered to be predisposed for development of allergic drug reactions.[9204] [9206]

Hydrochlorothiazide-induced fluctuations in serum electrolyte concentration can occur rapidly and precipitate hepatic coma in susceptible patients. Therefore, the drug should be used with caution in patients with hepatic disease.

Hyperglycemia, impaired glucose tolerance, and glycosuria can occur during hydrochlorothiazide therapy, and blood and/or urine glucose levels should be assessed more carefully in patients with diabetes mellitus who are receiving hydrochlorothiazide. Although hyperglycemia did occur, chlorthalidone, a related thiazide diuretic, has been shown to reduce cardiovascular disease events in elderly diabetic patients with isolated systolic hypertension.[1353] Greater sensitivity to the hypotensive and diuretic effects of hydrochlorothiazide is possible in elderly patients.

Hydrochlorothiazide should be used cautiously in patients with renal disease such as severe renal impairment or renal failure. Drug-induced hypovolemia can precipitate azotemia in these patients. Therapy should be interrupted or discontinued if renal impairment worsens, as evidenced by an increase in concentrations of BUN or serum creatinine. With the exception of metolazone, thiazide diuretics are considered ineffective when the creatinine clearance is less than 30 ml/minute. Hydrochlorothiazide is contraindicated in patients with *anuria*.

Patients with pre-existing hypovolemia or hypotension should have their condition corrected before diuretics are initiated. Orthostatic hypotension may occur during treatment with thiazide diuretics.[9371] Orthostatic hypotension can be exacerbated by concurrent use of alcohol, narcotics, or antihypertensive drugs (see Drug Interactions). Excessive hypotension during thiazide diuretic therapy can result in syncope. An increased risk of falls has been reported for elderly patients receiving thiazide diuretics.[9369] [9370] In addition, the antihypertensive effects of thiazides may be enhanced in other patients predisposed for orthostatic hypotension, including the post-sympathectomy patient.

Thiazide diuretics have been reported to cause pancreatitis. They should be used with caution in patients with a history of pancreatitis.

Caution should be used when hydrochlorothiazide is administered to patients with gout or hyperuricemia since thiazide diuretics have been reported to reduce the clearance of uric acid.

Hydrochlorothiazide has been reported to activate or exacerbate systemic lupus erythematosus (SLE).

Patients with pre-existing significant hyponatremia, hypokalemia, hypomagnesemia, and/or hypercalcemia should have their electrolyte imbalances corrected before hydrochlorothiazide is initiated. Initiation of thiazide diuretics in patients with electrolyte imbalances such as hypokalemia or hyponatremia can produce life-threatening situations such as cardiac arrhythmias, hypotension, and seizures. Elderly patients are more susceptible to dilutional hyponatremia induced by thiazide diuretics. Hydrochlorothiazide has been shown to increase the urinary excretion of magnesium and potassium. Thiazide diuretics may induce metabolic alkalosis associated with hypokalemia and hypochloremia; this acid/base imbalance is effectively treated with potassium chloride replacement.[9372] [9373] Hydrochlorothiazide can also increase serum calcium concentrations by decreasing excretion of urinary calcium. Patients receiving diuretics should be monitored closely for clinical signs of fluid or electrolyte imbalance.

Thiazide diuretics have been associated with a slight increase in serum cholesterol and triglyceride concentrations. Data from long-term studies, however, suggest diuretic-induced cholesterol changes are not clinically significant and do not contribute to coronary heart disease risk.[658]

Photosensitivity has been reported with thiazide diuretics.[7476] Patients should avoid excessive sunlight (UV) exposure and therapy should be discontinued if phototoxicity occurs.

Thiazides should be avoided in neonates with jaundice. Thiazide-induced hyperbilirubinemia is greater in this patient population.

Hydrochlorothiazide products are classified in FDA pregnancy risk category B. Many experts reserve the use of diuretics for pregnant patients with cardiac disease or essential hypertension, due to the fact that diuretic use may decrease placental perfusion and the data do not indicate a positive benefit of diuretic use on the outcome of preeclampsia during pregnancy.[7499] The pregnancy risk factor for thiazide diuretics increases to category D for those pregnant patients with *reduced uteroplacental perfusion* (e.g., preeclampsia or intrauterine growth retardation (IUGR).[7498] [7499] In general, the bulk of the evidence does not indicate that thiazide diuretics are teratogenic in the 1st trimester, although, many experts limit their use to the 2nd and 3rd trimesters.[7499] Neonatal thrombocytopenia has been reported following maternal use of thiazide diuretics near term; at term, thiazide diuretics have been reported to cross the placenta. Potential risks from thiazide use include electrolyte imbalances in the newborn, pancreatitis, jaundice, or neonatal complications resulting from such maternal complications such as hyperglycemia, electrolyte imbalance, or hypotension.

Thiazide diuretics distribute into breast milk, and it has been recommended by some manufacturers that women not nurse while receiving selected thiazide diuretics. Some thiazide diuretics have been used off-label to suppress lactation, and thus should be used with caution during the establishment of breast-feeding. In general, the use of bendroflumethiazide, chlorthalidone, chlorothiazide, and hydrochlorothiazide is considered compatible with breast-feeding by the American Academy of Pediatrics, due to lack of noted

adverse effects on the nursing infant.[4201]

Contraindications last revised 8/10/2006 9:16:00 PM

Drug Interactions

- Allopurinol
- Amantadine
- Amiodarone
- Amphotericin B
  Antidiabetic Agents
  Antihypertensive Agents
- Arsenic Trioxide
  Barbiturates
  Beta-agonists
- Calcium Carbonate
  Cardiac glycosides
- Cholestyramine
- Cisplatin
- Colestipol
  Corticosteroids
- Diazoxide
- Dofetilide
- Ephedra, Ma Huang
- Ethanol
- Fluconazole
- Griseofulvin
- Hawthorn, Crataegus laevigata
- Horse Chestnut, Aesculus hippocastanum
- Levomethadyl
- Lithium
- Memantine
- Methazolamide
  Monoamine oxidase inhibitors (MAOIs)
  Neuromuscular blockers
  Nonsteroidal antiinflammatory drugs (NSAIDs)
- Norepinephrine
  Opiate agonists
- Palonosetron
  Phenothiazines
  Photosensitizing Agents
  Potassium-sparing diuretics
  Retinoids
  Salicylates
- Sodium Phosphate Monobasic Monohydrate; Sodium Phosphate Dibasic Anhydrous
  Sulfonamides
  Tetracyclines

Hydrochlorothiazide can have additive effects when administered with other antihypertensive agents or diuretics.[5917] In some patients, these effects may be desirable, but orthostatic hypotension is possible. Dosages must be adjusted accordingly. In addition, potassium-sparing diuretics (amiloride hydrochloride, spironolactone, and triamterene) can reduce the risk of developing hypokalemia because of their potassium-sparing effects; these agents have been used as therapeutic alternatives to potassium supplements.
Electrolyte disturbances (e.g., hypokalemia, hypomagnesemia, hypercalcemia) may occur with administration of thiazide diuretics,[3085] [5917] increasing the potential for proarrhythmic effects (e.g., torsade de pointes) of arsenic trioxide [4951], cardiac glycosides [4999] [5219], dofetilide [4947], or levomethadyl [4951]. Potassium levels should be within the normal range prior and during administration of these agents. In the absence of electrolyte imbalances, these agents can be used together safely. In a population pharmacokinetic analysis of plasma dofetilide concentrations, the mean dofetilide clearance of dofetilide was 16% lower in patients on thiazide diuretics.
The risk of developing severe hypokalemia [5917] can be increased when other hypokalemia-causing agents (e.g., cisplatin, corticosteroids, corticotropin, ACTH, amphotericin B) [3085] are coadministered with hydrochlorothiazide. Monitoring serum potassium levels and cardiac function is advised, and potassium supplementation may be required.
Hypokalemia and/or ECG changes associated with loop diuretics or thiazide diuretics can be acutely worsened by beta-agonists, especially when the recommended dose of the beta-agonist is exceeded.[5262] Although the clinical significance of these effects is unknown, use caution when coadministering beta-agonists with non-potassium sparing diuretics.
Concomitant administration of hydrochlorothiazide to patients receiving nondepolarizing neuromuscular blockers (e.g., tubocurarine) can cause prolonged neuromuscular blockade due to hydrochlorothiazide-induced hypokalemia.[5917] Serum potassium concentrations should be determined and corrected (if necessary) prior to initiation of neuromuscular blockade therapy.
Thiazide diuretics reduce lithium renal clearance and can increase lithium serum concentrations.[5385] [5917] In some cases, thiazide diuretics can be used to counteract lithium-induced polyuria. Lithium dosage should be reevaluated and serum lithium concentrations monitored when a thiazide is added.
Thiazide diuretics can decrease insulin sensitivity thereby leading to glucose intolerance and hyperglycemia. Diuretic-induced hypokalemia may also lead to hyperglycemia. Because of this, a potential pharmacodynamic interaction exists between thiazide diuretics and antidiabetic agents.[5917] It appears that the effects of thiazide diuretics on glycemic control are dose-related and low doses can be instituted without deleterious effects on glycemic control.[6141] In addition, diuretics reduce the risk of stroke and cardiovascular disease in patients with diabetes.[7247] However, patients taking antidiabetic agents should be monitored for changes in blood glucose control if such diuretics are added or deleted. Dosage adjustments may be necessary. Finally, both thiazides and sulfonylureas have been reported to cause photosensitivity reactions; concomitant use may increase the risk of photosensitivity.
Enhanced hyperglycemia is possible during concurrent use of diazoxide and thiazide diuretics.[6278]
Hydrochlorothiazide can reduce the renal clearance of amantadine, with subsequent increased serum concentrations and possible toxicity. This interaction has been reported with a combination product of hydrochlorothiazide and triamterene.[4773] Since it is unclear which component was responsible for the interaction, caution should be exercised when administering either drug concurrently with amantadine.
NSAIDs can cause sodium and fluid retention as well as increase peripheral vascular resistance. NSAIDs can decrease the diuretic, natriuretic, and antihypertensive actions of diuretics,[5917] possibly through inhibition of renal prostaglandin synthesis. Concomitant administration of NSAIDs with diuretics can also increase the risk for renal insufficiency secondary to decreased renal blood flow.

Patients should be monitored for changes in the effectiveness of their diuretic therapy and for signs and symptoms of renal impairment. Among NSAIDs, indomethacin, naproxen, and piroxicam may have the greatest pressor effect, while the effects of sulindac and nabumetone may be significantly less.
Concomitant use of medicines with potential to alter renal perfusion or function such as hydrochlorothiazide may increase the risk of acute phosphate nephropathy in patients receiving sodium phosphate monobasic monohydrate; sodium phosphate dibasic anhydrous.[8973] [8974]
Cholestyramine (Questran®), an ion exchange resin, binds hydrochlorothiazide and reduces its absorption from the gastrointestinal tract by up to 85% when co-administered as single doses.[5917] [6153] [6155] Although the manufacturer for Questran® recommends that other medicines be taken at least 1 hour before or 4—6 hours after cholestyramine [4793], it has been recommended that thiazides be administered at least 4 hours before or after cholestyramine to minimize the reduction in absorption.[6155] By administering hydrochlorothiazide at least 4 hours before cholestyramine, the decrease in absorption of hydrochlorothiazide is approximately 30—35%. Although to a lesser extent than cholestyramine, colestipol also has been shown to inhibit the GI absorption and therapeutic response of thiazide diuretics. Single doses of colestipol resins reduce the absorption of HCTZ by up to 43%.[5917] [6153] Administering thiazide diuretics at least 2 hours before colestipol has been suggested to minimize the interaction.
Thiazide diuretics may cause photosensitivity [5917] [7476] and may increase the photosensitization effects of drugs like phenothiazines. Prevention of photosensitivity includes adequate protection from sources of UV radiation (e.g., avoiding sun exposure and tanning booths) and the use of protective clothing and sunscreens on exposed skin.[7476] Electrolyte disturbances (e.g., hypokalemia, hypomagnesemia, hypercalcemia) may occur with administration of thiazide diuretics,[3085] electrolyte disturbances may increase the potential for proarrhythmic effects (e.g., QT prolongation, torsade de pointes) of selected phenothiazines (e.g., mesoridazine, thioridazine). In the absence of electrolyte imbalances, these agents can be used together safely with appropriate monitoring; clinicians should monitor for evidence of electrolyte disturbances or cardiac-related patient complaints. Thiazide diuretics may potentiate the orthostatic hypotension that can be seen with the use of the phenothiazine antipsychotics.[5732]
Thiazide diuretics may cause photosensitivity [5917] [7476] and may increase the photosensitization effects of drugs like griseofulvin, phenothiazines, retinoids [5254], sulfonamides, sulfonylureas, tetracyclines, or photosensitizing agents used in photodynamic therapy. Prevention of photosensitivity includes adequate protection from sources of UV radiation (e.g., avoiding sun exposure and tanning booths) and the use of protective clothing and sunscreens on exposed skin.[7476]
The occurrence of hypersensitivity reactions may be increased in patients with renal impairment who receive allopurinol and thiazide diuretics in combination.[4770]
Hawthorn, Crataegus laevigata may lower peripheral vascular resistance.[4713] Hawthorn use in combination with antihypertensive agents may lead to additional reductions in blood pressure in some individuals. Patients receiving hawthorn concurrently with antihypertensive medications should receive periodic blood pressure monitoring.
Drug interactions with Horse chestnut, Aesculus hippocastanum are not well documented. Escin, an active saponin in the horse chestnut seed, appears to have weak diuretic activity, but the exact mechanism is not clear.[2728] The effect appears to be dose-dependent and may be additive with traditional diuretics.
Salicylates can increase the risk of renal toxicity in patients receiving diuretics.[6136] Salicylates inhibit renal prostaglandin synthesis, which can lead to fluid retention and increased peripheral vascular resistance. Salicylates may decrease the hyperuricemic effect of hydrochlorothiazide.
Ethanol, barbiturates, or opiate agonists may potentiate orthostatic hypotension when used concurrently with hydrochlorothiazide.[5917]
Thiazide diuretics can cause decreased arterial responsiveness to vasopressor amines (e.g., norepinephrine), but the effect is not sufficient to preclude their coadministration.[5917]
Thiazide diuretics may increase the risk of hypokalemia [3085] [5917] when used concurrently with methazolamide which may also cause hypokalemia [5023]. Monitor serum potassium levels to determine the need for potassium supplementation and/or alteration in drug therapy. There may also be an additive diuretic or hyperuricemic effect.
Ephedra, Ma huang can antagonize all types of antihypertensive agents. Blood pressure should be monitored closely in patients using antihypertensive agents with ephedra.[3490]
Memantine reduced the bioavailability of hydrochlorothiazide by roughly 20% in a drug interaction study.[8204] The clinical significance of this pharmacokinetic interaction, if any, is unknown.
Palonosetron may rarely cause prolongation of the QT interval. A potassium- and/or magnesium-depleted state may increase the risk of cardiac arrhythmias; use thiazide diuretics cautiously with palonosetron and monitor serum electrolyte levels frequently, if indicated.[5148]
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]
Additive hypotensive effects may be seen when monoamine oxidase inhibitors (MAOIs) are combined with antihypertensives.[4673] [6398] Careful monitoring of blood pressure is suggested during concurrent therapy of MAOIs with diuretics. Patients should be instructed to rise slowly from a sitting position, and to report syncope or changes in blood pressure or heart rate to their health care provider during concurrent use of an MAOI and hydrochlorothiazide, HCTZ.
Hydrochlorothiazide, HCTZ may decrease the renal clearance of fluconazole. Coadministration of fluconazole 100 mg PO and hydrochlorothiazide 50 mg PO for 10 days in normal volunteers (n=13) resulted in a significant increase in fluconazole AUC and Cmax compared to fluconazole given alone. There was a mean +/- SD increase in fluconazole AUC and Cmax of 45 +/- 31% and 43 +/- 31%, respectively. These changes are attributed to a mean +/- SD reduction in fluconazole renal clearance of 30% +/- 12%.[5405]
Use caution when coadministering amiodarone with drugs which may induce hypokalemia and/or hypomagnesemia including thiazide diuretics.[3085] [6115] Since antiarrhythmic drugs may be ineffective or may be arrhythmogenic in patients with hypokalemia, any potassium or magnesium deficiency should be corrected before and during amiodarone therapy.[4950]

Adverse Reactions

- abdominal pain
- agranulocytosis
- alopecia
- anemia
- anorexia
- aplastic anemia
- azotemia
- blurred vision
- constipation
- diarrhea
- dizziness
- exfoliative dermatitis
- glycosuria
- gout
- headache
- hemolytic anemia
- hyperbilirubinemia
- hypercalcemia
- hypercholesterolemia
- hyperglycemia
- hypertriglyceridemia
- hyperuricemia
- hypochloremia
- hypokalemia
- hypomagnesemia
- hyponatremia
- hypotension
- impotence (erectile dysfunction)
- interstitial nephritis
- jaundice
- leukopenia
- metabolic alkalosis
- nausea/vomiting
- orthostatic hypotension
- pancreatitis
- pancytopenia
- paresthesias
- photosensitivity
- polyuria
- Stevens-Johnson syndrome
- syncope
- thrombocytopenia
- toxic epidermal necrolysis
- vertigo
- weakness
- xanthopsia

Adverse GI effects associated with thiazide therapy include abdominal pain, anorexia, gastric irritation, nausea/vomiting, cramps, diarrhea, constipation, sialadenitis, and pancreatitis.

Patients receiving hydrochlorothiazide should be monitored closely for signs of electrolyte imbalance including hyponatremia, hypokalemia, hypomagnesemia, and hypochloremia. Patients should be aware of the symptoms of these disturbances (e.g., lassitude, mental confusion, fatigue, faintness, dizziness, muscle cramps, tachycardia, headache, paresthesia, thirst, anorexia, nausea, or vomiting), and report these signs immediately. Thiazide diuretics may induce metabolic alkalosis associated with hypokalemia and hypochloremia; this acid/base imbalance is effectively treated with potassium chloride replacement.[9372] [9373] Thiazides also can decrease urinary calcium excretion, resulting in hypercalcemia. Hypokalemia is one of the most common adverse effects associated with thiazide diuretic therapy and can lead to cardiac arrhythmias. This effect is especially important to consider in patients receiving cardiac glycoside therapy because potassium depletion increases the risk of cardiac toxicity. Hyperaldosteronism, secondary to cirrhosis or nephrosis, can predispose patients to hypokalemia when hydrochlorothiazide is administered. Low dietary-potassium intake, potassium-wasting states, or administration of potassium-wasting drugs also can predispose patients to hydrochlorothiazide-induced hypokalemia. Patients receiving hydrochlorothiazide therapy may require supplemental potassium to prevent hypokalemia or metabolic alkalosis.

Hypochloremic alkalosis can occur with hypokalemia during hydrochlorothiazide therapy, and it is particularly likely to occur in patients with other losses of potassium and/or chloride such as through severe vomiting, diarrhea, excessive sweating, GI drainage, paracentesis, or potassium-losing renal diseases.

Patients receiving hydrochlorothiazide can develop a dilutional hyponatremia, but it usually is asymptomatic and moderate. Withdrawal of the drug, fluid restriction, and potassium or magnesium supplementation typically will return the serum sodium concentration to normal, but severe hyponatremia can occur. Geriatric patients are especially susceptible to developing hyponatremia, so care should be taken when diuretics are administered to these patients.

Complications of thiazide diuretic therapy may include intravascular volume depletion (hypovolemia), with potential for development of prerenal azotemia.[9373] Hydrochlorothiazide reportedly has caused azotemia and interstitial nephritis, resulting in reversible renal failure. These effects have occurred mainly in patients with preexisting renal disease.

Hydrochlorothiazide can produce glycosuria and hyperglycemia in diabetic patients. Blood and/or urine glucose levels should be assessed more carefully in diabetic patients receiving hydrochlorothiazide.

Thiazide diuretics are well known to cause hyperuricemia. The Framingham Study showed that acute gout occurred in only 20% of patients with hyperuricemia. Thiazide diuretics appear to interfere with proximal tubule secretion of uric acid since thiazides are also organic acids and they compete with uric acid for binding at this site. Since thiazides reduce the clearance of uric acid, patients with gout or hyperuricemia may have exacerbations of their disease.

Hypercholesterolemia and/or hypertriglyceridemia have been associated with thiazide diuretic therapy. Although elevations in total cholesterol concentrations of 8% can negate the protection against coronary heart disease provided by a 5 mmHg reduction in blood pressure,[659] data from long-term studies suggest diuretic-induced cholesterol changes are not clinically significant and do not contribute to coronary heart disease risk. After approximately one year of treatment, total serum cholesterol concentrations will subside to baseline or lower, suggesting diuretic-induced cholesterol changes are not a significant coronary heart disease risk factor.[658]

Patients with pre-existing hypovolemia or hypotension should have their condition corrected before diuretics are initiated. Orthostatic hypotension may occur during treatment with thiazide diuretics.[9371] Orthostatic hypotension can be exacerbated by concurrent use of alcohol, narcotics, or antihypertensive drugs (see Drug Interactions). Excessive hypotension during thiazide diuretic therapy can result in syncope. An increased risk of falls has been reported for elderly patients receiving thiazide diuretics.[9369] [9370] In addition, the antihypertensive effects of thiazides may be enhanced in other patients predisposed for orthostatic hypotension, including the post-sympathectomy patient.

Thiazide diuretics have been associated with intrahepatic cholestatic jaundice (rare), and hyperbilirubinemia. Caution should be used when thiazides are administered to jaundiced infants due to the risk of hyperbilirubinemia.

Adverse CNS effects associated with thiazide therapy include dizziness, headache, paresthesias, vertigo, and xanthopsia.
While their incidence is rare, agranulocytosis, aplastic anemia, pancytopenia, hemolytic anemia, leukopenia, and thrombocytopenia have been reported with thiazide diuretic therapy.
Other adverse effects reported with hydrochlorothiazide include blurred vision, muscle spasm, impotence (erectile dysfunction), and weakness.
Due to the diuretic action of hydrochlorothiazide, polyuria can be troublesome for some patients during therapy.
Adverse dermatologic reactions to hydrochlorothiazide and other thiazide diuretics are uncommon but may occur. These reactions include purpura, photosensitivity, rash, alopecia, urticaria, erythema multiforme including Stevens-Johnson syndrome, exfoliative dermatitis including toxic epidermal necrolysis (TEN), and polyarteritis nodosa.

Adverse Reactions last revised 8/10/2006 8:18:00 AM

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Digoxin
Digitek™ | Lanoxicaps® | Lanoxin®
Classification:
- Cardiovascular Agents
  - Antiarrhythmics
- Cardiovascular Agents
  - Antiarrhythmics
    - Cardiac glycosides
- Cardiovascular Agents
  - Inotropes
- Cardiovascular Agents
  - Inotropes
    - Cardiac glycosides

Description, Mechanism of Action, Pharmacokinetics

Description: Digoxin is a cardiac glycoside similar to digitoxin, although the pharmacokinetic profiles differ between the two drugs. The ancient Egyptians used cardiac glycosides as a poison, and the Romans used them as a cardiovascular tonic. In 1785, Withering published his famous book on foxglove (i.e., digitalis purpurea) and its uses. (See also: 'Inotropes Overview'). Digoxin is indicated for the treatment of congestive heart failure and to control ventricular rate in patients with atrial fibrillation. The use of digoxin to control ventricular rate in patients with chronic atrial fibrillation has declined in recent years; its use is being replaced by more effective rate control agents such as calcium channel blockers.[4532] While digoxin increases left ventricular ejection fraction, improves symptoms, and reduces the need for hospitalization in heart failure patients, overall mortality is not affected.[1617] Although digoxin has been used for decades in patients with heart failure, ACE inhibitors have replaced digoxin as first line therapy for CHF due to systolic dysfunction, but digoxin continues to be used as adjunctive therapy for heart failure. In patients with atrial fibrillation or atrial flutter, calcium-channel blockers, such as verapamil and diltiazem, are generally more effective than digoxin for controlling ventricular rate. Although digoxin is used for the treatment and/or prophylaxis of supraventricular arrhythmias due to reentry mechanisms, calcium antagonists are usually preferred. The first commercially available digoxin products approved by the FDA went on the market in 1952. The patent for Lanoxicaps® expired in May 1995.

Mechanism of Action: Digoxin inhibits the Na-K-ATPase membrane pump. Na-K-ATPase regulates intracellular sodium and potassium. Inhibition of this enzyme leads to an increase in intracellular sodium concentration (i.e., decreased outward transport) and ultimately to an increase in intracellular calcium as sodium-calcium exchange is stimulated by high intracellular sodium concentrations. It is believed that increased intracellular concentrations of calcium allow for greater activation of contractile proteins

(e.g., actin, myosin). While the contractile proteins and the troponin-tropomysin system are directly involved in muscular contraction, it is not clear how digoxin augments their action. Digoxin does not directly affect these proteins or the cellular mechanisms that provide energy for contraction, nor does it affect contraction in skeletal muscle. Digoxin also increases sympathetic tone, however, this does not account for the positive inotropic effect which persists even in the presence of beta-adrenergic blockade.

Digoxin directly increases the force and velocity of myocardial contraction in both healthy and failing hearts. In the failing heart, an increased force of contraction raises cardiac output, resulting in greater systolic emptying and a smaller diastolic heart size. End-diastolic pressures decrease, leading to a reduction in pulmonary and systemic venous pressures. In patients with normal hearts, however, cardiac output remains unchanged. Digoxin also possesses direct vasoconstrictive properties and reflex CNS-mediated peripheral vasoconstriction. Although this increases vascular resistance, in patients with failing hearts, increased myocardial contractility predominates and total peripheral resistance drops. In patients with congestive heart failure, an increased cardiac output will decrease sympathetic tone, thereby reducing the heart rate and causing diuresis in edematous patients and improving coronary blood flow.

In addition to its inotropic effects, digoxin also possesses significant actions on the electrical activity of the heart. It increases the slope of phase 4 depolarization, shortens the action potential duration, and decreases the maximal diastolic potential. The increase in vagal activity mediated by cardiac glycosides decreases conduction velocity through the atrioventricular (AV) node, prolonging its effective refractory period. In atrial flutter or fibrillation, digoxin decreases the number of atrial depolarizations that reach the ventricle, thereby slowing ventricular rate. Sympathetic stimulation, however, easily overrides the beneficial inhibitory effects of digoxin on AV nodal conduction.[19] Thus, verapamil[20] and diltiazem[21] are gradually replacing digoxin as the agent to control ventricular rate in atrial tachyarrhythmias. While digoxin is somewhat effective in controlling ventricular rate in atrial fibrillation, it appears to be no better than placebo for converting recent-onset atrial fibrillation to normal sinus rhythm.[813]

Pharmacokinetics: Digoxin is commercially available as tablets, capsules, oral elixir, and injection. In general, digoxin is rapidly absorbed from the GI tract following an oral dose. Bioavailability from capsules is essentially complete but is approximately 75—85% from oral elixir and 70—80% from tablets. Digoxin distributes throughout the body tissues, with the highest concentrations found in the heart, kidneys, intestine, liver, stomach, and skeletal muscle. Small amounts can be found in the brain. The presence of congestive heart failure slows the rate at which steady-state distribution is achieved. Only 20—30% of the drug is plasma protein-bound. Digoxin crosses the placenta, and maternal and fetal plasma concentrations of the drug are equal. Onset of therapeutic effects generally occurs within 30 minutes to 2 hours after oral administration and within 5—30 minutes following IV administration. The peak effect generally occurs between 2—6 hours after oral administration of a dose.

A small amount of digoxin is metabolized in the liver to inactive metabolites. In approximately 10% of patients, however, significant amounts of orally ingested digoxin are metabolized in the gut by intestinal bacteria. Thirty to fifty percent of a dose is excreted unchanged in the urine. The elimination half-life of digoxin in adults is normally 30—40 hours, but heart failure or renal impairment can prolong digoxin elimination. Thus, in patients with renal impairment, the half-life is extended to as long as 4—6 days. The elimination half-life in infants and full-term neonates is 18—25 hours and 35—45 hours, respectively; digoxin half-life is prolonged in premature neonates (e.g., 61—170 hours).

Description, Mechanism of Action, Pharmacokinetics last revised 2/9/2004 2:12:00 PM

Indications

- atrial fibrillation
- atrial flutter†
- heart failure
- paroxysmal supraventricular tachycardia (PSVT)†
- paroxysmal supraventricular tachycardia (PSVT) prophylaxis†

† non-FDA-approved indication

Dosage

For ventricular rate control in patients with chronic atrial fibrillation and/or atrial flutter†; or for the treatment of narrow-complex paroxysmal supraventricular tachycardia (PSVT)† or for paroxysmal supraventricular tachycardia (PSVT) prophylaxis† in patients without a delta wave on ECG during sinus rhythm; or for the treatment of congestive heart failure:

NOTE: In patients with undetectable serum digoxin concentrations, the total loading dose should be based on lean body weight and clinical response, and divided into several doses administered at 6—8 hour intervals. Higher doses (i.e., concentrations) may be required for treating arrhythmias than for treating heart failure. Patients with moderate-severe renal impairment should receive smaller loading doses than patients with normal renal function due to a reduced volume of distribution.

NOTE: Maintenance doses should be based on lean body weight, clinical response, and renal function. Higher doses (i.e., concentrations) may be required for treating arrhythmias than for treating heart failure. Lower doses should be considered for geriatric patients or patients with impaired renal function. In one small study of men with NYHA class II or III heart failure who were in normal sinus rhythm, left ventricular function improved significantly on a dose of 0.125 mg/day that produced mean serum concentrations of 0.8 ng/ml but doses of 0.25 mg/day and corresponding higher concentrations of 1.5 ng/ml did not produce further improvement over the lower dosage.[155] In another small study of men with NYHA class II or III heart failure who were in normal sinus rhythm, left ventricular ejection fraction improved significantly when digoxin was increased from a mean dose of 0.2 mg/day (mean trough 0.67 ng/ml) to a mean dose of 0.39 mg/day (mean trough 1.22 ng/ml); however, no significant changes were observed in heart failure score or exercise tolerance.[233]

Loading Dose - Intravenous or Oral dosage (capsules):

NOTE: Liquid-filled capsules are approximately 100% bioavailable.

Adults: 10—15 mcg/kg IV or PO, given in 3 divided doses every 6—8 hrs, with the first dose equalling approximately one-half the total (e.g., 500 mcg IV or PO initially, followed by 250 mcg IV or PO every 6 hours x 2 doses). The manufacturer recommends a loading dose of 8—12 mcg/kg IV or PO, given in divided doses every 6—8 hours, for patients with heart failure and normal sinus rhythm. Doses above 12 mcg/kg may be required to control ventricular rate in patients with atrial fibrillation.

Children > 10 years: 8—12 mcg/kg IV or PO, divided into 3 or more doses, with the first dose equalling approximately one-half the total. Administer subsequent doses at 6—8 hour intervals.
Children 6—10 years: 15—30 mcg/kg IV or PO, divided into 3 or more doses, with the first dose equalling approximately one-half the total. Administer subsequent doses at 6—8 hour intervals.
Children 2—5 years: 25—35 mcg/kg IV or PO, divided into 3 or more doses, with the first dose equalling approximately one-half the total. Administer subsequent doses at 6—8 hour intervals.
Children and infants 1 month to 2 years: 30—50 mcg/kg IV or PO, divided into 3 or more doses, with the first dose equalling approximately one-half the total. Administer subsequent doses at 6—8 hour intervals.
Full term neonates: 20—30 mcg/kg IV or PO, divided into 3 or more doses, with the first dose equalling approximately one-half the total. Administer subsequent doses at 6—8 hour intervals.
Premature neonates: 15—25 mcg/kg IV or PO, divided into 3 or more doses, with the first dose equalling approximately one-half the total. Administer subsequent doses at 6—8 hour intervals.
Loading Dose- Oral dosage (elixir or tablets):
NOTE: Elixir and tablets are approximately 80% bioavailable.
Adults and children over 10 years: Total dose of 10—15 mcg/kg PO, given in 3 divided doses every 6—8 hours, with the first dose equalling approximately one-half the total (e.g., 500 mcg PO initially, followed by 250 mcg PO every 6 hours x 2 doses).
Children 5—10 years: 20—35 mcg/kg PO, divided into 3 doses, given every 6—8 hours.
Children 2—5 years: 30—40 mcg/kg PO, divided into 3 doses, given every 6—8 hours.
Children and infants 1 month to 2 years of age: 35—60 mcg/kg PO, divided into 3 doses, given every 6—8 hours.
Full term neonate: 25—35 mcg/kg PO, divided into 3 doses, given every 6—8 hours.
Premature neonate: 20—30 mcg/kg PO, divided into 3 doses, given every 6—8 hours.
Maintenance Dose -Intravenous dosage or Oral dosage (capsules):
Adults: 125—350 mcg PO or IV per day, depending on CrCl, given in 1—2 divided doses. Usual daily maintenance dose requirements for the treatment of congestive heart failure in adults based on corrected CrCl (ml/min per 70 kg) and lean body weight (LBW) are listed below. For patients with a CrCl < 60 ml/min, refer to dosing in patients with renal impairment.
LBW = 50—59 kg, CrCl >= 100 ml/min: 200 mcg PO in 1 or 2 divided doses.
LBW = 50—59 kg, CrCl 60—99 ml/min: 150 mcg PO in 1 or 2 divided doses.
LBW = 60—69 kg, CrCl 70—100 ml/min: 200 mcg PO in 1 or 2 divided doses.
LBW = 60—69 kg, CrCl 60—69 ml/min: 150 mcg PO in 1 or 2 divided doses.
LBW = 70—79 kg, CrCl 90—100 ml/min: 250 mcg PO in 1 or 2 divided doses.
LBW = 70—79 kg, CrCl 60—89 ml/min: 200 mcg PO in 1 or 2 divided doses.
LBW = 80—89 kg, CrCl >= 100 ml/min: 300 mcg PO in 1 or 2 divided doses.
LBW = 80—89 kg, CrCl 70—99 ml/min: 250 mcg PO in 1 or 2 divided doses.
LBW = 80—89 kg, CrCl 60—69 ml/min: 200 mcg PO in 1 or 2 divided doses.
LBW = 90—99 kg, CrCl >= 80 ml/min: 300 mcg PO in 1 or 2 divided doses.
LBW = 90—99 kg, CrCl 60—79 ml/min: 250 mcg PO in 1 or 2 divided doses.
LBW >= 100 kg, CrCl >= 90 ml/min: 350 mcg PO in 1 or 2 divided doses.
LBW >= 100 kg, CrCl 60—89 ml/min: 300 mcg PO in 1 or 2 divided doses.
Children over 10 years: 2—3 mcg/kg/day PO or IV in 1 daily dose.
Children 5—10 years: 4—8 mcg/kg/day PO or IV in 2 daily doses.
Children 2—5 years: 6—9 mcg/kg/day PO or IV in 2 daily doses.
Children and infants 1 month—2 years: 7.5—12 mcg/kg/day PO or IV in 2 daily doses.
Full term neonates: 5—8 mcg/kg/day PO or IV in 2 daily doses.
Preterm neonates: 4—6 mcg/kg/day PO or IV in 2 daily doses.
Maintenance Dose - Oral dosage (elixir or tablets):
Adults: 125—500 mcg PO once daily, depending on CrCl. Usual daily maintenance dose requirements for the treatment of congestive heart failure in adults based on corrected CrCl (ml/min per 70 kg) and lean body weight (LBW) are listed below. For patients with a CrCl < 60 ml/min, refer to dosing in patients with renal impairment.
LBW = 50—59 kg, CrCl >= 100 ml/min: 250 mcg PO once daily.
LBW = 50—59 kg, CrCl 60—99 ml/min: 188 mcg PO once daily.
LBW = 60—69 kg, CrCl 70—100 ml/min: 250 mcg PO once daily.
LBW = 60—69 kg, CrCl 60—69 ml/min: 188 mcg PO once daily.
LBW = 70—79 kg, CrCl 60—100 ml/min: 250 mcg PO once daily.
LBW = 80—89 kg, CrCl >= 100 ml/min: 375 mcg PO once daily.
LBW = 80—89 kg, CrCl 60—99 ml/min: 250 mcg PO once daily.
LBW = 90—99 kg, CrCl 80—100 ml/min: 375 mcg PO once daily.
LBW = 90—99 kg, CrCl 60—79 ml/min: 250 mcg PO once daily.
LBW >= 100 kg, CrCl 60—100 ml/min: 375—500 mcg PO once daily.
Children over 10 years of age: 2.5—5 mcg/kg PO once daily.
Children 5—10 years: 5—10 mcg/kg/day PO in 2 daily doses. The manufacturer recommends a dose of 7—10 mcg/kg/day PO in 2 divided doses.
Children 2—5 years: 7.5—10 mcg/kg/day PO in 2 daily doses. The manufacturer recommends a dose of 10—15 mcg/kg/day PO in 2 divided doses.
Children and infants 1 month—2 years: 10—15 mcg/kg/day PO in 2 daily doses.
Full term neonates: 6—10 mcg/kg/day PO in 2 daily doses.
Preterm neonates: 5—7.5 mcg/kg/day PO in 2 daily doses.
Maximum Dosage Limits:
Digoxin has a narrow therapeutic index. In all populations, the dosage is individualized based on patient weight, renal function, clinical goals, patient response, and when needed, serum digoxin concentrations.
Therapeutic Drug Monitoring:
NOTE: Serum digoxin concentrations can be used to help to guide dosage adjustments; however, they should always be interpreted in the context of the patient's overall clinical status.
•Serum digoxin concentrations should be drawn at least 6—8 hours after a dose (a trough concentration is preferrable) to avoid the distribution phase, which may produce falsely elevated levels. About two-thirds of adults considered adequately digitalized (without

evidence of toxicity) have serum digoxin concentrations ranging from 0.8—2.0 ng/ml and about two-thirds with clinical toxicity have concentrations > 2 ng/ml. However, since one-third of patients with clinical digoxin toxicity have a digoxin concentration below 2 ng/ml, values below 2 ng/ml do not rule out the possibility that a sign or symptom is related to digoxin toxicity, especially in the presence of electrolyte imbalances like hypokalemia or hypomagnesemia.

Patients with hepatic impairment:

No specific dosage adjustments are recommended for patients with hepatic impairment. However, patients with combined renal and hepatic impairment may have reduced digoxin clearance and potential for drug accumulation; monitor serum digoxin concentrations and therapeutic response closely in such patients.

Patients with renal impairment:

Dosage in patients with renal impairment is based on CrCl and lean body weight.

Patients with renal impairment have a lower volume of distribution than patients with normal renal function; therefore, both loading and maintenance doses should be reduced. The manufacturer recommends a loading dose of 6—10 mcg/kg in patients with renal insufficiency. Usual daily maintenance dose requirements for the treatment of congestive heart failure in adults based on corrected CrCl (ml/min per 70 kg) and lean body weight (LBW) are listed below. Higher doses may be required for treating arrhythmias than for treating heart failure. For patients with a CrCl >= 60 ml/min, refer to dosing in patients with normal renal function (see above).

Oral dosage (capsules) or intravenous dosage:

CrCl 50—59 ml/min, LBW 50—69 kg: 150 mcg PO/IV once daily.
CrCl 50—59 ml/min, LBW 70—89 kg: 200 mcg PO/IV once daily.
CrCl 50—59 ml/min, LBW 90—100 kg: 250—300 mcg PO/IV once daily.
CrCl 20—49 ml/min, LBW 50—59 kg: 100 mcg PO/IV once daily.
CrCl 20—49 ml/min, LBW 60—69 kg: 100—150 mcg PO/IV once daily.
CrCl 20—49 ml/min, LBW 70—79 kg: 150 mcg PO/IV once daily.
CrCl 20—49 ml/min, LBW 80—99 kg: 150—200 mcg PO/IV once daily.
CrCl 20—49 ml/min, LBW >= 100 kg: 200—250 mcg PO/IV once daily.
CrCl < 20 ml/min, LBW 50—59 kg: 100 mcg PO/IV once daily or every other day.
CrCl < 20 ml/min, LBW 60—79 kg: 100 mcg PO/IV once daily.
CrCl < 20 ml/min, LBW 80—89 kg: 100—150 mcg PO/IV once daily.
CrCl < 20 ml/min, LBW 90—100 kg: 150 mcg PO/IV once daily.
Patients with a CrCl < 10 ml/min or those on hemodialysis may require an every 48 hour dosing interval.

Oral dosage (elixir or tablets):

CrCl 50—59 ml/min, LBW 50—69 kg: 188 mcg PO once daily.
CrCl 50—59 ml/min, LBW 70—89 kg: 250 mcg PO once daily.
CrCl 50—59 ml/min, LBW >= 90 kg: 250—375 mcg PO once daily.
CrCl 20—49 ml/min, LBW 50—59 kg: 125 mcg PO once daily.
CrCl 20—49 ml/min, LBW 60—69 kg: 125—188 mcg PO once daily.
CrCl 20—49 ml/min, LBW 70—79 kg: 250 mcg PO once daily.
CrCl 20—49 ml/min, LBW 80—99 kg: 188—250 mcg PO once daily.
CrCl 20—49 ml/min, LBW >= 100 kg: 250 mcg PO once daily.
CrCl < 20 ml/min, LBW 50—59 kg: 125 mcg PO once daily or every other day.
CrCl < 20 ml/min, LBW 60—79 kg: 125 mcg PO once daily.
CrCl < 20 ml/min, LBW 80—89 kg: 125—188 mcg PO once daily.
CrCl < 20 ml/min, LBW 90—100 kg: 188 mcg PO once daily.
Patients with a CrCl < 10 ml/min or those on hemodialysis may require an every 48 hour dosing interval.

The daily maintenance dose can also be estimated using the patient's CrCl and loading dose (LD) according to the method of Jelliffe and Brooker:[2885]

Daily % loss = 14 + CrCl/5

Maintenance dose/day (in mg) = Loading dose (in mg) x Daily % loss (expressed as a decimal) divided by Bioavailability of the desired dosage form (expressed as a decimal)

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Administration Guidelines

NOTE: Serum digoxin concentrations can be used to help to guide dosage adjustments; however, they should always be interpreted in the context of the patient's overall clinical status (see Therapeutic Drug Monitoring in Dosage section).

Oral Administration

NOTE: Bioavailability varies between different oral dosage forms of digoxin and between different brands of the same dosage form. Changing from one preparation to another may require dosage adjustments.

•*All dosage forms*: May be administered without regard to meals.
•*Tablets*: May be crushed and administered with food or fluids.
•*Pediatric elixir*: Administer using a calibrated measuring device.

Parenteral Administration

•Digoxin is administered intramuscularly or intravenously. The IV route is preferred due to more rapid therapeutic effect and less pain.
•Oral therapy should replace parenteral therapy as soon as possible.
•Visually inspect parenteral products for particulate matter and discoloration prior to administration whenever solution and container permit.

Intramuscular injection:

•Do not administer more than 2 ml at any one IM injection site.
•Inject deeply into gluteal muscle. Massage area following administration.

Intravenous injection:

•May be given undiluted or each 1 ml may be diluted in 4 ml of sterile water for injection, NS, D5W, or lactated Ringer's injection solution. Diluent volumes less than 4 ml will cause precipitation. Use diluted solutions immediately.
•Inject over at least 5 minutes via Y-site or 3-way stopcock. In patients with pulmonary edema, administer over 10—15 minutes. To avoid inadvertent overdosage, do not flush the syringe following administration.

†non-FDA approved

Administration last revised 7/1/2002

†non-FDA-approved indication

Contraindications/Precautions

- *ventricular fibrillation*
- acute myocardial infarction
- Adams-Stokes syndrome
- AV block
- bradycardia
- breast-feeding
- cardiomyopathy
- carotid sinus hypersensitivity
- constrictive pericarditis
- cor pulmonale
- elderly
- electrolyte imbalance
- hepatic disease
- hypercalcemia
- hyperkalemia
- hypertension
- hyperthyroidism
- hypocalcemia
- hypokalemia
- hypomagnesemia
- hypothyroidism
- hypoxemia
- idiopathic hypertrophic subaortic stenosis
- myxedema
- pregnancy
- pulmonary disease
- renal disease
- renal failure
- renal impairment
- sick sinus syndrome
- ventricular arrhythmias
- ventricular tachycardia
- Wolff-Parkinson-White syndrome

• *Absolute contraindications are in italics.*

Digoxin is contraindicated in patients with sick sinus syndrome because the drug can exacerbate bradycardia or SA block. In patients with sinus node disease or significant AV block, consideration should be given to the insertion of a pacemaker before treatment with digoxin. Digoxin should be used with great caution in patients with severe bradycardia or significant AV block (including second degree or intermittent complete heart block), particularly in unstable patients (e.g., acute myocardial infarction or acute myocarditis) or patients with Adams-Stokes syndrome, because complete heart block can result. Digoxin should be used with caution in patients with severe pulmonary disease, acute cor pulmonale, hypoxemia, hypothyroidism or myxedema, acute myocardial infarction, severe heart failure, acute myocarditis, amyloid cardiomyopathy, restrictive cardiomyopathy, or an otherwise damaged myocardium because the myocardium is more sensitive to the effects of digoxin, increasing the risk of digitalis-induced arrhythmias. Digoxin should not be used in patients with left ventricular failure associated with predominant diastolic dysfunction, since increased cytosolic calcium levels could worsen diastolic dysfunction and digoxin is less effective for this type of heart failure. Patients with hyperthyroidism may be less sensitive to digoxin and may require higher doses.
Digoxin use is relatively contraindicated in patients with ventricular arrhythmias including premature ventricular contractions or ventricular tachycardia because the drug can exacerbate these arrhythmias. Digoxin is absolutely contraindicated in patients with *ventricular fibrillation*; carotid sinus massage has been reported to cause *ventricular fibrillation* in patients receiving digoxin. Digoxin is relatively contraindicated in patients with carotid sinus hypersensitivity because the drug increases vagal tone. The use of digoxin in patients with Wolff-Parkinson-White syndrome can cause fatal ventricular arrhythmias, especially when this condition is associated with atrial fibrillation.
Patients with renal disease, such as acute glomerulonephritis, associated with heart failure should use digoxin with caution. Use of a lower daily dose is recommended with appropriate ECG monitoring based on clinical goals and patient conditions. Digoxin should be used with caution in patients with renal impairment including renal failure because 50% of digoxin is eliminated unchanged via the kidneys. Renal impairment reduces the excretion of the drug and can cause toxicity. Dosages should be decreased, and it should be kept in mind that the time required to reach steady-state concentrations can be prolonged in patients with renal failure.
Elderly patients and debilitated patients require careful dosage titration because they can be more sensitive to the effects of digoxin and can experience toxic reactions at dosages that are usually well tolerated in other patients. Toxicity may occur even if serum digoxin levels appear to be within the accepted therapeutic range.
Digoxin should be used with caution in patients with hepatic disease. No specific dosage adjustments are recommended for patients with hepatic impairment. However, patients with combined renal and hepatic impairment may have reduced digoxin clearance and potential for drug accumulation; monitor serum digoxin concentrations and therapeutic response closely in such patients. The risk of digoxin accumulation in patients with hepatic disease is much less than with digitoxin, which is extensively metabolized.
Patients with chronic constrictive pericarditis can respond unfavorably to digoxin therapy because the drug slows the heart rate, which further reduces cardiac output. Digoxin is relatively contraindicated in patients with idiopathic hypertrophic subaortic stenosis because the drug can increase the obstruction to left ventricular outflow.
Digoxin can lower heart rate and paradoxically worsen low cardiac output states of patients with valvular stenosis, chronic pericarditis, or chronic cor pulmonale.
Digoxin should be used with caution in patients with electrolyte imbalance. Conditions such as hypokalemia, hypomagnesemia, hypercalcemia, chronic pulmonary disease, and acute hypoxemia can increase cardiac sensitivity to digoxin, resulting in toxicity and potential for proarrhythmias. Patients with hypercalcemia or severe hyperkalemia can have an increased risk of digitalis-induced arrhythmias, particularly heart block. Digoxin may not be effective in patients with hypocalcemia; administration of calcium may be necessary.

IV administration of digoxin can transiently increase blood pressure and should be used cautiously in patients with hypertension.
Digoxin is classified in FDA pregnancy risk category C, although digoxin is considered by many cardiologists to be one of the safest antiarrhythmics for use during pregnancy. Digoxin readily passes to the fetal circulation; however, this drug has been used safely and effectively off-label for decades to treat both maternal and fetal arrhythmias. No teratogenic effect has been reported in humans. The typical dosage in pregnancy is similar to that given a non-pregnant woman. There may be difficulty, particularly in the third trimester, in interpreting serum digoxin levels as a result of an increase in an endogenous digoxin-like substance that may interfere with the digoxin assays. Thus, digoxin levels may give the impression of supratherapeutic dosing; clinicians should interpret the results in accordance with the clinical status of the mother and fetus before making dosage adjustments based on levels alone. As with most drugs, the use of digoxin during pregnancy should be avoided unless the potential benefit of digoxin therapy to the fetus or mother outweighs the potential risk to the fetus.
Although digoxin is transferred to breast milk to some degree, digoxin therapy during lactation appears to be safe. The American Academy of Pediatrics generally considers the use of digoxin to be compatible with breast-feeding.[4201]

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Drug Interactions

- Acarbose
- Acetazolamide
- Albuterol
- Alprazolam
- Amiloride
- Amiodarone
- Amphotericin B
  Antacids
  Antimuscarinics
  Antineoplastic Agents
- Atorvastatin
  Barbiturates
  Beta-blockers
- Calcium Salts
- Captopril
- Cholestyramine
  Cholinesterase Inhibitors
- Clarithromycin
- Colestipol
  Corticosteroids
- Cyclosporine
- Diazepam
- Diltiazem
- Dofetilide
- Doxorubicin
- Entecavir
- Erythromycin
- Exenatide
- Felodipine
- Flaxseed
- Fluvastatin
- Gatifloxacin
- Ginger, Zingiber officinale
- Ginseng, Panax ginseng
- Hawthorn, Crataegus laevigata
- Indomethacin
- Itraconazole
- Kaolin; Pectin
- Ketoconazole
- Levalbuterol
  Loop diuretics
- Magnesium Citrate
- Magnesium Salts
- Memantine
- Metformin
- Methazolamide
- Miglitol
- Neomycin
- Nifedipine
- Omeprazole
- Phenytoin
- Potassium Salts
- Propafenone
- Psyllium
- Quinidine
- Quinine
- Rabeprazole
- Rifampin
- Ritonavir
- Sevelamer
- Simvastatin
- Sodium Polystyrene Sulfonate
- Sotalol
- Spironolactone
- St. John's Wort, Hypericum perforatum
- Succinylcholine
- Sulfasalazine
  Sympathomimetics
- Tegaserod
- Telmisartan
  Tetracyclines
  Thiazide diuretics
  Thyroid hormones
- Tramadol
- Trazodone
- Trimethoprim
- Verapamil

Several drugs, if administered concomitantly with digoxin, can reduce GI absorption of orally administered digoxin.[4999] [5802] These drugs include: antacids containing aluminum hydroxide, magnesium hydroxide [5802]; flaxseed [4999] [5802]; kaolin; pectin [4999]; or psyllium [5802]. In most cases, staggering the administration times by two hours will minimize the magnitude of these interactions.
Concurrent use of indomethacin and digoxin caused increased plasma digoxin concentrations and a prolongation of the digoxin half-life.[7305] Carefully monitor serum digoxin concentrations if indomethacin is also used. Observe patients carefully for signs of digoxin toxicity.
Although colestipol and cholestyramine have been reported to reduce the bioavailability of digitoxin, their effects on digoxin

absorption are hypothesized to be less since digoxin undergoes less enterohepatic recycling than digitoxin. However, cholestyramine has been shown to significantly interfere with the absorption of digoxin.[4999] The administration of cholestyramine twice daily (8 hours before and after digoxin administration) or the use of digoxin solution or capsules may minimize this interaction.[5802] Colestipol is also expected to decrease the absorption of digoxin,[4794] and has been shown to produce a clinically significant decrease in the serum half-life of digoxin.[5802] Patients should be observed for change in digitalis effect if these bile resins are added or discontinued in a patient stabilized on cardiac glycosides.[4794]

Pharmacokinetic studies of concomitant sevelamer and digoxin have not demonstrated an interaction.[5909] However, sevelamer may interfere with the absorption of many drugs; this is especially important with narrow therapeutic index drugs such as digoxin. Per the manufacturer of sevelamer, administering such drugs at least 1 hour before or 3 hours after sevelamer doses can minimize the potential for a drug interaction.[4827]

Acarbose, an alpha-glucosidase inhibitor, has been found to decrease the mean bioavailability (AUC) of digoxin by 16% (90% confidence interval: range 8—23%), decrease the mean Cmax of digoxin by 26% (90% confidence interval: range 16—34%), and decrease the mean trough concentration of digoxin by 9% (90% confidence limit: 19% decrease to 2% increase).[4995] Miglitol, also an alpha-glucosidase inhibitor, may impair the oral absorption of digoxin and lead to subtherapeutic serum digoxin concentrations in some patients. In healthy volunteers, coadministration of miglitol 50 mg or 100 mg with digoxin reduced the average plasma concentrations of digoxin by 19% and 28%, respectively. However, in diabetic patients under treatment with digoxin, plasma digoxin concentrations were not altered when coadministered with miglitol.[6106] The mechanism of the interaction is not well understood. Some experts have recommended that these agents be administered 6 hours after an oral digoxin dose to ensure time for adequate digoxin absorption.[2498] In addition, patients should be closely observed for the loss of clinical effect of digoxin therapy if either acarbose or miglitol is added to the medication regimen. In some cases, digoxin serum concentration monitoring may be helpful and digoxin dosage adjustment may be required.

Gastric acid pump-inhibitors may increase digoxin bioavailability, however, the magnitude of the interaction is small. When rabeprazole is co-administered with digoxin, the AUC and Cmax for digoxin increases approximately 19% and 29%, respectively.[5515] Omeprazole increases the AUC of digoxin by about 10%.[6108] Patients with digoxin serum levels at the upper end of the therapeutic range may need to be monitored for potential increases in serum digoxin levels when rabeprazole or omeprazole is coadministered with digoxin.

The addition of erythromycin to digoxin therapy may lead to a significant increase (43—116%) in serum digoxin concentration.[5802] Clarithromycin may also increase serum digoxin levels; clarithromycin has been reported to increase serum digoxin concentrations by 70%.[6109] Originally, this interaction was thought to be due to inhibition of intestinal flora, which leads to decreased intestinal metabolism of digoxin to inactive digoxin reduction products (DRPs). While this may occur, only 5% of a digoxin dose is subject to metabolism by gut flora and this mechanism does not account for the large increases in digoxin levels that occur with the co-administration of these 2 macrolides. A more important factor is erythromycin or clarithromycin inhibition of P-glycoprotein, an energy-dependent drug efflux pump. Inhibition of this protein in the intestinal cell wall leads to increased oral absorption and decreased renal and non-renal clearance of digoxin.[6114] [6488] Dosage reduction of digoxin may be necessary.

In approximately 10% of patients, a small portion of a digoxin dose is metabolized in the gut by intestinal *Eubacterium lentum,* an anaerobic bacillus*,* to inactive digoxin reduction products (DRPs). DRPs have little cardiac activity due to poor cardiac receptor binding and rapid excretion. Certain antibiotics can reduce the activity of intestinal bacteria, which, in turn, may enhance digoxin bioavailability via decreased DRP formation and increased enterohepatic recycling of digoxin in some patients. Digoxin toxicity has been reported in patients previously stabilized on digoxin who receive antibiotics that affect *E. lentum*, such as tetracyclines.[5802] Other antibiotics that have activity against *E. lentum* may produce similar effects on digoxin metabolism.

Neomycin and sulfasalazine have been reported to reduce the absorption of digoxin. Sulfasalazine was shown to reduce the absorption of digoxin by 20% while large doses of neomycin reduced steady-state digoxin concentrations by 28%. It is thought that the decrease in digoxin absorption is due to alterations in the properties of the gut wall. Therefore, separating the time of administration between these drugs and digoxin will probably not reduce the potential interaction.[5802]

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

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

Studies in healthy volunteers have shown that dofetilide does not affect the pharmacokinetics of digoxin. However, the concomitant administration of digoxin with dofetilide was associated with a higher occurrence of torsade de pointes. It is not clear whether this represents a pharmacodynamic interaction with dofetilide or the presence of more severe structural heart disease in patients on digoxin; structural heart disease is a known risk factor for arrhythmia. No increase in mortality was observed in patients taking digoxin as a concomitant medication.[4947]

Digoxin used concomitantly with sotalol can increase the possibility of proarrhythmia. Sotalol does not appear to interfere substantially with digoxin serum levels. Proarrhythmic events were more common in sotalol-treated patients also receiving digoxin; it is not clear whether this represents an interaction or is related to the presence of CHF, a known risk factor for proarrhythmia, in the patients receiving digoxin.[5558] Despite potential for interactions, digoxin sometimes is intentionally used in combination with sotalol. Nevertheless, these combinations should be used cautiously, and therapy dosages may need adjustment in some patients.

Interactions occur between digoxin and a variety of other cardiovascular agents. These can be categorized into two groups: a) pharmacokinetic interactions that reduce the clearance of digoxin and may lead to digoxin toxicity: amiodarone [5802], felodipine [5827], diltiazem [5802], propafenone [5001] [5014], quinidine [5802], quinine [6113] and verapamil [5802]; and b) pharmacodynamic interactions that may potentiate the actions of digoxin: amiodarone, dofetilide, sotalol, beta-blockers [5001], diltiazem, and verapamil. Digoxin is a substrate for P-glycoprotein.[4718] Quinidine and verapamil inhibit P-glycoprotein, an energy-dependent cellular drug efflux pump. The inhibition of p-glycoprotein in the intestinal cell wall may lead to increased oral absorption

of digoxin; however, it has been shown that both quinidine and verapamil inhibit the secretion of digoxin by p-glycoprotein transporters in the kidney leading to decreased renal tubular elimination of digoxin and increased serum concentrations.[6114] It has been recommended that digoxin doses be reduced by 50% when adding quinidine therapy, and serum digoxin levels closely monitored thereafter.[5001] Despite potential for interactions, digoxin sometimes is intentionally used in combination with a beta-blocker, diltiazem, or verapamil to further reduce conduction through the AV node. Nevertheless, these combinations should be used cautiously, and digoxin dosages may need adjustment in some patients.[4999]

Serum digoxin concentrations have been reported to be significantly increased in patients with congestive heart failure who are given digoxin and captopril concomitantly.[7720] However, another study has shown no effect of captopril on serum digoxin concentrations in patients with mild heart failure.[7721] Captopril and digoxin have been administered to patients with congestive heart failure without apparent adverse effects. The clinical significance of this potential interaction is not clear. Until further data are available, it is prudent to monitor serum digoxin levels and clinical response in patients who are receiving digoxin and captopril.

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

Amiloride can alter the response to digoxin therapy if administered concomitantly. Typically, digoxin concentrations are slightly elevated by amiloride, and a reduced responsiveness to the positive inotropic effects of digoxin therapy has been noted in patients receiving both agents simultaneously. Patients receiving these two drugs concurrently should be monitored for altered responses to digoxin therapy.[5802]

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.[3085] Both hypokalemia and hyperkalemia increase the risk of digoxin toxicity.[3085] [7653] Although hyperkalemia can impair AV conduction, potassium salts are frequently coadministered with digoxin because these patients are often receiving potassium-depleting diuretics. Nevertheless, potassium salts should be used cautiously in patients receiving digoxin.

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

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

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

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

Concurrent use of digoxin or other cardiac glycosides with oral magnesium citrate may inhibit absorption and possibly decrease plasma concentrations of the glycoside.[4999] Because cardiac conduction changes and heart block may occur if electrolyte imbalances occur, saline laxatives such as magnesium citrate must be administered with caution to patients receiving cardiac glycoside therapy as electrolyte disturbances, particularly hypokalemia, are possible with their use.[6115] The patient's electrolytes and renal function should be closely monitored.

Thyroid disease is known to alter the response to digoxin. Digoxin toxicity is more likely to occur in patients with hypothyroidism, while the response to digoxin is diminished in patients with hyperthyroidism. These reactions should be kept in mind when therapy with thyroid hormones is begun or interrupted. When hypothyroid patients are administered thyroid hormone, the dose requirement of digoxin may be increased.[4999]

Spironolactone can reduce the renal clearance of digoxin. Monitoring for this event is complicated by the fact that spironolactone also can cross-react with some digoxin assays. In some cases, digoxin doses will need to be reduced if spironolactone is added.[5802]

Some antineoplastic agents have been reported to decrease the absorption of digoxin tablets due to their adverse effects on the GI mucosa; no significant change was seen with digoxin capsules, and the effect on digoxin liquid is not known.[4668] The reduction in digoxin tablet absorption has resulted in plasma concentrations that are 50% of pretreatment levels and has been clinically significant in some patients. Digoxin capsules (Lanoxicaps®) may be utilized to avoid this interaction in patients receiving antineoplastic agents and digoxin tablets. It is prudent to closely monitor patients for loss of clinical efficacy of digoxin while receiving antineoplastic therapy.

Digoxin can reduce the uptake of doxorubicin into cardiac tissue and thus temper the cardiomyopathy caused by doxorubicin.[6016] Digoxin can be used to treat congestive heart failure due to doxorubicin cardiomyopathy and may offer improvement to some patients, although angiotensin-converting enzyme inhibitors may be of greater benefit. Some antineoplastic agents have been reported to decrease the absorption of digoxin tablets due to their adverse effects on the GI mucosa; no significant change was seen with digoxin capsules, and the effect on digoxin liquid is not known.[4668] The reduction in digoxin tablet absorption has resulted in plasma concentrations that are 50% of pretreatment levels and has been clinically significant in some patients. Digoxin capsules (Lanoxicaps®) may be utilized to avoid this interaction in patients receiving antineoplastic agents and digoxin tablets. It is prudent to closely monitor patients for loss of clinical efficacy of digoxin while receiving antineoplastic therapy. It is not known if digoxin has similar effects on doxorubicin liposomal.

Reduced clearance of digoxin has been observed when it is given concurrently with cyclosporine. This may be due to cyclosporine inhibition of P-glycoprotein, an energy-dependent drug efflux pump. Inhibition of the P-glycoprotein-mediated renal tubular secretion of digoxin is the postulated mechanism for decreased renal clearance.[6102] A decrease in the apparent volume of distribution of digoxin has been reported after cyclosporine administration. Severe digitalis toxicity has been seen within days of starting

cyclosporine in patients previously taking digoxin. A reduction in the digoxin dosage may be required. With discontinuation of cyclosporine, patients may require increased digoxin doses.[5936]
In vitro studies have demonstrated the positive inotropic effects of ginger, Zingiber officinale.[2217] It is theoretically possible that ginger could affect the action of antiarrhythmics, however, no clinical data are available.
It has been reported that hawthorn, Crataegus laevigata may potentiate the effects of the cardiac glycosides (i.e., digoxin) through a pharmacodynamic interaction.[5314] Clinical documentation of an interaction is lacking; it is reported that hawthorn is commonly used in conjunction with digoxin in European communities in selected patients with heart failure. The pharmacokinetic effect of hawthorn on digoxin has been evaluated, due to the fact that flavonoids in hawthorn might affect P-glycoprotein function and cause interactions with P-glycoprotein substrates (e.g., digoxin [4718]). In a small cross-over study in 8 volunteers, researchers evaluated digoxin 0.25 mg/day PO alone x 10 days and digoxin 0.25 mg/day PO with *Crataegus* commercial extract WS1442 (Schwabe Pharmaceuticals) 450 mg PO twice daily x 21 days. Following 3 weeks of concomitant therapy, hawthorn did not significantly alter any pharmacokinetic parameters for digoxin. The authors suggested that both hawthorn and digoxin, in the doses and dosage form studied, may be coadministered safely.[5315] However, despite these reassuring data, it appears prudent to recommend close clinical observation if digoxin is administered concurrently with hawthorn, due to the potential for pharmacodynamic effects, and the potential for wide variability in the potency and purity of herbal products. Patients should be advised to only use hawthorn with digoxin after discussion with their prescriber.
An interaction between digoxin, when administered concomitantly with either alprazolam [4761] or diazepam [5802], has been reported. Digoxin toxicity has occurred in a patient receiving alprazolam and digoxin.[6129] This interaction may be the result of increased plasma protein binding of digoxin and/or an effect of the benzodiazepine at the renal tubules that results in decreased digoxin elimination. A subsequent interaction study of intravenous digoxin with alprazolam revealed no significant effect of alprazolam on the pharmacokinetics of digoxin.[6130] Pending further clarification of this interaction, patients receiving alprazolam or diazepam and digoxin concurrently should be monitored for increased serum digoxin levels.
An increased incidence of digoxin toxicity has been reported in some patients during post-marketing reports with the concurrent use of tramadol and digoxin.[5043]
Concomitant administration of gatifloxacin and digoxin did not produce significant alterations in gatifloxacin pharmacokinetics. However, an increase in digoxin serum concentrations was observed in 3 of 11 healthy volunteers. Patients taking digoxin should therefore be monitored for signs and symptoms of digoxin toxicity. In patients who display signs and/or symptoms of digoxin intoxication, serum digoxin concentrations should be determined, and digoxin dosage should be adjusted as appropriate. Adjustments of digoxin dosage prior to initiating gatifloxacin therapy are not warranted.[5152]
An interaction between St. John's wort, Hypericum perforatum and digoxin has been noted. After the achievement of steady state digoxin levels, 25 healthy volunteers received digoxin (0.25 mg/day) either with placebo or with St. John's wort extract (900 mg/day) for another 10 days. After 10 days of co-treatment with hypericum extract LI160™, the patients' digoxin AUCs decreased by 25%. Digoxin trough concentrations and Cmax decreased by 33% and 26%, respectively. The effect of St. John's wort on digoxin concentrations became increasingly pronounced until the tenth day of co-medication. The authors have postulated that St. John's wort induces the P-glycoprotein intestinal drug transporter, which extrudes digoxin back into the GI tract and results in decreased systemic bioavailability.[2716] Clinically, patients should be monitored for decreased efficacy of digoxin if St. John's wort is added to a stable digoxin regimen. Conversely, the discontinuation of St. John's wort could lead to increased digoxin bioavailability and potential toxicity in a patient previously stabilized on digoxin.
A case of an elevated digoxin serum concentration was reported in a 74 year old man who was taking Siberian ginseng concomitantly. The serum digoxin concentration returned to an acceptable level after ginseng was discontinued. The patient's serum digoxin concentration rose again several months later upon reinitiation of ginseng. It is unclear whether some component of the ginseng interfered with digoxin elimination, was converted to digoxin *in vivo*, or caused a false serum assay result.[1817] Although Panax ginseng has not been reported to alter digoxin serum concentrations, the possibility of an interaction should be considered.
Certain medications used concomitantly with metformin may increase the risk of lactic acidosis. Cationic drugs that are eliminated by renal tubular secretion (e.g., digoxin) [4999] may decrease metformin elimination by competing for common renal tubular transport systems.[5280] Although most such interactions remain theoretical, careful patient monitoring and dose adjustment of metformin and/or the interfering cationic drug is recommended.
Some HMG Co-A reductase inhibitors may increase serum digoxin levels. Due to studies that indicate fluvastatin increases digoxin serum concentrations, the manufacturer recommends closer monitoring of patients stabilized on digoxin if high doses (i.e., 80 mg) of fluvastatin are added.[5045] Simvastatin causes a slight elevation of serum digoxin levels.[5336] Simvastatin should be used cautiously in patients receiving digoxin. Coadministration of atorvastatin 80 mg (but not 10 mg) with digoxin resulted in an approximately 20% increase in digoxin plasma concentrations.[5460] Patients receiving atorvastatin should be monitored for potential increases in digoxin effects or toxicity.
The increase in vagal tone induced by some cholinesterase inhibitors may produce bradycardia, hypotension, or syncope.[7719] The vagotonic effect of these drugs may theoretically be increased when given with other medications known to cause bradycardia such as digoxin. These interactions are pharmacodynamic in nature rather than pharmacokinetic.
Conflicting data have been reported on the potential for interaction between digoxin and cimetidine; the interaction is not considered clinically significant.
When telmisartan is coadministered with digoxin, median increases in digoxin peak concentration (49%) and in trough concentration (20%) are observed. Therefore, if a patient is taking digoxin, it is recommended that serum digoxin concentrations be monitored upon initiation, adjustment, or discontinuation of telmisartan.[5870]
Cationic drugs that are eliminated by renal tubular secretion (e.g., digoxin) may compete with memantine for common renal tubular transport systems, thus possibly decreasing the elimination of one of the drugs. Although theoretical, careful patient monitoring of response to memantine and/or digoxin is recommended to assess for needed dosage adjustments. In selected individuals, digoxin serum concentration monitoring may be appropriate.[8204]
In a pharmacokinetic study of 11 healthy men, digoxin AUC, volume of distribution, and half-life increase, while renal and non-renal clearance decrease, when coadministered with ritonavir.[6945] It appears that this interaction is mediated by ritonavir's inhibition or P-glycoprotein-mediated renal tubular secretion of digoxin.[5110] [6945] Patients who are stabilized on digoxin should be monitored for altered serum concentrations if ritonavir is added or removed from the drug regimen.[5110]
Increased serum digoxin levels have been reported in patients taking trazodone and digoxin concomitantly.[5450] The clinical significance of this interaction is not known.
Digoxin serum concentrations may be increased by up to 45% by concomitant administration of nifedipine.[5802] This is believed to be due to decreased renal and nonrenal clearance of digoxin by nifedipine. Despite some reports showing no effect on digoxin, plasma levels of digoxin should be monitored carefully when nifedipine is administered.

Oral formulations of digoxin can produce higher serum concentrations when administered concurrently with antimuscarinics (e.g., propantheline) because of decreased GI motility induced by the antimuscarinic agent.[4999] [7704] This interaction has mostly occurred in the literature with slowly-dissolving, large-particle formulations of digoxin tablets; the manufacture of oral digoxin products today, utilizing liquid formulations and/or smaller particle sizes, theoretically reduces the potential for absorption interactions. However, there is wide variability expected in individual responses to many digoxin-drug interactions.[4999] [7704]
Other pharmacodynamic and pharmacokinetic systemic interactions are possible between digoxin and select antimuscarinic agents. Both trospium (a selective antimuscarinic) and digoxin are eliminated by active renal tubular secretion;[4999] [5974] coadministration has the potential to increase serum concentrations of trospium or digoxin due to competition for the drug elimination pathway. Darifenacin (30 mg daily) coadministered with digoxin (0.25 mg daily) resulted in a 16% increase in digoxin exposure.[7474] Anticholinergics, because of their ability to cause tachycardia [6824], can also antagonize the beneficial actions of digoxin in atrial fibrillation/flutter. Routine therapeutic monitoring should be continued when an antimuscarinic agent is prescribed with digoxin until the effects of combined use are known.
Concomitant use of digoxin with either itraconazole or ketoconazole has resulted in increased digoxin serum concentrations. Both itraconazole and ketoconazole inhibit p-glycoprotein, an enzyme which metabolizes digoxin. Fluconazole and voriconazole do not inhibit p-glycoprotein. Plasma concentrations of digoxin should be monitored closely if itraconazole or ketoconazole is added.[4699] [4700] [4718] [6488] [6935] [6936]
When digoxin is combined with tegaserod, a 15% reduction in digoxin peak plasma concentration occurs. Digoxin dose adjustments are unlikely to be required when combined with tegaserod.[5691] Until further clinical use is gained with tegaserod, use caution and consider monitoring digoxin levels more frequently if combined with tegaserod.
Repeat doses of exenatide (10 mcg SQ twice daily) decreased the Cmax of digoxin (0.25 mg PO daily) by 17% and delayed Tmax by roughly 2.5 hours. Overall steady state AUC of digoxin was not altered. The mechanism of the interaction is not known (although it may be due to delayed gastric emptying), nor is the clinical significance of this potential interaction. If digoxin and exenatide are co-prescribed, it may be prudent to initially monitor the patient for altered digoxin effect.[8017]
Both entecavir and digoxin are secreted by active tubular secretion.[8007] [5082] In theory, coadministration of entecavir with digoxin may increase the serum concentrations of either drug due to competition for the drug elimination pathway. The manufacturer of entecavir recommends monitoring for adverse effects when these drugs are coadministered.

Interactions last revised 5/18/2005 4:59:00 PM

Adverse Reactions

- abdominal pain
- anorexia
- anxiety
- atrial fibrillation
- atrial tachycardia
- AV block
- blurred vision
- confusion
- constipation
- delirium
- depression
- diarrhea
- dizziness
- drowsiness
- erythema
- fatigue
- gynecomastia
- hallucinations
- headache
- hyperkalemia
- hypokalemia
- impaired cognition
- impotence
- libido decrease
- maculopapular rash
- nausea/vomiting
- paresthesias
- photophobia
- PR prolongation
- premature ventricular contractions (PVCs)
- pruritus
- psychosis
- sinus bradycardia
- sinus tachycardia
- Stevens-Johnson syndrome
- ST-T wave changes
- syncope
- thrombocytopenia
- ventricular tachycardia
- visual impairment
- weakness
- xanthopsia

Cardiac effects of cardiac glycosides include primarily disturbances of cardiac rhythm. Digoxin can induce almost any type of cardiac arrhythmia, which makes it difficult to assess efficacy in some patients. Cardiac effects may occur in the absence of non-cardiac toxicity (e.g. GI side effects). Common cardiac effects associated with digitalis toxicity include variable degrees of AV block including complete heart block, PR prolongation, unifocal or multifocal premature ventricular contractions (PVCs), atrial tachycardia with or without block, sinus bradycardia with junctional escape, AV dissociation, and an accelerated junctional rhythm. Other rhythm disturbances have included bigeminal or trigeminal rhythms, premature atrial contractions (PACs), atrial fibrillation, sinus tachycardia, and ventricular tachycardia. ECG changes such as ST-T wave changes, can occur during digitalis administration and may or may not indicate digitalis toxicity. Early manifestations of overdose in children are usually arrhythmias; however, ventricular arrhythmias are relatively rare in children. Cardiac glycoside-induced cardiac toxicity should be treated by discontinuing therapy, instituting appropriate antiarrhythmic therapy if indicated, and correcting any associated electrolyte imbalances (e.g., potassium, magnesium). Digoxin serum concentrations may be used to evaluate and to prevent digoxin toxicity. However, digoxin serum concentrations do not consistently correlate with drug toxicity as there is considerable overlap between the therapeutic range for efficacy and toxicity, especially when used for the treatment of atrial arrhythmias. Chronic digoxin intoxication can lead to hypokalemia, which can in turn increase the risk of digoxin-induced cardiac toxicity. Patients receiving digoxin who are at risk for potassium deficiency should be treated preventively with potassium supplements. Acute intoxication with digoxin can cause

hyperkalemia, presumably due to inhibition of the Na-K-ATPase pump. Hyperkalemia can lead to AV block and asystole; patients who develop hyperkalemia during the initial stages of intoxication generally have a poor prognosis.
The extracardiac effects of cardiac glycoside intoxication include GI disturbances, CNS disturbances, ocular problems, potassium-level alterations, and idiosyncratic reactions which are unrelated to serum drug concentration or dosage. Anorexia, nausea/vomiting, and diarrhea are early signs of intoxication, and these effects can precede or follow cardiotoxicity. Such symptoms, however, also can be associated with uncontrolled heart failure. The symptoms of overdose or toxicity, in order of occurrence, are: stimulation of medullary centers resulting in GI disturbances including abdominal pain, anorexia, nausea/vomiting, diarrhea or constipation; electrolyte imbalance; and CNS effects. CNS effects due to digoxin include anxiety, depression, dizziness, drowsiness, fatigue, weakness, headache, apathy, syncope, confusion (impaired cognition), delirium, hallucinations, psychosis, and paresthesias. Seizures have rarely been associated with digoxin, usually when used in excessive dosage or in overdosage settings. Elderly patients with atherosclerotic disease may be more likely to experience CNS adverse effects. Neuropsychiatric manifestations of digoxin toxicity may be overlooked in elderly and psychiatric patients, due to coexisting conditions.
Visual disturbances due to digoxin toxicity are very common (50—95% of patients with digitalis intoxication) may include: blurred vision, visual impairment, xanthopsia, transient retrobulbar neuritis, photophobia, light flashes, disturbed color vision, decreased visual acuity and visual fields, altered pupil size, ocular muscle palsies, shimmering lights around bright objects, or yellow-green halos surrounding visual images. Visual hallucinations have also been reported. Ocular effects are most likely the result of cardiac glycoside-induced functional changes in the retina and are generally reversible following drug withdrawal.
Idiocratic adverse effects with digoxin (not related to serum concentration or dosage) include skin rash, gynecomastia, sexual dysfunction, and thrombocytopenia (immunologically-mediated). Digoxin therapy can increase plasma estrogen and can cause gynecomastia in men. Similar effects can be seen in women. Sexual dysfunction can be seen with digoxin therapy including libido decrease and impotence. Cases of erythema, pruritus, maculopapular rash, and Stevens-Johnson syndrome have been rarely reported in patients receiving cardiac gycosides.

Adverse Reactions last revised 7/1/2002

Monitoring Parameters
Monitoring Parameters
•ECG
•serum calcium
•serum creatinine/BUN
•serum magnesium
•serum potassium

Product Information

More information about the following products is available:
• Digitek™
• Lanoxicaps®
• Lanoxin®

Patient Education

Digoxin injection

What is digoxin injection?
DIGOXIN (Lanoxin®) is a cardiac glycoside that can help a weakened heart to function properly. Digoxin increases the strength of the heart muscle, helps to maintain a normal heart rhythm, and helps to remove excess water from the body. Digoxin can relieve symptoms of congestive heart failure, a condition that reduces the ability of the heart to pump enough blood through the body. These symptoms include swelling of the feet and legs, difficulty breathing, and extreme tiredness or weakness. It can also help to regulate heart rhythm problems. Generic digoxin injections are available.

What should my health care professional know before I receive digoxin?
They need to know if you have any of these conditions:
•heart disease
•heart rhythm disorders such as slow heart rate or heart block, sick sinus syndrome, ventricular arrhythmias, Wolff-Parkinson-White syndrome, or Adams-Stokes syndrome
•high blood pressure (IV injection can temporarily increase blood pressure)
•kidney disease
•liver disease
•lung disease
•over- or under-active thyroid
•recent heart attack
•too much calcium, potassium, or magnesium in the body
•an unusual or allergic reaction to digoxin, other medicines, foods, dyes, or preservatives
•pregnant or trying to get pregnant
•breast-feeding

How should I use this medicine?
Digoxin is for injection or infusion into a vein. (Injection into a muscle can be painful and is rarely used.) It is usually given by a

health-care professional in a hospital, long-term-care, or clinic setting.
Contact your pediatrician or health care professional regarding the use of this medicine in children. Special care may be needed. Do not administer adult preparations to children.
Elderly patients over 65 years old may have a stronger reaction to this medicine and may need smaller doses.

What if I miss a dose?
This does not apply.

What drug(s) may interact with digoxin?
•acarbose
•agents used to treat cancer
•alprazolam, diazepam
•amphotericin B
•antacids
•barbiturate medicines for inducing sleep or treating seizures (convulsions)
•beta blockers, often used for high blood pressure or heart problems
•calcium, magnesium, or potassium salts
•captopril
•certain medicines used to decrease cholesterol (cholestyramine, colestipol, atorvastatin, fluvastatin, simvastatin)
•clarithromycin or erythromycin
•cyclosporine
•diet pills (stimulants) or drugs used to control weight
•diltiazem
•entecavir
•felodipine
•gatifloxacin
•herbal products such as flaxseed, ginger, ginseng, hawthorn, St. John's wort
•hormones such as prednisone or cortisone
•indomethacin
•medicine for colds and breathing difficulties
•medicines to control heart rhythm (dofetilide, amiodarone, sotalol, and others)
•metformin
•neomycin
•omeprazole
•phenytoin
•psyllium
•quinine
•rabeprazole
•rifampin
•sevelamer
•sodium polystyrene sulfonate
•spironolactone
•St. John's wort
•succinylcholine
•sulfasalazine
•tetracycline antibiotics (doxycycline, tetracycline)
•thyroid hormones
•tramadol
•trimethoprim
•verapamil
•water pills (diuretics)
Tell your prescriber or health care professional about all other medicines you are taking, including non-prescription medicines, nutritional supplements, or herbal products. Also tell your prescriber or health care professional if you are a frequent user of drinks with caffeine or alcohol, if you smoke, or if you use illegal drugs. These may affect the way your medicine works. Check with your health care professional before stopping or starting any of your medicines.

What side effects may I notice from taking digoxin?
Side effects that you should report to your prescriber or health care professional as soon as possible:
•anxiousness or nervousness
•changes in color vision (more yellow color), blurred vision, eyes sensitive to light, light flashes, or halos around bright lights
•changes in behavior, mood, or mental ability
•chest pain or palpitations
•confusion
•diarrhea, or constipation
•dizziness or drowsiness
•fainting spells
•fast heartbeat (more likely in children)
•headache
•irregular, slow heartbeat (less than 50 beats per minute)
•loss of appetite
•nausea, vomiting
•skin rash or itching
•stomach pain
•tingling or numbness in the hands or feet

•unusual bruising, or pinpoint red spots on the skin
•weakness or tiredness
Side effects that usually do not require medical attention (report to your prescriber or health care professional if they continue or are bothersome):
•breast enlargement in men and women
•sexual problems such as impotence

What should I watch for while taking digoxin?
Your prescriber or health care professional may want to put you on digoxin tablets or capsules once you are stabilized with injections.
Check your heart rate (pulse) and blood pressure regularly while you are taking digoxin. Ask your prescriber or health care professional what your heart rate and blood pressure should be, and when you should contact him or her. Your prescriber or health care professional also may schedule regular blood tests and electrocardiograms to check your progress.
If you are going to have surgery, tell your prescriber or health care professional that you are taking digoxin.

Where can I keep my medicine?
Keep out of the reach of children.
Store at room temperature between 15 and 25 degrees C (59 and 77 degrees F). Protect from light. Throw away any unused medicine after the expiration date.

NOTE: This information is not intended to cover all possible uses, precautions, interactions, or adverse effects for this drug. If you have questions about the drug(s) you are taking, check with your health care professional.

[Revised: 05/18/2005]

Digoxin oral liquid

What is digoxin oral liquid?
DIGOXIN (Lanoxin®) is a cardiac glycoside that can help a weakened heart to function properly. Digoxin increases the strength of the heart muscle, helps to maintain a normal heart rhythm, and helps to remove excess water from the body. Digoxin can relieve symptoms of congestive heart failure, a condition that reduces the ability of the heart to pump enough blood through the body. These symptoms include swelling of the feet and legs, difficulty breathing, and extreme tiredness or weakness. It can also help to regulate heart rhythm problems. Generic digoxin oral liquid is available.

What should my health care professional know before I receive digoxin?
They need to know if you have any of these conditions:
•heart disease
•heart rhythm disorders such as slow heart rate or heart block, sick sinus syndrome, ventricular arrhythmias, Wolff-Parkinson-White syndrome, or Adams-Stokes syndrome
•kidney disease
•liver disease
•lung disease
•over- or under-active thyroid
•recent heart attack
•too much calcium, potassium, or magnesium in the body
•an unusual or allergic reaction to digoxin, other medicines, foods, dyes, or preservatives
•pregnant or trying to get pregnant
•breast-feeding

How should I take this medicine?
Take digoxin oral liquid by mouth. Follow the directions on the prescription label. Measure your medicine carefully with the specially marked dropper provided. Take your doses at regular intervals. Do not take your medicine more often than directed.
Contact your pediatrician or health care professional regarding the use of this medicine in children. Special care may be needed. Do not administer adult preparations to children.
Elderly patients over 65 years old may have a stronger reaction to this medicine and may need smaller doses.

What if I miss a dose?
If you miss a dose, take it as soon as you can (if you only take one dose a day, not more than 12 hours since your dose was due). If it is almost time for your next dose, take only that dose. Do not take double or extra doses.

What drug(s) may interact with digoxin?
•acarbose
•agents used to treat cancer
•alprazolam, diazepam
•amphotericin B
•antacids
•barbiturate medicines for inducing sleep or treating seizures (convulsions)
•beta blockers, often used for high blood pressure or heart problems
•calcium, magnesium, or potassium salts
•captopril
•certain medicines used to decrease cholesterol (cholestyramine, colestipol, atorvastatin, fluvastatin, simvastatin)
•clarithromycin or erythromycin
•cyclosporine
•diet pills (stimulants) or drugs used to control weight
•diltiazem

•entecavir
•felodipine
•gatifloxacin
•herbal products such as flaxseed, ginger, ginseng, hawthorn, St. John's wort
•hormones such as prednisone or cortisone
•indomethacin
•medicine for colds and breathing difficulties
•medicines to control heart rhythm (dofetilide, amiodarone, sotalol, and others)
•metformin
•neomycin
•omeprazole
•phenytoin
•psyllium
•quinine
•rabeprazole
•rifampin
•sevelamer
•sodium polystyrene sulfonate
•spironolactone
•St. John's wort
•succinylcholine
•sulfasalazine
•tetracycline antibiotics (doxycycline, tetracycline)
•thyroid hormones
•tramadol
•trimethoprim
•verapamil
•water pills (diuretics)
Tell your prescriber or health care professional about all other medicines you are taking, including non-prescription medicines, nutritional supplements, or herbal products. Also tell your prescriber or health care professional if you are a frequent user of drinks with caffeine or alcohol, if you smoke, or if you use illegal drugs. These may affect the way your medicine works. Check with your health care professional before stopping or starting any of your medicines.

What side effects may I notice from taking digoxin?
Side effects that you should report to your prescriber or health care professional as soon as possible:
•anxiousness or nervousness
•changes in color vision (more yellow color), blurred vision, eyes sensitive to light, light flashes, or halos around bright lights
•changes in behavior, mood, or mental ability
•chest pain or palpitations
•confusion
•diarrhea, or constipation
•dizziness or drowsiness
•fainting spells
•fast heartbeat (more likely in children)
•headache
•irregular, slow heartbeat (less than 50 beats per minute)
•loss of appetite
•nausea, vomiting
•skin rash or itching
•stomach pain
•tingling or numbness in the hands or feet
•unusual bruising, or pinpoint red spots on the skin
•weakness or tiredness
Side effects that usually do not require medical attention (report to your prescriber or health care professional if they continue or are bothersome):
•breast enlargement in men and women
•sexual problems such as impotence

What should I watch for while taking digoxin?
Visit your prescriber or health care professional for regular checks on your progress. Do not stop taking your digoxin without your prescriber's advice, even if you feel better.
Check your heart rate (pulse) and blood pressure regularly while you are taking digoxin. Ask your prescriber or health care professional what your heart rate and blood pressure should be, and when you should contact him or her. Your prescriber or health care professional also may schedule regular blood tests and electrocardiograms to check your progress.
Watch your diet. Less digoxin may be absorbed from the stomach if you have a diet high in bran fiber.
If you are going to have surgery, tell your prescriber or health care professional that you are taking digoxin.
Do not take antacids, or treat yourself with non-prescription medicines for pain, allergies, coughs or colds, without advice from your prescriber or health care professional. You will be able to take some of these medicines if you space doses several hours apart.

Where can I keep my medicine?
Keep out of the reach of children in a container that small children cannot open.
Store at room temperature between 15 and 25 degrees C (59 and 77 degrees F). Protect from light. Throw away any unused medicine after the expiration date.

NOTE: This information is not intended to cover all possible uses, precautions, interactions, or adverse effects for this drug. If you have questions about the drug(s) you are taking, check with your health care professional.

[Revised: 05/18/2005]

Digoxin tablets or capsules

What are digoxin tablets or capsules?

DIGOXIN (Lanoxin®, Lanoxicaps®) is a cardiac glycoside that can help a weakened heart to function properly. Digoxin increases the strength of the heart muscle, helps to maintain a normal heart rhythm, and helps to remove excess water from the body. Digoxin can relieve symptoms of congestive heart failure, a condition that reduces the ability of the heart to pump enough blood through the body. These symptoms include swelling of the feet and legs, difficulty breathing, and extreme tiredness or weakness. It can also help to regulate heart rhythm problems. Generic digoxin tablets are available, but not generic digoxin capsules.

What should my health care professional know before I receive digoxin?

They need to know if you have any of these conditions:
•heart disease
•heart rhythm disorders such as slow heart rate or heart block, sick sinus syndrome, ventricular arrhythmias, Wolff-Parkinson-White syndrome, or Adams-Stokes syndrome
•kidney disease
•liver disease
•lung disease
•over- or under-active thyroid
•recent heart attack
•too much calcium, potassium, or magnesium in the body
•an unusual or allergic reaction to digoxin, other medicines, foods, dyes, or preservatives
•pregnant or trying to get pregnant
•breast-feeding

How should I take this medicine?

Take digoxin tablets or capsules by mouth. Follow the directions on the prescription label. Swallow the tablets or capsules with a drink of water. It is best to take digoxin on an empty stomach, at least 1 hour before, or 2 hours after meals. Take your doses at regular intervals. Do not take your medicine more often than directed.
Contact your pediatrician or health care professional regarding the use of this medicine in children. Special care may be needed. Do not administer adult preparations to children.
Elderly patients over 65 years old may have a stronger reaction to this medicine and may need smaller doses.

What if I miss a dose?

If you miss a dose, take it as soon as you can (if you only take one dose a day, not more than 12 hours since your dose was due). If it is almost time for your next dose, take only that dose. Do not take double or extra doses.

What drug(s) may interact with digoxin?

•acarbose
•agents used to treat cancer
•alprazolam, diazepam
•amphotericin B
•antacids
•barbiturate medicines for inducing sleep or treating seizures (convulsions)
•beta blockers, often used for high blood pressure or heart problems
•calcium, magnesium, or potassium salts
•captopril
•certain medicines used to decrease cholesterol (cholestyramine, colestipol, atorvastatin, fluvastatin, simvastatin)
•clarithromycin or erythromycin
•cyclosporine
•diet pills (stimulants) or drugs used to control weight
•diltiazem
•entecavir
•felodipine
•gatifloxacin
•herbal products such as flaxseed, ginger, ginseng, hawthorn, St. John's wort
•hormones such as prednisone or cortisone
•indomethacin
•medicine for colds and breathing difficulties
•medicines to control heart rhythm (dofetilide, amiodarone, sotalol, and others)
•metformin
•neomycin
•omeprazole
•phenytoin
•psyllium
•quinine
•rabeprazole
•rifampin
•sevelamer
•sodium polystyrene sulfonate
•spironolactone

•St. John's wort
•succinylcholine
•sulfasalazine
•tetracycline antibiotics (doxycycline, tetracycline)
•thyroid hormones
•tramadol
•trimethoprim
•verapamil
•water pills (diuretics)
Tell your prescriber or health care professional about all other medicines you are taking, including non-prescription medicines, nutritional supplements, or herbal products. Also tell your prescriber or health care professional if you are a frequent user of drinks with caffeine or alcohol, if you smoke, or if you use illegal drugs. These may affect the way your medicine works. Check with your health care professional before stopping or starting any of your medicines.

What side effects may I notice from taking digoxin?
Side effects that you should report to your prescriber or health care professional as soon as possible:
•anxiousness or nervousness
•changes in color vision (more yellow color), blurred vision, eyes sensitive to light, light flashes, or halos around bright lights
•changes in behavior, mood, or mental ability
•chest pain or palpitations
•confusion
•diarrhea, or constipation
•dizziness or drowsiness
•fainting spells
•fast heartbeat (more likely in children)
•headache
•irregular, slow heartbeat (less than 50 beats per minute)
•loss of appetite
•nausea, vomiting
•skin rash or itching
•stomach pain
•tingling or numbness in the hands or feet
•unusual bruising, or pinpoint red spots on the skin
•weakness or tiredness
Side effects that usually do not require medical attention (report to your prescriber or health care professional if they continue or are bothersome):
•breast enlargement in men and women
•sexual problems such as impotence

What should I watch for while taking digoxin?
Visit your prescriber or health care professional for regular checks on your progress. Do not stop taking your digoxin without your prescriber's advice, even if you feel better. Do not change the brand you are taking, other brands may affect you differently.
Check your heart rate (pulse) and blood pressure regularly while you are taking digoxin. Ask your prescriber or health care professional what your heart rate and blood pressure should be, and when you should contact him or her. Your prescriber or health care professional also may schedule regular blood tests and electrocardiograms to check your progress.
Digoxin tablets are easily confused with other look-alike tablets. This can have serious consequences. If you take other tablets that look similar, ask your pharmacist how to avoid mix-ups.
Watch your diet. Less digoxin may be absorbed from the stomach if you have a diet high in bran fiber.
If you are going to have surgery, tell your prescriber or health care professional that you are taking digoxin.
Do not take antacids, or treat yourself with non-prescription medicines for pain, allergies, coughs or colds, without advice from your prescriber or health care professional. You will be able to take some of these medicines if you space doses several hours apart.

Where can I keep my medicine?
Keep out of the reach of children in a container that small children cannot open.
Store at room temperature between 15 and 25 degrees C (59 and 77 degrees F). Protect from light. Throw away any unused medicine after the expiration date.

NOTE: This information is not intended to cover all possible uses, precautions, interactions, or adverse effects for this drug. If you have questions about the drug(s) you are taking, check with your health care professional.

[Revised: 05/18/2005]

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Furosemide
Delone™ | Lasix®
Classification:
- Cardiovascular Agents
  - Antihypertensive Agents
    - Diuretics
- Electrolytic and Renal Agents
  - Diuretics
    - Loop diuretics

Description, Mechanism of Action, Pharmacokinetics

Description: Furosemide is a sulfonamide-derived loop diuretic used in the management of edema associated with congestive heart failure, cirrhosis, and renal disease, including the nephrotic syndrome. Other uses include mild to moderate hypertension and as an adjunct in hypertensive crisis and acute pulmonary edema. Furosemide is also useful in treating hypercalcemia, although it is not FDA approved for this indication. Furosemide is effective in managing edema associated with congestive heart failure, and it may be useful in patients who are unresponsive to other diuretics or who have severe renal impairment. Furosemide was approved by the FDA in 1966.

Mechanism of Action: Furosemide is a loop diuretic that acts to inhibit the reabsorption of sodium and chloride in the ascending

limb of the loop of Henle by interfering with the chloride-binding of the Na+/K+/2Cl- cotransport system, altering electrolyte transfer in the proximal tubule. A profound diuresis results from the increased urinary excretion of sodium, chloride, potassium, and hydrogen ions. In addition, furosemide increases the excretion of calcium, magnesium, bicarbonate, ammonium, and phosphate. The diuresis caused by furosemide can lead to increased aldosterone production, resulting in increased sodium resorption, and increased potassium and hydrogen excretion. Excessive loss of these electrolytes can lead to metabolic alkalosis.
Furosemide's effectiveness is independent of the acid-base status of the patient. Renal vasodilation occurs following administration of furosemide; renal vascular resistance decreases, and renal blood flow is enhanced. Reduced peripheral vascular resistance and increased peripheral venous capacitance also occur, and the subsequent decrease in left ventricular filling pressure may contribute to the drug's beneficial effect in patients with congestive heart failure. Initially, diuretics lower blood pressure by causing hypovolemia (decreased plasma and extracellular fluid), a temporary increase in glomerular filtration rate, and a decreased cardiac output. Cardiac output eventually returns to normal, but peripheral resistance is now reduced, resulting in lower blood pressure. In general, diuretics worsen left ventricular hypertrophy (LVH) and glucose tolerance. In addition, loop diuretics have been associated with hypercholesterolemia and hypertriglyceridemia.
Pharmacokinetics: Furosemide is administered orally and intravenously. It is absorbed erratically following an oral dose, and food will delay this absorption but will not alter the diuretic response. Diuresis generally begins 30 to 60 minutes after oral administration and about 5 minutes after IV administration. The drug is 95% plasma protein-bound, crosses the placenta, and appears in breast milk.
Furosemide undergoes minimal metabolism in the liver, with 50—80% of a dose excreted in the urine within 24 hours. The remainder of the drug is eliminated through nonrenal mechanisms including excretion in the feces. In patients with significant renal impairment, nonrenal elimination can increase to 98%. The half-life of furosemide is approximately 0.5—1 hour.
•***Special Populations:*** In neonates and in patients with renal and hepatic impairment, half-lives are prolonged. Larger doses may be necessary in patients with renal impairment.

Description, Mechanism of Action, Pharmacokinetics last revised 8/23/2006 8:11:00 PM

Indications

- ascites†
- edema
- heart failure
- hypercalcemia†
- hypertension
- hypertensive emergency†
- hypertensive urgency†
- nephrotic syndrome
- pulmonary edema

† non-FDA-approved indication

Dosage

For the treatment of peripheral edema, or edema associated with heart failure or nephrotic syndrome:

Oral dosage:

Adults: Initially, 20—80 mg PO as a single dose, which may be repeated in 6—8 hours. Titrate doses upward in 20—40 mg increments. The usual dosage is 40—120 mg/day PO. Maximum dosage is 600 mg/day PO.
Elderly: See adult dosage. Elderly patients may be more sensitive to the effects of the usual adult dosage.
Children and infants: Initially, 1—2 mg/kg PO every 6—12 hours. Maximum dosage is 6 mg/kg/dose PO.
Premature neonates: Doses of 1—4 mg/kg PO, given 1—2 times daily, have been used. Bioavailability is poor.

Parenteral dosage:

Adults: Initially, 20—40 mg IV or IM, increasing by 20 mg every 2 hours as needed to attain clinical response. IV doses should be given slowly. A maximum infusion rate of 4 mg/min has been recommended for patients receiving IV doses greater than 120 mg or for patients with cardiac or renal failure.[52]
Elderly: See adult dosage. Elderly patients may be more sensitive to the effects of the usual adult dosage.
Children and infants: 1—2 mg/kg IV or IM every 6—12 hours. Maximum dosage is 6 mg/kg/dose IV or IM.
Premature neonates: 1—2 mg/kg IV or IM every 12—24 hours.

For adjunctive treatment of acute pulmonary edema:

Parenteral dosage:

Adults: Initially, 40 mg IV injected slowly; then 80 mg IV injected slowly in 2 hours if needed.
Elderly: See adult dosage. Elderly patients may be more sensitive to the effects of the usual adult dosage.
Children: Initially, 1—2 mg/kg IV or IM, every 6—12 hours. Maximum dosage is 6 mg/kg/dose.
Premature neonates: 1—2 mg/kg IV or IM every 12—24 hours.

For the treatment of hypertension:

Oral dosage:

Adults: Initially, 40 mg PO twice daily. Adjust dosage according to response. Alternative dosage regimen is 10—20 mg PO twice daily, then adjusting dosage according to response. Maximum dosage is 600 mg/day PO.
Elderly: See adult dosage. Elderly patients may be more sensitive to the effects of the usual adult dosage.
Children and infants: Initially, 1—2 mg/kg PO every 6—12 hours. Maximum dosage is 6 mg/kg/dose PO.
Premature neonates: Doses of 1—4 mg/kg PO, given 1—2 times daily, have been used. Bioavailability is poor.

For adjunctive treatment of hypertensive urgency† or hypertensive emergency†:

Intravenous dosage:

Adults: Doses of 40—80 mg IV have been used in patients with normal renal function.
Elderly: See adult dosage. Elderly patients may be more sensitive to the effects of the usual adult dosage.

For adjunctive treatment of edema in patients with acute or chronic renal failure:

Oral dosage:

Adults: Initially, 80 mg PO once daily, increasing dose in increments of 80—120 mg/day until desired clinical response. For immediate diuresis, 320—400 mg PO once daily has been suggested.

Elderly: See adult dosage. Elderly patients may be more sensitive to the effects of the usual adult dosage.
Intravenous dosage:
Adults: Initially, 100—200 mg IV. Traditionally, it has been recommended that doses can be doubled every 2—24 hours until desired clinical response, however, most clinicians would probably consider 600—800 mg IV a maximum dose and either administer a different loop-active agent, or add a second agent in combination with furosemide. A maximum infusion rate of 4 mg/min has been recommended for patients receiving doses greater than 120 mg or for patients with cardiac or renal failure.[52]
Elderly: See adult dosage. Elderly patients may be more sensitive to the effects of the usual adult dosage.
For the acute treatment of hypercalcemia† associated with neoplastic disease in combination with intravenous saline:
Parenteral dosage:
Adults: Initially, 80—100 mg IV or IM with the dose being repeated every 1—2 hours as needed based on clinical response. Less severe cases may use smaller doses every 2—4 hours. Saline administration should begin before the first dose of furosemide is administered to avoid volume contraction which may limit the desired calciuric response.
Elderly: See adult dosage. Elderly patients may be more sensitive to the effects of the usual adult dosage.
Neonates, infants, and children: Initially, 25—50 mg IV or IM. The dose may be repeated every 4 hours as needed based on clinical response. Saline administration should begin before the first dose of furosemide is administered to avoid volume contraction which may limit the desired calciuric response.
For the treatment of ascites† in combination with spironolactone or amiloride:
Oral dosage:
Adults: Initially, 40 mg PO once daily, in the morning in combination with spironolactone; dosage may be increased after 2—3 days if no clinical response.[602]
Elderly: See adult dosage. Elderly patients may be more sensitive to the effects of the usual adult dosage.
Maximum Dosage Limits:
•*Adults:* 600 mg/day PO or 6 g/day IV infusion. Up to 4 g/day PO has been given to treat chronic renal failure.
•*Elderly:* 600 mg/day PO or 6 g/day IV infusion. Up to 4 g/day PO has been given to treat chronic renal failure.
•*Adolescents:* 6 mg/kg/dose PO.
•*Children:* 6 mg/kg/dose PO.
•*Infants:* 6 mg/kg/dose PO.
•*Neonates:* No maximum dosage information is available.
Patients with hepatic impairment:
No specific dosage adjustment is needed; see the dosage for the treatment of ascites. Diuretics should be used with caution in patients with hepatic disease since minor alterations of fluid and electrolyte balance may precipitate hepatic coma.
Patients with renal impairment:
No specific dosage adjustments are recommended. Higher doses with extended dosage intervals may be effective in patients with end-stage renal disease (ESRD).
†non-FDA-approved indication

Indications...Dosage last revised 8/23/2006 7:52:00 PM

Administration Guidelines

NOTE: In patients with acute or chronic renal failure, larger doses of oral or IV furosemide have been used.
NOTE: The risk of ototoxicity increases with larger doses and/or more rapid parenteral administration of furosemide.[51] A maximum infusion rate of 4 mg/min has been recommended for patients receiving IV doses greater than 120 mg or for patients with cardiac or renal failure.[52]
NOTE: Half-life in neonates will be prolonged. Increasing the dosage interval is suggested to help prevent toxicity. Elderly patients may be more sensitive to the effects of normal adult doses.
Oral Administration
•Administer with meals to minimize indigestion or GI irritation. If patient has difficulty swallowing, the tablets may be crushed.
Parenteral Administration
•The maximum concentration for administration is 10 mg/ml.
•Visually inspect parenteral products for particulate matter and discoloration prior to administration whenever solution and container permit.
Intramuscular injection:
•No dilution necessary.
•Inject deeply into a large muscle. Aspirate prior to injection to avoid injection into a blood vessel.
Direct IV injection:
•Inject each 20 mg slowly IV over 1—2 minutes.
Intermittent IV infusion:
•Dilute in NS, lactated Ringer's, or D5W injection solution; adjust pH to greater than 5.5 when necessary.
•Infuse intravenously at a rate not to exceed 4 mg/minute in adults or 0.5 mg/kg/minute in children.

Administration last revised 7/1/2002

Contraindications/Precautions

- *anuria*
- acid/base imbalance
- acute myocardial infarction
- breast-feeding
- hyponatremia
- hypotension
- hypovolemia
- metabolic alkalosis

- diabetes mellitus
- diarrhea
- eclampsia
- elderly
- electrolyte imbalance
- gout
- hearing impairment
- heart failure
- hepatic disease
- hyperglycemia
- hyperuricemia
- hypocalcemia
- hypochloremia
- hypokalemia
- hypomagnesemia
- neonatal prematurity
- orthostatic hypotension
- pancreatitis
- preeclampsia
- pregnancy
- renal disease
- renal failure
- renal impairment
- sulfonamide hypersensitivity
- sympathectomy
- syncope
- systemic lupus erythematosus (SLE)
- thiazide diuretic hypersensitivity
- ventricular arrhythmias

• *Absolute contraindications are in italics.*

Furosemide is contraindicated in patients with known hypersensitivity to this drug. Because cross-sensitivity with furosemide has rarely been observed, bumetanide can be substituted for furosemide in patients allergic to furosemide.[3521] [5351] The risk of an allergic reaction after administration of a loop diuretic in a patient with sulfonamide hypersensitivity or thiazide diuretic hypersensitivity appears to be very low.[53] [178] Although furosemide is a sulfonamide derivative, sulfonamide cross-sensitivity has been rarely documented.[53] [3600] [9205] A case report, published in 1987, documents an anaphylactic reaction to IV furosemide in a patient who was subsequently skin-tested with furosemide, bumetanide, ethacrynic acid, chlorothiazide, and sulfamethoxazole-trimethoprim. A positive reaction was elicited to all except ethacrynic acid.[3520] This case documents hypersensitivity to both furosemide and bumetanide in a patient with sulfonamide hypersensitivity. Prior to this, neither the FDA nor the manufacturer of furosemide (Lasix®) had received any reports of cross-sensitivity between furosemide and sulfonamide antibiotics.[178] [3520] Furosemide does not contain the N4-aromatic amine or the N1-substituent which are present in sulfonamide antibiotics.[9204] Non-arylamine sulfonamide derivatives, such as loop diuretics, have been proposed to have a lower risk of allergic reactions in patients with sulfonamide allergy, presumably due to lack of an arylamine group at the N4 position (a proposed structural site of action for sulfonamide allergy).[9204] [9205] One large retrospective cohort study has reported that in patients with the presence of an allergic reaction after exposure to a sulfonamide antibiotic, 9.9% had an allergic reaction after receiving a non-antibiotic sulfonamide derivative, while in patients who lacked an allergic reaction after sulfonamide antibiotic exposure, 1.6% had an allergic reaction after administration of a non-antibiotic sulfonamide derivative (adjusted odds ratio 2.8; 95% CI, 2.1—3.7).[9206] A causal relationship between sulfonamide hypersensitivity and allergic reactions with non-arylamine sulfonamide derivatives has not been definitively established and remains controversial.[53] [3600] [9204] [9205] In general, patients with a documented sulfonamide allergy are considered to be predisposed for development of allergic drug reactions.[9204] [9206]

Preexisting electrolyte imbalance such as severe hyponatremia, hypokalemia, hypocalcemia, hypochloremia, or hypomagnesemia should be corrected before initiating furosemide therapy. Loop diuretics may induce metabolic alkalosis associated with hypokalemia and hypochloremia; this acid/base imbalance is effectively treated with potassium chloride replacement.[9372] [9373] Furosemide-induced fluctuations in serum electrolyte concentrations can occur rapidly and precipitate hepatic encephalopathy and coma in susceptible patients. Therefore, furosemide should be used with caution in patients with hepatic disease such as cirrhosis. Furosemide is contraindicated in patients with hepatic coma until this condition is corrected.
Blood and urine glucose levels should be assessed in patients with diabetes mellitus or hyperglycemia during treatment with furosemide; loop diuretics can impair glucose tolerance.
Patients with ventricular arrhythmias, heart failure, potassium-losing nephropathy, aldosterone excess, or diarrhea should be monitored closely since furosemide-induced hypokalemia can exacerbate these conditions.
Excessive diuresis with furosemide should be avoided in patients with acute myocardial infarction due to the risk of precipitating shock.
Furosemide should not be used in *anuria*. It should be used cautiously in any patient with renal disease such as severe renal impairment or renal failure. Drug-induced hypovolemia can precipitate azotemia in these patients. Furosemide is an effective diuretic for many patients with renal impairment. Renal impairment may reduce clearance and warrant the use of higher doses with extended dosing intervals. Furosemide may be less effective in these patients and delayed excretion of drug may increase the risk of toxicity.
Patients with pre-existing hypovolemia or hypotension should have their condition corrected before furosemide is initiated.
Orthostatic hypotension may occur during treatment with loop diuretics.[9371] Excessive hypotension can result in syncope. The antihypertensive effects of diuretics may be enhanced in patients predisposed for orthostatic hypotension, including the post-sympathectomy patient. Greater sensitivity to the hypotensive and diuretic effects of furosemide is possible in elderly patients. Controlled clinical studies of furosemide did not include sufficient numbers of subjects aged 65 or older to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for elderly patients should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. Furosemide is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection and it may be useful to monitor renal function.
Furosemide has been reported to activate or exacerbate systemic lupus erythematosus (SLE), although the association is less certain than with procainamide or other drugs.
Since loop diuretics can reduce the clearance of uric acid, patients with gout or hyperuricemia can have exacerbations of their disease.
High doses and accumulation of furosemide may cause ototoxicity (see Adverse Reactions). Furosemide should be used with caution in patients with hearing impairment. The recommended rate of infusion should not be exceeded when IV doses are administered (see Dosage).

Furosemide has been reported to cause pancreatitis. It should be used with caution in patients with a history of pancreatitis.
Because no well-controlled studies have been performed with furosemide in pregnant women, it is classified as pregnancy category C. After the first trimester, it has been used for edema and hypertension. However, it is important to note that diuretics are generally not recommended for the treatment of pregnancy-induced hypertension (preeclampsia, eclampsia) since they do not alter the course of toxemia and may exacerbate maternal hypovolemia associated with this condition.
Because furosemide appears in breast milk, caution should be exercised when furosemide is administered to a breast-feeding mother. In addition, diuretics such as furosemide may suppress lactation.
Patients with neonatal prematurity who receive furosemide in the first few weeks of life can have an increased risk of persistent patent ductus arteriosus.

Contraindications last revised 9/12/2006 5:27:00 PM

Drug Interactions

- Alendronate
- Aminoglycosides
- Amiodarone
- Amphotericin B
- Angiotensin-converting enzyme inhibitors (ACE inhibitors)
- Antidiabetic Agents
- Antihypertensive Agents
- Arsenic Trioxide
- Beta-agonists
- Cardiac glycosides
- Cholestyramine
- Cisplatin
- Colestipol
- Corticosteroids
- Dofetilide
- Ephedra, Ma Huang
- Ethacrynic Acid
- Ethanol
- Ginseng, Panax ginseng
- Hawthorn, Crataegus laevigata
- Horse Chestnut, Aesculus hippocastanum
- Ibandronate
- Levomethadyl
- Lithium
- Metformin
- Methazolamide
- Metolazone
- Monoamine oxidase inhibitors (MAOIs)
- Neuromuscular blockers
- Nitroglycerin
- Nonsteroidal antiinflammatory drugs (NSAIDs)
- Norepinephrine
- Palonosetron
- Pamidronate
- Phenytoin
- Potassium-sparing diuretics
- Radiopaque Contrast Agents
- Risperidone
- Salicylates
- Sodium Phosphate Monobasic Monohydrate; Sodium Phosphate Dibasic Anhydrous
- Sucralfate
- Zoledronic Acid

Electrolyte disturbances (e.g., hypokalemia, hypomagnesemia, hypercalcemia) may occur with administration of loop diuretics, including furosemide.[5159] Hypokalemia increases the potential for proarrhythmic effects (e.g., torsade de pointes) due to arsenic trioxide, cardiac glycosides, dofetilide [4947], or levomethadyl. Potassium levels should be within the normal range prior and during administration of these agents. In the absence of electrolyte imbalances, furosemide and these agents can be used together safely.
Concomitant use of metolazone with a loop diuretic can cause severe electrolyte loss.[6135] Metolazone should only be used in combination with furosemide in patients who are refractory to loop diuretics alone. Close monitoring of serum electrolytes and cardiac function is advised. In patients with creatinine clearances > 30 ml/min, the combination of a loop diuretic with a thiazide diuretic may also lead to profound fluid and electrolyte loss. Thus, furosemide should be used very cautiously in combination with either metolazone or thiazide diuretics. Conversely, potassium-sparing diuretics (amiloride, spironolactone, and triamterene) can counteract furosemide-induced hypokalemia.[5159] These agents have been used as therapeutic alternatives to potassium supplements in patients receiving loop diuretics. In addition, amiloride and triamterene may counteract the magnesium wasting actions of furosemide.
Furosemide may cause hyperglycemia and glycosuria in patients with diabetes mellitus,[5159] probably due to diuretic-induced hypokalemia. Because of this, a potential pharmacodynamic interaction exists between furosemide and all antidiabetic agents. This interference can lead to a loss of diabetic control, so diabetic patients should be monitored closely. Also, an pharmacokinetic interaction has been noted between furosemide and metformin. In pharmacokinetic studies, furosemide increased the plasma and blood maximum concentrations of metformin by 22% and blood AUC by 15%, without any significant change in metformin renal clearance.[5280] On the other hand, metformin decreased furosemide plasma and blood maximum concentrations by 31% and 12%, respectively, than when administered alone. Furosemide's terminal half-life was also decreased by 32% without any significant change in furosemide renal clearance.
Additive hypotension is possible if furosemide used in combination with any other antihypertensive agents,[5159] including drugs such as nitroglycerin. Hyponatremia or hypovolemia predisposes patients to acute hypotensive episodes following initiation of ACE inhibitor therapy. While ACE inhibitors and loop diuretics are routinely administered together in the treatment of heart failure, if an ACE inhibitor is to be administered to a patient receiving furosemide, initial doses should be conservative.
Ethanol interacts with antihypertensive agents by potentiating their hypotensive effect.[5944] Ethanol, since it also possesses diuretic properties, should be taken in small quantities in patients receiving loop diuretics. The diuretic properties may be additive, leading to dehydration in some patients.
Fludrocortisone and glucocorticoids with mineralocorticoid activity (e.g., cortisone, hydrocortisone) can cause sodium retention and hypokalemia.[3085] Additive hypokalemia may occur when loop diuretics are coadministered with other corticosteroids or

corticotropin, ACTH.[5159] Concomitant administration of furosemide with any of these agents can lead to significant hypokalemia and/or hypomagnesemia. While it is possible to use loop diuretics with these agents safely, close monitoring of serum potassium and serum magnesium should occur in these patients.
In a study of 6 healthy volunteers, concurrent administration of cholestyramine with oral furosemide reduced the bioavailability of furosemide by 95% and reduced the diuretic response by 77%.[6315] Concomitant administration with colestipol reduced furosemide bioavailability by 80% and the diuretic response by 58%.[6315] Although it was not evaluated in this study, staggering the times of administration (e.g., giving furosemide either 2 hours before or 6 hours after cholestyramine or colestipol) may alleviate this pharmacokinetic interaction.
Lithium renal clearance may decrease in patients receiving diuretics such as furosemide.[5159] [5385] Nevertheless, careful monitoring of lithium serum concentrations is recommended when these drugs are administered together as concomitant administration could result in lithium toxicity.
NSAIDs can cause sodium and fluid retention as well as increase peripheral vascular resistance. NSAIDs can decrease the diuretic, natriuretic, and antihypertensive actions of diuretics, possibly through inhibition of renal prostaglandin synthesis.[805] [5159] Concomitant administration of NSAIDs with diuretics can also increase the risk for renal insufficiency secondary to decreased renal blood flow. Patients should be monitored for changes in the effectiveness of their diuretic therapy and for signs and symptoms of renal impairment. Among NSAIDs, indomethacin, naproxen, and piroxicam may have the greatest pressor effect, while the effects of sulindac and nabumetone may be significantly less.
Concomitant use of medicines with potential to alter renal perfusion or function such as furosemide may increase the risk of acute phosphate nephropathy in patients receiving sodium phosphate monobasic monohydrate; sodium phosphate dibasic anhydrous.[8973] [8974]
Salicylates may decrease the diuretic, natriuretic, and antihypertensive actions of diuretics, possibly through inhibition of renal prostaglandin synthesis.[6136] Patients receiving furosemide and salicylates should be monitored for changes in the effectiveness of their diuretic therapy.[5159]
Concurrent use of cisplatin and other agents known to be ototoxic (e.g., loop diuretics) may increase the risk of drug-induced ototoxicity, but confirmatory data are not available. Usually, reports indicate that furosemide ototoxicity is associated with rapid injection, severe renal impairment, higher than recommended furosemide dosages or infusion rates, or concomitant therapy with other ototoxic drugs.[51] [5159] Additive effects of cisplatin and loop diuretics on renal parameters and electrolyte balance should also be considered. Saline hydration and diuretic use are common during cisplatin therapy to manage hydration status. If furosemide and cisplatin are used together, it is prudent to monitor renal function parameters and serum electrolyte concentrations during co-therapy. Audiologic monitoring may be advisable during high dose therapy or therapy of long duration, when hearing loss is suspected, or in selected risk groups.
The risk of ototoxicity or nephrotoxicity secondary to aminoglycosides may be increased by the addition of concomitant therapies with similar side effects, including loop diuretics.[5159] Ototoxicity from furosemide or other loop diuretics, while uncommon, can be a transient or permanent side effect of significance. Ototoxicity is best documented with the loop diuretics ethacrynic acid [5138] and furosemide [5159], but may also occur with either bumetanide [5351] or torsemide [6091]. The exact mechanism by which furosemide or other loop diuretics produce ototoxicity is unknown. Usually, reports indicate that furosemide ototoxicity is associated with rapid injection, severe renal impairment, higher than recommended dosages or infusion rates, or concomitant therapy with aminoglycoside antibiotics, ethacrynic acid, or other ototoxic drugs.[51] [52] [5159] Additionally, loop diuretics may cause volume depletion and allow for the concentration of aminoglycosides within the nephron; concurrent therapy has been considered a risk-factor for aminoglycoside-induced nephrotoxicity.[4921] Some experts, based on data from controlled trials, do not consider administration of furosemide a major risk for aminoglycoside-induced auditory or nephro-toxicity.[5180] However, caution is advised and risk should be determined individually. If loop diuretics and aminoglycosides are used together, it would be prudent to monitor renal function parameters, serum electrolytes, and serum aminoglycoside concentrations during therapy. Audiologic monitoring may be advisable during high dose therapy or therapy of long duration, when hearing loss is suspected, or in selected risk groups (e.g., neonates).
Amphotericin B-induced hypokalemia can result in interactions with other drugs.[3085] Concurrent use of amphotericin B with loop diuretics can cause additive hypokalemia or hypomagnesemia due to renal potassium and magnesium wasting. It is prudent to monitor renal function parameters and serum electrolyte concentrations during co-therapy with loop diuretics and drugs which induce hypokalemia.[3085] [5159]
Furosemide-induced hypokalemia [5351] can potentiate neuromuscular blockade with nondepolarizing neuromuscular blockers. In addition, furosemide may antagonize the skeletal muscle relaxing effect of tubocurarine and can potentiate neuromuscular blockade following succinylcholine administration.[5149]
Limited clinical data suggest that phenytoin, and perhaps other anticonvulsants, can interfere with the clinical response to furosemide. Phenytoin has been shown to decrease furosemide oral bioavailability by up to 50% without affecting its systemic clearance.
Hawthorn, Crataegus laevigata may lower peripheral vascular resistance.[4713] Hawthorn use in combination with antihypertensive agents may lead to additional reductions in blood pressure in some individuals. Patients receiving hawthorn concurrently with antihypertensive medications should receive periodic blood pressure monitoring.
Drug interactions with Horse chestnut, Aesculus hippocastanum are not well documented. Escin, an active saponin in the horse chestnut seed, appears to have weak diuretic activity, but the exact mechanism is not clear.[2728] The effect appears to be dose-dependent and may be additive with traditional diuretics.
Ginseng may decrease the effectiveness of loop diuretics. One case report described a temporal relationship between the use of ginseng and resistance to furosemide therapy, resulting in edema, hypertension, and hospitalization on 2 separate occasions.[2976] Other nutritional products were taken concurrently by the patient involved and were not specified in the report. A mechanism of action or causal relationship has not been definitively established.
Furosemide can cause decreased arterial responsiveness to vasopressor amines (e.g., norepinephrine), but the effect is not sufficient to preclude their coadministration.[5159]
Hypokalemia and/or ECG changes associated with loop diuretics [5159] can be acutely worsened by beta-agonists. Hypokalemia due to beta-agonists appears to be dose-related.[5262] Caution is advised when loop or thiazide diuretics are coadministered with high doses of beta-agonists; potassium levels may need to be monitored.
Loop diuretics may increase the risk of hypokalemia if used concurrently with methazolamide.[5023] Monitor serum potassium levels to determine the need for potassium supplementation and/or alteration in drug therapy. There may also be an additive diuretic or hyperuricemic effect.
Ephedra, Ma huang can antagonize all types of antihypertensive agents. Blood pressure should be monitored closely in patients using

antihypertensive agents with ephedra.[3490]
Palonosetron may rarely cause prolongation of the QT interval. A potassium- and/or magnesium-depleted state may increase the risk of cardiac arrhythmias; use loop diuretics cautiously with palonosetron and monitor serum electrolyte levels frequently, if indicated.[5148]
According to the manufacturer for furosemide, simultaneous administration of sucralfate and furosemide may reduce its natriuretic and antihypertensive effects.[5159] Patients receiving both drugs should be observed closely to determine if the desired diuretic and/or antihypertensive effect of furosemide is achieved. The intake of furosemide and sucralfate is recommended to be separated by at least two hours.[5159]
Because patients should be well-hydrated prior to the administration of contrast media, loop diuretics such as furosemide that cause intravascular volume depletion might increase the risk of nephrotoxicity when using radiopaque contrast agents. In addition, furosemide plus normal saline have been evaluated for the prevention of contrast induced nephropathy; in one retrospective review, the incidence of contrast-induced nephropathy in the furosemide plus saline group was almost four times that of the saline only group (40% versus 11%, respectively). Other studies have shown no benefit with combination therapy.[5433]
Because both loop diuretics and intravenously administered bisphosphonates (i.e., alendronate, ibandronate, pamidronate, and zoledronic acid) can cause a decrease in serum calcium, caution is advised when used concomitantly in the treatment of hypercalcemia of malignancy in order to avoid hypocalcemia.[6318] [5159] In patients with hypercalcemia of malignancy, the initial treatment typically includes the use of loop diuretics, in combination with saline hydration, however, diuretic therapy should not be employed prior to correction of hypovolemia and dehydration.
Additive hypotensive effects may be seen when monoamine oxidase inhibitors (MAOIs) are combined with antihypertensives.[4673] [6398] Careful monitoring of blood pressure is suggested during concurrent therapy of MAOIs with diuretics. Patients should be instructed to rise slowly from a sitting position, and to report syncope or changes in blood pressure or heart rate to their health care provider during concurrent use of an MAOI and furosemide.
Two of four placebo-controlled trials showed that elderly patients with dementia-related psychosis receiving the combination of risperidone and furosemide had a higher incidence of mortality than those receiving either agent alone.[5144] The mechanism for this adverse association is unknown. Until further information becomes available, caution should be exercised when the combined use of risperidone and furosemide is necessary in those with dementia-related psychosis.
Use caution when coadministering amiodarone with drugs which may induce hypokalemia and/or hypomagnesemia including loop diuretics.[3085] [6115] Since antiarrhythmic drugs may be ineffective or may be arrhythmogenic in patients with hypokalemia, any potassium or magnesium deficiency should be corrected before instituting and during amiodarone therapy.[4950]

Interactions last revised 4/2/2007 12:54:00 PM

Adverse Reactions

- abdominal pain
- acute generalized exanthematous pustulosis (AGEP)
- agranulocytosis
- anemia
- anorexia
- aplastic anemia
- azotemia
- blurred vision
- cholestasis
- constipation
- diarrhea
- dizziness
- headache
- hearing loss
- hypercholesterolemia
- hyperglycemia
- hypertriglyceridemia
- hyperuricemia
- hypocalcemia
- hypochloremia
- hypokalemia
- hypomagnesemia
- hyponatremia
- hypotension
- hypovolemia
- interstitial nephritis
- jaundice
- leukopenia
- metabolic alkalosis
- nausea/vomiting
- oliguria
- orthostatic hypotension
- pancreatitis
- paresthesias
- photosensitivity
- polyuria
- syncope
- thrombocytopenia
- tinnitus

Polyuria during furosemide therapy can cause excessive fluid loss and dehydration. This results in hypovolemia and electrolyte imbalance. Large doses of furosemide and restricted sodium intake increases this possibility. Hypovolemia can lead to orthostatic hypotension, syncope, and hemoconcentration, potentially more serious in chronic cardiac or geriatric patients. Close monitoring is necessary to check for hyponatremia, hypokalemia, hypocalcemia, hypochloremia, and hypomagnesemia. Symptoms of fluid or electrolyte imbalance are: lassitude, mental confusion, fatigue, dizziness, muscle cramps, headache, paresthesias, tachycardia, arrhythmia, thirst, anorexia, nausea, or vomiting. Hyperaldosteronism, secondary to cirrhosis or nephrosis, can predispose patients to developing potassium depletion when furosemide is administered. Hypokalemia and hypochloremia can cause metabolic alkalosis, particularly in patients with other conditions that cause potassium loss including vomiting, diarrhea, or excessive sweating. Volume loss secondary to loop diuretic therapy can also cause oliguria and/or azotemia (elevation of BUN), which may lead to a risk factor for nephrotoxicity in selected patients or an allergic interstitial nephritis.
Furosemide occasionally can cause hyperuricemia. This condition may be associated with dehydration and should be avoided, especially in patients with renal insufficiency or gout.
Ototoxicity, manifested as tinnitus and reversible or permanent hearing loss has occurred during furosemide therapy and is usually

associated with too rapid administration of large, parenteral doses. Ototoxicity increased proportionately as the rate of infusion of parenteral furosemide increased from 4 mg/min (no ototoxicity), to 5.6 mg/min (no ototoxicity), to 25 mg/min (9/15 patients developed reversible hearing loss), to 67 mg/min (10/10 patients developed tinnitus and deafness that persisted for 90 minutes).[51] It has been recommended that parenteral furosemide not be administered more rapidly than 4 mg/min.[52] Adverse otic effects occur more frequently in patients receiving other ototoxic agents (see Drug Interactions) or in those with severe renal impairment.

Furosemide can produce impaired glucose tolerance, glycosuria, and hyperglycemia. There have been occasional reports of precipitation of diabetes mellitus.

Diuretics, particularly thiazide and loop diuretics, have been shown to cause hypercholesterolemia, hypertriglyceridemia, as well as increased plasma concentrations of LDL. Some studies have suggested that these effects may decrease or cease with long-term therapy, and are not clinically important.

Adverse central nervous system effects associated with furosemide therapy include dizziness, lightheadedness, vertigo, headache, blurred vision, xanthopsia and paresthesias.

Adverse hematologic effects reported during furosemide therapy include anemia, hemolytic anemia, aplastic anemia, pancytopenia, leukopenia, neutropenia, thrombocytopenia, and agranulocytosis. Fever and weakness may result from blood dyscrasias.

Dermatitis and/or photosensitivity can occur during furosemide therapy. Patients who are sensitive to sulfonamides may also have a hypersensitivity reaction to furosemide. Systemic lupus erythematosus may be exacerbated or activated. Other hypersensitivity reactions reported are systemic vasculitis and necrotizing angiitis. Furosemide has been associated with acute generalized exanthematous pustulosis (AGEP). The nonfollicular, pustular, erythematous rash starts suddenly, is associated with fever above 38 degrees C, and is distinct from pustular psoriasis, although biopsy results in each reveal spongiform subcorneal pustules. Drugs are the main cause of AGEP. A period of 2—3 weeks after an inciting drug exposure appears necessary for a first episode of AGEP. Unintentional reexposure may cause a second episode within 2 days. Clinical presentation is diverse with cutaneous lesions beyond erythema and pustules present in half of the cases. For example, bullous lesions, edema, purpura, pruritus, and mucosal erosions are possible. The mean duration of the pustules is 9.7 days followed by an annular desquamation, as long as the causative drug or factor is discontinued. The physiopathological mechanisms of AGEP have not been determined but the pathological criteria of edema, leukocytoclastic vasculitis, eosinophil exocytosis, and keratinocyte focal necrosis are distinctive. Pustule confluence or very small pustules may lead a clinician to make an incorrect diagnosis of TEN, of drug-induced erythroderma, or of staphylococcal scalded skin syndrome.[4446]

Severe abdominal pain with nausea/vomiting may indicate pancreatitis which has been attributed to furosemide therapy. Other adverse gastrointestinal effects of furosemide include anorexia, constipation, and diarrhea. Furosemide may rarely cause jaundice due to cholestasis.

Adverse Reactions last revised 9/8/2006 4:27:00 PM

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Fosinopril
Monopril®
Classification:
- Cardiovascular Agents
  - Antihypertensive Agents
    - Angiotensin-converting enzyme inhibitors (ACE inhibitors)

Description, Mechanism of Action, Pharmacokinetics

Description: Fosinopril is an oral angiotensin-converting enzyme (ACE) inhibitor used in the treatment of hypertension. Fosinopril is a prodrug that is hydrolyzed by esterases to the active metabolite fosinoprilat. It is longer-acting than captopril or enalapril, which allows for once-daily administration. Its pharmacodynamic characteristics most closely resemble those of benazepril, quinapril, and ramipril, all of which are prodrugs. Neither fosinopril nor fosinoprilat contains a sulfhydryl group, which has implications regarding the drug's adverse reaction profile. Fosinopril (Monopril®) was approved by the FDA in May 1991. A generic version of fosinopril was approved by the FDA on November 25, 2003.

Mechanism of Action: Fosinoprilat, the active moiety of fosinopril, competes with angiotensin-converting enzyme (ACE) for the substrate angiotensin I, thereby blocking its conversion to angiotensin II. Angiotensin II is a potent vasoconstrictor and a negative feedback mediator for renin activity. Thus, when fosinopril lowers angiotensin II plasma levels, blood pressure decreases and plasma renin activity increases. In addition, baroreceptor reflex mechanisms are stimulated in response to the fall in blood pressure. Kininase II, identical to ACE, is an enzyme that degrades bradykinin, a potent vasodilator, to inactive peptides. Whether increased bradykinin levels play a part in the therapeutic effects of ACE inhibitors is presently unclear. Bradykinin-induced vasodilation is thought to be of secondary importance in the blood-pressure lowering effect of ACE inhibitors. A bradykinin mechanism may, however, contribute to ACE-inhibitor-induced angioneurotic edema.[570]
ACE-inhibiting drugs can act locally to reduce vascular tone by decreasing local angiotensin II-induced sympathetic and/or vasoconstrictive activity. Decreases in plasma angiotensin II levels also reduce aldosterone secretion, subsequently decreasing sodium and water retention. As antihypertensives, ACE inhibitors reduce LVH, do not worsen insulin resistance or hyperlipidemia, and do not cause sexual dysfunction.
Fosinopril causes arterial dilation, thereby lowering total peripheral vascular resistance. In hypertensive patients, blood pressure is decreased, with little or no change in heart rate, stroke volume, or cardiac output. Both standing and supine blood pressure are reduced following administration of fosinopril, and although symptomatic hypotension is rare, it may occur more often in patients who are hypovolemic or hyponatremic.
Pharmacokinetics: Fosinopril is administered orally and is absorbed slowly from the GI tract, with an absolute biovailability of

about 36%. Food slows the rate but not the extent of absorption. Hepatic metabolism is required to generate the active metabolite fosinoprilat; thus, peak concentrations occur in approximately 3 hours. After oral administration, noticeable cardiovascular effects begin within 1 hour, with peak reductions occurring after 2—6 hours. The hypotensive effects last approximately 24 hours, allowing for once-daily dosing. Fosinoprilat is approximately 99.4% bound to plasma proteins. Fosinopril pharmacokinetics are linear. About half of the absorbed dose of fosinopril (as parent drug and metabolites) is excreted in the urine and the remainder is excreted in the feces. After an oral dose of radiolabeled fosinopril, 75% of radioactivity in plasma is present as active fosinoprilat, 20—30% as a glucuronide conjugate of fosinoprilat, and 1—5% as a p -hydroxy metabolite of fosinoprilat. In rats, the p-hydroxy metabolite of fosinoprilat is as potent an inhibitor of ACE as fosinoprilat; whereas the glucuronide conjugate is devoid of ACE inhibitory activity. Fosinoprilat is eliminated approximately equally by the liver and kidney. The elimination half-life of fosinopril is about 11.5 hours in hypertensive patients with normal renal function; and the half-life is about 14 hours in patients with congestive heart failure.
•***Special Populations:*** Fosinoprilat clearance is decreased in patients with hepatic disease or end-stage renal disease, but not in the elderly or patients with mild to severe renal impairment (CrCl >= 10 ml/min). In patients with hepatic impairment, the extent of hydrolysis of fosinopril is not appreciably reduced, although the rate of hydrolysis may be slowed; however, fosinoprilat clearance is approximately one-half that observed in patients with normal hepatic function. In patients with end-stage renal disease (CrCl < 10 mL), the total body clearance of fosinoprilat is approximately one-half of that in patients with normal renal function. In patients with mild-to-severe renal insufficiency (CrCl 10—80 ml/min), the clearance of fosinoprilat does not differ appreciably from normal, because of the large contribution of hepatobiliary elimination. Fosinopril is not well dialyzed. The clearance of fosinoprilat by hemodialysis and peritoneal dialysis averages 2% and 7%, respectively, of urea clearances. In elderly subjects with clinically normal renal and hepatic function, there appear to be no significant differences in fosinoprilat pharmacokinetic compared to younger subjects. In pediatric patients aged 6—16 years with glomerular filtration rate >= 25 ml/min, the mean AUC and Cmax values following 0.3 mg/kg fosinopril solution are similar to that observed for healthy adults receiving 20 mg fosinopril solution (about 0.3 mg/kg for 70 kg adult). In this pediatric study (manufacturer data), the terminal half-life of fosinopril ranges from 11 to 13 hours, similar to that observed for adults.

Description, Mechanism of Action, Pharmacokinetics last revised 12/1/2003 1:22:00 PM

Indications

- heart failure
- hypertension
- proteinuria†

† non-FDA-approved indication

Dosage

For the treatment of hypertension:

Oral dosage:

Adults and adolescents > 16 years: Initially, 10 mg PO once daily. Adjust dosage according to blood pressure response. The average dosage range is 20—40 mg/day PO (maximum 80 mg/day), given in 1—2 divided doses. NOTE: Although the manufacturer does not recommend lower initial doses in patients receiving diuretic therapy, these patients should be monitored carefully.

Elderly: See adult dosage. Greater sensitivity to the antihypertensive effects of fosinopril is possible. Dosage should be adjusted based on clinical response.

Adolescents and children 6—16 years, weighing > 50 kg: Based on manufacturer data, the recommended dose is 5—10 mg PO once daily for patients weighing > 50 kg. An appropriate dosage strength is not available for children weighing < 50 kg. Doses of 0.1, 0.3, and 0.6 mg/kg have been studied in a randomized study of 252 pediatric patients aged 6—16 years; all doses reduced blood pressure to a similar extent. The maximum dosage studied was 40 mg/day PO.

Children < 6 years: Safe and effective use has not been established.

For the adjunctive treatment of congestive heart failure in patients receiving other antihypertensive therapy:

Oral dosage:

Adults: Initially, 10 mg PO once daily. Reduce dosage to 5 mg PO once daily in patients with CHF, moderate to severe renal failure, or hypovolemia (e.g., vigorously diuresed). Patients should be observed for at least 2 hours after the initial dose for occurrence of hypotension or orthostasis. If either one occurs, observe patient until blood pressure is stabilized. Gradually titrate up to target dosage of 40 mg/day as tolerated over several weeks.

Elderly: See adult dosage. Greater sensitivity to the antihypertensive effects of fosinopril is possible. Dosage should be adjusted based on clinical response.

Children: Safe and effective use has not been established.

For the treatment of proteinuria† (albuminuria) in patients with non-diabetic nephropathy†:

Oral dosage:

Adults: 2 mg PO once daily has been studied in patients with IgA nephropathy.

Elderly: See adult dosage. Greater sensitivity to the antihypertensive effects of fosinopril is possible. Dosage should be adjusted based on clinical response.

Children: Safe and effective use has not been established.

Maximum Dosage Limits:

•*Adults:* 80 mg/day PO for hypertension; 40 mg/day PO for heart failure.
•*Elderly:* 80 mg/day PO for hypertension; 40 mg/day PO for heart failure.
•*Adolescents > 16 years:* 80 mg/day PO for hypertension.
•*Adolescents <= 16 years:* 40 mg/day PO for hypertension.
•*Children >= 6 years:* 40 mg/day PO for hypertension.
•*Children < 6 years:* Safe and effective use has not been established.

Patients with hepatic impairment:

No specific dosage adjustment is recommended for patients with hepatic impairment; adjust dosage based on clinical response. Fosinoprilat clearance is approximately one-half that observed in patients with normal hepatic function.

Patients with renal impairment:
No dosage adjustment needed.
Intermittent hemodialysis:
Fosinoprilat is poorly removed by hemodialysis; no dosage adjustment is needed.

Indications...Dosage last revised 9/16/2003 2:19:00 PM

Administration Guidelines

Oral Administration
•May administer fosinopril orally without regard to food.

Administration last revised 8/30/2006 10:47:00 AM

Contraindications/Precautions

- *angioedema*
- *Angiotensin-converting enzyme inhibitors (ACE inhibitors) hypersensitivity*
- aortic stenosis
- autoimmune disease
- Black patients
- bone marrow suppression
- breast-feeding
- cardiomyopathy
- cerebrovascular disease
- children
- collagen-vascular disease
- coronary artery disease
- dialysis
- elderly
- heart failure
- hepatic disease
- hyperkalemia
- hyponatremia
- hypotension
- hypovolemia
- immunosuppression
- low-density lipoprotein apheresis
- pregnancy
- renal artery stenosis
- renal disease
- surgery

• *Absolute contraindications are in italics.*

Angiotensin-converting enzyme inhibitors (ACE inhibitors) hypersensitivity usually manifests as a result of alterations in kinin generation in sensitive individuals; there is no evidence of a specific immune-mediated reaction.[5157] However, such reactions can be potentially life-threatening, even if they are not true 'allergic' reactions. Fosinopril is contraindicated in patients with a history of *ACE inhibitor-induced angioedema*, hereditary *angioedema*, or idiopathic *angioedema*. If angioedema occurs, ACE inhibitor therapy should be halted and appropriate treatment instituted (see Adverse Reactions). The incidence of ACE inhibitor-induced *angioedema* is higher in Black patients than non-Black patients.[5896] [9108] In addition, ACE inhibitors are less effective in lowering blood pressure in Black patients, including the African-American population.[9109] [9110] [9111]
Neutropenia or agranulocytosis have been reported in patients receiving ACE inhibitor therapy. Patients who have preexisting renal disease, are receiving concomitant immunosuppression, or have collagen-vascular disease or autoimmune disease are at an increased risk of developing this complication. Data from clinical trials of fosinopril are insufficient to show that the drug does not cause agranulocytosis; therefore, complete blood counts should be established before and during fosinopril therapy whenever the drug is administered to these patient populations. Fosinopril should be used with caution in patients with pre-existing bone marrow suppression.
Patients with renal artery stenosis should not receive fosinopril (or any other ACE inhibitor) because renal insufficiency can result from inhibition of the renin-angiotensin system, which supports GFR in post-stenotic kidneys. Other types of renal disease can actually improve during fosinopril therapy. The dose of fosinopril does not need to be adjusted in patients with renal impairment.
Greater sensitivity to the hypotensive effects of fosinopril is possible in elderly patients.
Fosinopril should be used with caution in patients with hepatic disease since minor alterations of fluid and electrolyte balance may precipitate hepatic coma in patients receiving thiazide diuretics. Fosinoprilat clearance is approximately one-half that observed in patients with normal hepatic function. No specific dosage adjustment is recommended by the manufacturer; however, care should be exercised when dosing fosinopril in patients with liver disease. Dosage should be adjusted based on clinical response.
Fosinopril should be used with caution patients with hyperkalemia. ACE inhibitors can elevate serum potassium concentrations and could worsen pre-existing condition. Hyperkalemia is associated with serious cardiac arrhythmias.
Treatment with ACE inhibitors may increase the risk of anaphylactoid reactions in patients undergoing desensitization procedures. Two patients undergoing desensitizing treatment with hymenoptera venom while receiving ACE inhibitors sustained life-threatening anaphylactoid reactions. In the same patients, these reactions were avoided when ACE inhibitors were temporarily withheld, but they reappeared upon inadvertent rechallenge. Anaphylactoid reactions have been reported in patients taking ACE inhibitors (enalapril) who were receiving dialysis with high-flux membranes; the mechanism is unknown. When anaphylactoid symptoms such as nausea, abdominal cramps, burning, angioedema, shortness of breath or low blood pressure are recognized, the dialysis should be stopped and the patient should receive aggressive treatment for the hypersensitivity reaction. Anaphylactoid reactions have also occurred in patients undergoing low-density lipoprotein apheresis with dextran sulfate absorption (a procedure dependent upon devices not approved in the United States). Although a causal relationship to ACE inhibitor therapy has not been firmly established, treatment with fosinopril may increase the risk for anaphylactoid reactions during membrane exposure. ACE inhibitors may also precipitate low blood pressure in dialysis patients who are volume-depleted.
Greater sensitivity to fosinopril is possible in elderly patients (see Dosage).

Fosinopril is relatively contraindicated in patients who exhibit hypotension. Hypotension can occur if fosinopril is administered to patients with hypovolemia or hyponatremia, or to patients receiving dialysis, diuretics or other antihypertensives. Fosinopril should be used cautiously in patients with congestive heart failure (initial doses should be lower than in the treatment of hypertension) because of a greater risk of developing hypotension. Hypotension may aggravate ischemia in patients with coronary artery disease or cerebrovascular disease precipitating a myocardial infarction or cerebrovascular accident. Fosinopril should be used with caution in patients with aortic stenosis or hypertrophic cardiomyopathy. As with all vasodilators, ACE inhibitors should be given with caution to patients with obstruction in the outflow tract of the left ventricle.
In patients undergoing major surgery or during anesthesia with agents that lower blood pressure, fosinopril may block angiotensin II formation secondary to compensatory renin release. Therefore, hydrochlorothiazide-fosinopril should be used with caution prior to surgery. If hypotension occurs during surgery and/or anesthesia and is considered to be due to blockade of angiotensin II formation, it can be corrected by volume expansion.
Fosinopril has been evaluated in children aged 6—16 years, and has been shown to be well-tolerated in this population with adverse effects similar to adults. Safety and efficacy have not been established for children aged < 6 years. Infants and newborns may be susceptible to prolonged, excessive, and unpredictable decreases in blood pressure associated with ACE inhibitor therapy. Oliguria and seizures have been reported in this age group with other ACE inhibitor therapy.
Fosinopril is classified as FDA pregnancy risk category D. ACE inhibitors have been associated with fetal and neonatal morbidity and mortality when administered to pregnant women (see Adverse Reactions). In addition, use of ACE inhibitors during the first trimester of pregnancy has been associated with a potentially increased risk of birth defects. In women planning to become pregnant, ACE inhibitors should not be used. Women of child-bearing age should be made aware of the potential risk and ACE inhibitors should only be given after careful counseling and consideration of individual risks and benefits. When pregnancy is detected, ACE inhibitors should be discontinued as soon as possible and monitoring of the fetal development should be performed on a regular basis. Rarely (probably less often than once per every thousand pregnancies), no alternative to ACE inhibitors will be found.[5896] In these rare cases, the pregnant women should be apprised of the potential hazards to their fetuses, and serial ultrasound examinations should be performed to assess the intraamniotic environment. The reported adverse fetal and neonatal effects (e.g., hypotension, neonatal skull hypoplasia and craniofacial deformation, fetal limb contractures, hypoplastic lung development, anuria, oligohydramnios, reversible or irreversible renal failure, and death) have been reported during ACE inhibitor exposure during the second and third trimesters.[5896] In addition, a recent observational study based on Tennessee Medicaid data has reported that the risk of congenital malformations is significantly increased during first-trimester exposure to ACE inhibitors.[9113] Further evaluation of teratogenicity data associated with ACE inhibitor exposure during pregnancy is ongoing.[9114] [9133]
Ingestion of fosinopril 20 mg daily for three days resulted in detectable levels of fosinoprilat in breast milk. Fosinopril sodium should not be administered to breast-feeding mothers.

Contraindications last revised 3/23/2007 2:37:00 PM

Drug Interactions

- Antacids
- Antidiabetic Agents
- Antihypertensive Agents
- Azathioprine
- Cyclosporine
- Diuretics
- Drospirenone; Ethinyl Estradiol
- Entecavir
- Ephedra, Ma Huang
- Eplerenone
- Ethanol
- Gold compounds
- Hawthorn, Crataegus laevigata
- Heparin
- Hymenoptera Venom
- Lithium
- Monoamine oxidase inhibitors (MAOIs)
- Nonsteroidal antiinflammatory drugs (NSAIDs)
- Potassium Salts
- Potassium-sparing diuretics
- Radiopaque Contrast Agents
- Salicylates
- Sodium Phosphate Monobasic Monohydrate; Sodium Phosphate Dibasic Anhydrous
- Trimethoprim

The addition of eplerenone to angiotensin-converting enzyme inhibitor (ACE inhibitors) therapy causes an overall slight increase in mean serum potassium levels of approximately 0.09—0.13 mEq/L.[4707] In a study of diabetic patients with microalbuminuria, 200 mg of eplerenone daily added to enalapril treatment increased the risk of hyperkalemia from 17% on enalapril alone to 38% on combination therapy. Also, because using other mineralocorticoid receptor blocking agents with ACE inhibitors has historically led to clinically relevant hyperkalemia, caution should be used when administering eplerenone with ACE inhibitors.
Fosinopril causes a decrease in aldosterone secretion, leading to small increases in serum potassium levels.[5894] Due to the risk of developing hyperkalemia, drugs that increase serum potassium concentration, such as potassium-sparing diuretics, potassium salts, and heparin, should be given cautiously to patients receiving fosinopril.
Fosinopril can enhance the hypotensive effects of antihypertensive agents or diuretics if given concomitantly.[5894] This additive effect can be desirable, but dosages must be adjusted accordingly. Patients with hyponatremia or hypovolemia are more susceptible to developing reversible renal insufficiency when given fosinopril and diuretic therapy concomitantly.
In the low-renin or volume-dependent hypertensive patient, prostaglandins play an important role in the hypotensive effects of ACE inhibitors. NSAIDs may attenuate the antihypertensive effects of ACE inhibitors by inhibiting the synthesis of vasodilatory prostaglandins.[805] In some patients with compromised renal function who are being treated with NSAIDs, the coadministration of ACE inhibitors may result in a further deterioration of renal function. Therefore, blood pressure and renal function should be monitored closely when an NSAID is administered to a patient taking an ACE inhibitor. Among NSAIDs, indomethacin, naproxen, and piroxicam may have the greatest pressor effect, while the effects of sulindac and nabumetone may be significantly less. The potential clinical effects of selective or preferential COX-2 inhibitors are not known. Mean arterial blood pressure increased 3 mmHg in patients receiving ACE inhibitor (benazepril 10—40 mg daily for 4 weeks) with rofecoxib 25 mg once daily compared to the ACE inhibitor

regimen alone.
Concomitant use of medicines with potential to alter renal perfusion or function such as fosinopril may increase the risk of acute phosphate nephropathy in patients receiving sodium phosphate monobasic monohydrate; sodium phosphate dibasic anhydrous.[8973] [8974]
Increased lithium levels have been reported during ACE inhibitor therapy.[5894] Although additional information on this drug interaction is needed, lithium concentrations should be monitored closely if fosinopril is added.
Hawthorn, Crataegus laevigata may lower peripheral vascular resistance.[4713] Hawthorn use in combination with antihypertensive agents may lead to additional reductions in blood pressure in some individuals. Patients receiving hawthorn concurrently with antihypertensive medications should receive periodic blood pressure monitoring.
The use of ACE inhibitors in hypertensive patients receiving azathioprine has been reported to induce anemia and severe leukopenia.[2872] [4710] This combination should be avoided where possible. When concurrent azathioprine and ACE inhibitor therapy is necessary, the patient should be monitored cautiously for potential myelosuppression.
Aspirin, ASA may reduce the vasodilatory efficacy of ACE inhibitors by inhibiting the synthesis of vasodilatory prostaglandins. This interaction has been documented primarily in heart failure patients. However, the established benefits of using aspirin in combination with an ACE inhibitor in patients with ischemic heart disease and left ventricular dysfunction generally outweigh this concern.[5718] [6060] Patients receiving concurrent salicylates and ACE inhibitor therapy should be monitored for antihypertensive or vasodilatory efficacy; the dose of the ACE inhibitor can be adjusted if indicated based on clinical evaluation.
Coadministration of an antacid (aluminum hydroxide, magnesium hydroxide, and simethicone) with fosinopril reduced serum levels and urinary excretion of fosinoprilat, suggesting that antacids may impair absorption of fosinopril.[5894] Therefore, if concomitant administration of these agents is indicated, dosing should be separated by 2 hours.
Fosinopril may cause a false low measurement of serum digoxin levels with the Digi-Tab® RIA Kit for Digoxin. Other kits, such as the Coat-A-Count® RIA Kit, may be used.[5894]
Neither fosinopril nor its metabolites have been found to interact with food. In separate single or multiple dose pharmacokinetic interaction studies with chlorthalidone, nifedipine, propranolol, hydrochlorothiazide, cimetidine, metoclopramide, propantheline, digoxin, and warfarin, the bioavailability of fosinoprilat was not altered by coadministration of fosinopril with any one of these drugs.[5894] In a pharmacokinetic interaction study with warfarin, bioavailability parameters, the degree of protein binding, and the anticoagulant effect (measured by prothrombin time) of warfarin were not significantly changed.[5894] In a study with concomitant administration of aspirin and fosinopril, the bioavailability of unbound fosinoprilat was not altered.[5894]
Several cases of acute renal failure have been associated with the addition of enalapril to cyclosporine therapy in renal transplant patients.[6061] [6062] In response to cyclosporine-induced renal afferent vasoconstriction and glomerular hypoperfusion, angiotensin II is required to maintain an adequate glomerular filtration rate. Inhibition of angiotensin-converting enzyme (ACE) could reduce renal function acutely. Closely monitor renal function in patients receiving cyclosporine concurrently with ACE inhibitors.
Treatment with ACE inhibitors may increase the risk of anaphylactoid reactions in patients undergoing desensitization procedures.[5894] Two patients undergoing desensitizing treatment with hymenoptera venom while receiving ACE inhibitors sustained life-threatening anaphylactoid reactions. In the same patients, these reactions were avoided when ACE inhibitors were temporarily withheld, but they reappeared upon inadvertent rechallenge. The mechanism is unknown.
Drospirenone has antimineralocorticoid effects and may increase serum potassium. The concurrent use of ACE inhibitors may increase the risk of hyperkalemia, especially in the presence of renal impairment.[4716] Monitor serum potassium during the 1st month of drospirenone; ethinyl estradiol (Yasmin®) treatment if fosinopril is used concurrently.
Ephedra, Ma huang can antagonize all types of antihypertensive agents. Blood pressure should be monitored closely in patients using antihypertensive agents with ephedra.[3490]
Concurrent use of ACE inhibitors (e.g., enalapril, quinapril) and trimethoprim has been associated with hyperkalemia. Trimethoprim has a potassium-sparing effect on the distal nephron and may induce hyperkalemia, especially with pre-existing risk factors for hyperkalemia (e.g., renal disease).[5073] Patients, especially those with renal dysfunction, should be monitored for hyperkalemia during concomitant use of ACE inhibitors and trimethoprim.
Ethanol interacts with antihypertensive agents by potentiating their hypotensive effect.[5944]
Because the use of other nephrotoxic drugs (including ACE inhibitors) is an additive risk factor for nephrotoxicity in patients receiving radiopaque contrast agents, ACE inhibitor therapy should be withheld, when possible, during radiopaque contrast agent administration.[5423]
ACE inhibitors may enhance the hypoglycemic effects of antidiabetic agents by improving insulin sensitivity.[6141] [7347] Patients receiving these drugs concomitantly with antidiabetic agents should be monitored for changes in glycemic control.
Because entecavir is primarily eliminated by the kidneys and ACE inhibitors can affect renal function, concurrent administration with ACE inhibitors may increase the serum concentrations of entecavir and adverse events. The manufacturer of entecavir recommends monitoring for adverse effects when these drugs are coadministered.[8007]
Additive hypotensive effects may be seen when monoamine oxidase inhibitors (MAOIs) are combined with antihypertensives.[4673] [6398] Careful monitoring of blood pressure is suggested during concurrent therapy of MAOIs with angiotensin-converting enzyme inhibitors (ACE inhibitors). Patients should be instructed to rise slowly from a sitting position, and to report syncope or changes in blood pressure or heart rate to their health care provider during concurrent use of an MAOI and fosinopril.
Nitritoid or vasomotor reactions have been reported rarely in patients receiving injectable gold (sodium aurothiomalate) and concomitant ACE inhibitor therapy.[9660] [9661] In some cases, the reactions have occurred after early (e.g., 1 week) or latent (e.g., 1 year) exposure to ACE inhibitors in patients receiving long-term therapy with gold sodium thiomalate.[9611] The mechanism for a possible drug interaction has not been established. It has been proposed that ACE inhibitor potentiation of kinins might unmask potential nitritoid reactions during therapy with gold compounds.[9661] Monitor closely for nitritoid reactions during gold therapy, including patients receiving ACE inhibitor therapy. Nitritoid reactions occur in approximately 5% of patients receiving gold therapy and symptoms may include facial flushing, diaphoresis, dizziness, nausea/vomiting, hypotension, tachycardia, and/or syncope. Nitritoid reactions may present as anaphylactic type reactions; some reactions may be life-threatening (e.g., cardiac arrest). Nitritoid reactions are most common with gold sodium thiomalate but have also been reported with auranofin.[9661] If signs of nitritoid reactions occur, it is prudent to discontinue the gold compound and re-evaluate treatment options, weighing the risks and benefits for the individual patient.

Adverse Reactions

- anaphylactoid reactions
- angioedema
- azotemia
- cholestasis
- cough
- dizziness
- fatigue
- headache
- hepatic failure
- hepatic necrosis
- hepatitis
- hyperkalemia
- hypotension
- jaundice
- orthostatic hypotension
- sinus tachycardia
- syncope
- teratogenesis

Adverse reactions associated with the use of fosinopril are usually mild and transient. Most commonly seen are hypotensive symptoms including orthostatic hypotension, sinus tachycardia, fatigue, dizziness, syncope, and headache. These symptoms occasionally require discontinuance of therapy. Other adverse reactions occurring in more than 1% of patients receiving the drug during clinical trials include diarrhea, nausea/vomiting, and sexual dysfunction. The drug occasionally was discontinued because of elevated transaminases. Similar adverse effects have been noted between adults and pediatric patients receiving fosinopril.
ACE inhibition can result in the accumulation of kinins in the respiratory tract, sometimes causing a persistent, nonproductive cough. However, accumulation of kinins does not adequately explain the mechanism of ACE inhibitor-induced cough. Kinins have a very short plasma half-life, therapeutic doses of ACE inhibitors are usually not high enough to cause accumulation of circulating bradykinin, and there is a female preponderance of cases. Rather, evidence is growing that ACE inhibitor-induced cough may be related to substance P stimulation of C-fiber receptors in the respiratory tract.[570] This cough may occur more frequently in patients with chronic obstructive pulmonary disease and is often overlooked as a potential adverse effect of fosinopril therapy. Dyspnea and bronchospasm also have been reported rarely during fosinopril therapy.
ACE inhibitors have been associated with anaphylactoid reactions, likely due to their inhibitory effect on eicosanoid and polypeptide metabolism, including bradykinin metabolism. Angioedema, or angioneurotic edema, of the face, edema of the extremities, mucous membranes, tongue, lips, larynx (laryngeal edema), and glottis has occurred rarely during ACE inhibitor therapy but is reversible following discontinuance of the drug. Involvement of the upper respiratory tract can induce acute respiratory distress. The onset usually occurs within hours or at most 1 week after starting ACE inhibitor therapy, but may occur at any time during therapy. The mechanism is unknown but may involve drug-induced auto-antibodies, bradykinin accumulation, dysregulation of the complement system, or histamine.[570] Black patients receiving ACE inhibitors have been reported to have a higher incidence of angioedema compared to non-Black patients.[5896] [9108] If angioedema occurs during therapy with an ACE inhibitor, the drug should be discontinued immediately. Appropriate monitoring and therapy should be provided until signs and symptoms have resolved completely. Angioedema associated with laryngeal edema or tongue edema may be fatal. If there is involvement of the tongue, glottis or larynx, appropriate therapy (e.g., 0.3 to 0.5 ml subcutaneous epinephrine 1:1000) and/or measures to ensure a patent airway should be promptly provided. Even in those instances where swelling of only the tongue is involved, without respiratory distress, patients may require prolonged observation since treatment with antihistamines and corticosteroids may not be sufficient. Patients with involvement of the tongue, glottis or larynx are likely to experience airway obstruction, especially those with a history of airway surgery. Rarely, intestinal angioedema has been reported during post-marketing experience with ACE inhibitors. Patients with intestinal angioedema may present with abdominal pain (with or without nausea or vomiting). In some cases there is no prior history of facial angioedema and C-1 esterase levels are normal. Intestinal angioedema can be diagnosed by procedures including abdominal CT scan or ultrasound, or at surgery. Symptoms resolve after stopping the ACE inhibitor. Intestinal angioedema should be included in the differential diagnosis of patients receiving ACE inhibitors who present with abdominal pain.
Patients receiving drugs that can increase serum potassium, or patients with congestive heart failure or impaired renal function, can be at an increased risk for developing hyperkalemia if given fosinopril concomitantly.
Renal insufficiency can occur during therapy with ACE inhibitors. Renal function should be monitored closely during initial therapy with fosinopril. If acute azotemia (elevated serum creatinine or BUN occurs, or if renal artery stenosis is suspected, fosinopril therapy should be discontinued.
Hepatotoxicity (including hepatitis) has been reported rarely in patients receiving ACE inhibitors. Although not completely understood, hepatotoxicity has included cholestasis with jaundice, fulminant hepatic necrosis, hepatic failure and death. Patients who develop jaundice should discontinue fosinopril therapy and receive appropriate treatment.
ACE inhibitors have been associated with teratogenesis and are classified as FDA pregnancy risk category D. ACE inhibitors have resulted in fetal and neonatal morbidity and mortality when administered to pregnant women. In women planning to become pregnant, ACE inhibitors should not be used. Women of child-bearing age should be made aware of the potential risk and ACE inhibitors should only be given after careful counseling and consideration of individual risks and benefits. Rarely (probably less often than once per every thousand pregnancies), no alternative to ACE inhibitors will be found.[5896] In these rare cases, the pregnant women should be apprised of the potential hazards to their fetuses, and serial ultrasound examinations should be performed to assess the intraamniotic environment. Adverse fetal and neonatal effects (e.g., hypotension, oligohydramnios, renal failure, skull hypoplasia, and death) have been reported during ACE inhibitor exposure, primarily during the second and third trimesters.[5896] In addition, a recent observational study based on Tennessee Medicaid data has reported that the risk of congenital malformations is significantly increased during first-trimester exposure to ACE inhibitors.[9113] Based on this trial, the reported risk ratio for development of birth defects is 2.71 (95% CI, 1.72—4.27) for infants with ACE inhibitor exposure limited to the first trimester when compared to infants who had no exposure to antihypertensive agents. An increased risk of developing malformations of the cardiovascular system (risk ratio 3.72; 95% CI, 1.89—7.3) and central nervous system (risk ratio 4.39; 95% CI, 1.37—14.02) has been observed. A post hoc analysis has reported a risk ratio of 9.32 for developing congenital malformations of the renal system (95% CI, 1.79—48.5).[9113] Although findings from one epidemiologic study do not establish causality between first trimester ACE inhibitor exposure and congenital malformations, the observations introduce the possibility that ACE inhibitors could be associated with teratogenic effects during early pregnancy. Further evaluation of teratogenicity data associated with ACE inhibitor exposure during pregnancy is ongoing.[9114] [9133] When pregnancy is detected, ACE inhibitors should be discontinued as soon as possible and monitoring of the fetal development should be performed on a regular basis. Infants with histories of *in utero* exposure to ACE inhibitors should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed

toward support of blood pressure and renal perfusion. Exchange transfusion or dialysis may be required as means of reversing hypotension and/or substituting for disordered renal function.[5896] There have been occasional reports of benefit with such methods to remove ACE inhibitors from the neonatal circulation, but experience is limited. Specific adverse fetal and neonatal effects of ACE inhibitor exposure during the last six months of pregnancy have included hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure (e.g., renal tubular dysplasia), oligohydramnios, and death. Oligohydramnios has been attributed to decreased fetal renal function and has been associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development. If oligohydramnios is observed, ACE inhibitors should be discontinued unless it is considered life-saving for the mother.[5896] Contraction stress testing (CST), a nonstress test (NST), or biophysical profiling (BPP) may be appropriate, depending upon the week of pregnancy. Patients and physicians should be aware that oligohydramnios may not appear until after the fetus has sustained irreversible injury. Prematurity, intrauterine growth retardation, and patent ductus arteriosus have also been reported, although it is not clear whether these occurrences are due to ACE inhibitor exposure.

Adverse Reactions last revised 3/23/2007 4:37:00 PM

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Aliskiren
Tekturna®
Classification:
• Cardiovascular Agents
  • Antihypertensive Agents
    • Direct Renin Inhibitors
Description, Mechanism of Action, Pharmacokinetics

Description: Aliskiren (SPP 100) is the first drug of the class of non-peptide, orally active renin inhibitors. It is approved for the treatment of hypertension, either alone or in combination with other antihypertensive agents.[10048] When used in combination, most clinical experience available is with diuretics or valsartan. The clinical effects of combination therapy with aliskiren and angiotensin-converting enzyme inhibitors or beta blockers has not been established; specifically, its use in combination with maximum doses of ACE inhibitors has not been adequately studied. Aliskiren is unique in the way it interupts the generation of angiotensin II by inhibiting renin within the renin-angiotesnin system (RAS) cascade. The ability of aliskiren to act on this highly specific rate-limiting step may present an advantage over ACE inhibitors and ARBs. Futhermore, inhibition of angiotensin-converting enzymes causes an increase in angiotensin I (Ang I), which is then available for conversion to angiotensin II (Ang II) through pathways not blocked by ACE inhibitors. Given that renin inhibitors prevent the formation of both Ang I and Ang II, they may offer a therapeutic profile distinct from those of both ACE inhibitors and ARBs. Renin inhibitors do not affect kinin metabolism and therefore would be expected to cause less dry cough or angioedema, which are characteristic side effects of ACE inhibitors. In addition, ARBs increase levels of Ang II, a biologically active vasoconstrictor, an effect that does not occur with renin inhibitors, resulting in major potential benefits in blood pressure control.[10050] Use of drugs that inhibit the RAS is an effective way to interfere in the pathogenesis of cardiovascular and renal disorders. Aliskiren is also in phase III clinical trials for its potential use in the treatment of left ventricular hypertrophy and heart failure. Aliskiren was approved by the FDA on March 5, 2007.

Mechanism of Action: Aliskiren has an innovative mechanism of action for the treatment of hypertension and end organ damage. It is the first renin inhibitor approved and acts within the renin-angiotensin system (RAS), a hormone system important in the regulation of blood pressure, electrolyte homeostasis, and vascular growth. The RAS includes a cascade of events, beginning with renin, which cleaves the inactive peptide angiotensinogen, converting it to angiotensin I. Angiotensin I (Ang I) is then converted by angiotensin-converting enzyme (ACE) to the biologically active vasoconstrictor angiotensin II (Ang II). Aliskiren significantly inhibits the RAS in a dose-dependent manner with maximum reductions in Ang II observed within one hour following oral administration.[10051] ACE inhibitors and angiotensin II receptor antagonists (ARBs) have been developed to block this system 'down stream' and have shown clinical efficacy in patients with hypertension, chronic renal failure, congestive heart failure, and other cardiovascular diseases. Because renin catalyzes the first and rate-limiting step of the RAS and has high specificity for its substrate, angiotensinogen, renin inhibitors present the new mechanism for blocking this complex hormonal system at its initial point of activation resulting in major potential benefits in blood pressure control and perhaps a more beneficial side effect profile. In contrast to ACE, which acts on bradykinin in addition to Ang I, renin is highly selective for angiotensinogen. Although the increased levels of bradykinin and substance P that occur with ACE inhibition may contribute to blood pressure reduction, they are also responsible for side effects associated with ACE inhibitors. Clinical trial evidence suggests that blockade of the RAS by angiotensin-converting enzyme inhibition or by angiotensin receptor blockade may influence large vessel atherosclerosis and cardiovascular morbidity and mortality independent of lowering blood pressure.[3632]
Pharmacokinetics: Aliskiren is administered orally. As with other previously studied renin inhibitors, it is poorly absorbed following oral administration and has a bioavailability of about 2.5%. Peak plasma concentrations are reached within 1—3 hours of dosing; steady-state blood concentrations are reached in about 7—8 days.[10048] Administration with a high fat meal decreases the mean AUC and Cmax by 71% and 85%, respectively.[10048] Although patients are encouraged to take their dose on a fixed schedule with regard to meals, aliskiren was dosed without regard to meals in clinical evaluation. It appears that metabolism does not play a large role in the elimination of aliskiren, as 91% of a radiolabeled dose is eliminated unchanged in the feces. It is unclear how much of the dose is metabolized, but hepatobiliary clearance seems to be the main route of elimination.[10052] Following oral administration, a small portion of the absorbed dose is also present in the urine as parent drug. Based on in vitro studies, the major enzyme responsible for aliskiren metabolism is CYP3A4; no inhibition or induction of CYP450 isoenzymes by aliskiren have been noted. Aliskiren has an approximate accumulation half life of 24 hours, allowing for once daily dosing.
•***Special Populations:*** Aliskiren has not been investigated in patients < 18 years of age. Elderly patients (>= 65 years) included in pharmacokinetic assessments experienced an increase in drug exposure as measured by AUC; however, adjustments of the starting dose is not required. Minimal differences are observed in the pharmacokinetics of Black patients, Caucasian patients, and Japanese patients, with Black patients experiencing slightly smaller reductions in blood pressure as compared to other subgroups. Pharmacokinetic parameters have been evaluated in patients with varying degrees of renal insufficiency. Rate and extent of exposure (AUC and Cmax) in subjects with renal impairment does not correlate consistently with severity of renal impairment. Pharmacokinetic parameters are not significantly affected in patients with mild to severe liver disease. Therefore, dosage adjustments are not recommended for patients with renal or hepatic impairment; however, cautions do apply (see Contraindications/Precautions).

Description, Mechanism of Action, Pharmacokinetics last revised 4/2/2007 4:05:00 PM

Indications

- hypertension

Dosage

For the treatment of hypertension either as monotherapy or in combination with other antihypertensive agents:
NOTE: In clinical evaluation, aliskiren was studied in combination with diuretics and an angiotensin receptor blocker (valsartan) in the treatment of hypertension; combination therapy with these agents resulted in greater effects at their maximum recommended dose as compared to either drug alone. The clinical effects of combination therapy with aliskiren and angiotensin-converting enzyme inhibitors or beta blockers has not been established.
Oral dosage:
Adults, including the elderly: Initially, 150 mg PO once daily. The dose may be increased to 300 mg PO once daily if blood pressure is not adequately controlled. Doses > 300 mg/day have been studied, but the incidence of diarrhea is increased without an increase in blood pressure response. By 2 weeks, 85—90% of the effects of a given dose are achieved.
Adolescents: Safety and efficacy have not been established.
Children: Safety and efficacy have not been established.
Maximum Dosage Limits:
•*Adults:* 300 mg/day PO.
•*Elderly:* 300 mg/day PO.
•*Adolescents:* Safety and efficacy have not been established.
•*Children:* Safety and efficacy have not been established.
Patients with hepatic impairment:
Specific guidelines for dosage adjustments in patients with hepatic impairment are not available; it appears that no dosage adjustments are needed.
Patients with renal impairment:
Specific guidelines for dosage adjustments in patients with renal impairment are not available; it appears that no dosage adjustments are needed. However, the manufacturer advises cautious use in patients with a CrCl < 30 ml/min (SCr >= 1.7 mg/dl in females or 2 mg/dl in males) as clinical experience in this population is limited.

Indications...Dosage last revised 4/2/2007 4:05:00 PM

Administration Guidelines

Oral Administration
•May be given with or without food. However, should be administered consistently with regards to meals; high fat meals can significantly decrease drug absorption and may alter the clinical efficacy.

Administration last revised 3/27/2007 12:37:00 PM

Contraindications/Precautions

- angioedema
- aortic stenosis
- biliary cirrhosis
- Black patients
- breast-feeding
- cardiomyopathy
- cerebrovascular disease
- children
- coronary artery disease
- dialysis
- elderly
- hepatic disease
- hyperkalemia
- hypokalemia
- hyponatremia
- hypotension
- hypovolemia
- pregnancy
- renal artery stenosis
- renal disease
- renal failure
- renal impairment
- surgery

Following administration of aliskiren, angioedema of the face, extremities, lips, tongue, glottis, and/or larynx has been reported. This may occur at any time during treatment. It is unknown if the occurrence of angioedema is higher in Black patients compared to other demographic subgroups, as has been reported with the use of angiotensin-converting enzyme inhibitors (ACE inhibitors). Black patients do, however, experience a slightly smaller reduction in blood pressure as compared to other subgroups, a trend that is consistent with experience in ACE inhibitor and angiotensin receptor antagonists therapy.[10048] If angioedema occurs, aliskiren should be promptly discontinued and appropriate therapy and monitoring provided until complete and sustained resolution of signs and symptoms has occurred. Patients may require prolonged observation even with minor reactions where only swelling of the tongue is initially seen, without respiratory complications. In these patients, treatment with antihistamines and corticosteroids may not be sufficient to prevent respiratory involvement. Experience with ACE-inhibitors shows that rare fatalities can occur in patients with angioedema associated with laryngeal edema or tongue edema secondary to ACE inhibitors administration. Patients with involvement of the tongue, glottis, or larynx, and especially a history of airway surgery are more likely to experience airway obstruction. ACE-inhibitors are contraindicated in patients with a history of ACE inhibitor-induced angioedema, hereditary angioedema, or idiopathic angioedema, similar precautions should be observed when administering aliskiren.
Aliskiren should be used with caution in patients who exhibit hypotension. A transient hypotensive response is not a contraindication

to further treatment, and the drug can usually be continued without difficulty once the blood pressure has stabilized. Rarely (0.1%), an excessive fall in blood pressure was observed in patients with uncomplicated hypertension treated with aliskiren.[10048] When aliskiren was combined with other antihypertensive agents, the occurrence of hypotension was only slightly increased (< 1%).[10048] Hypotension is more likely to occur if aliskiren is administered to patients with preexisting hypovolemia or hyponatremia. Hypotension may aggravate ischemia in patients with coronary artery disease or cerebrovascular disease precipitating a myocardial infarction or cerebrovascular accident. Aliskiren should be used with caution in patients with aortic stenosis or hypertrophic cardiomyopathy.

Patients with a creatinine clearance of < 30 ml/min or a serum creatinine of >= 1.7 mg/dl in women or 2 mg/dl in men were excluded from clinical trials of aliskiren.[10048] Patients with a history of dialysis, nephrotic syndrome, or renovascular hypertension were also excluded. Aliskiren should be used with caution in patients with renal impairment, renal disease, or renal failure as safety and efficacy information is not available. Patients with renal artery stenosis should not receive aliskiren or therapy with any other drug affecting the renin-angiotensin system. Because affected kidneys depend on the renin-angiotensin system to maintain GFR, inhibition of the mechanism can lead to renal decompensation. Greater sensitivity to the hypotensive effects of aliskiren is possible in elderly patients, who may have reduced renal function. In clinical evaluation, blood pressure responses and adverse events were similar in the 1,275 (19%) elderly patients 65 years or older and in the 231 (3.4%) elderly patients 75 years or older as compared to younger patients.[10048]

Patients with pre-existing hyperkalemia or hypokalemia should have their electrolyte imbalances corrected before aliskiren is initiated. Hyperkalemia may be associated with serious cardiac arrhythmias. Risk factors for the development of hyperkalemia include renal insufficiency, diabetes mellitus, and the concomitant use of potassium-sparing diuretics, potassium supplements, and/or potassium-containing salt substitutes. Increases in serum potassium > 5.5 mEq/L were infrequent with aliskiren alone (0.9%, compared to 0.6% with placebo).[10048] However, increases in serum potassium were more frequent (5.5%) when combined with an ACE inhibitor in a diabetic population.[10048] Clinicians should monitor electrolytes along with renal function in this population.

Limited data are available regarding the use of aliskiren in patients with hepatic disease. In pharmacokinetic analysis, no significant differences were seen among patients with mild to severe hepatic impairment. Consequently, the manufacturer does not recommend adjustment in the initial dosing of aliskiren for this population.[10048] However, because hepatobiliary excretion seems to be prominent in the elimination of aliskiren, clinicians should observe caution when prescribing aliskiren in patients with biliary cirrhosis or Child-Pugh class B or C until further data become available.[10052]

The safety and efficacy of aliskiren in children have not been established.[10048]

Aliskiren is classified as a FDA pregnancy risk category D drug for the second and third trimesters, but categorized as pregnancy risk category C for the first trimester. The use of drugs that act directly on the renin-angiotensin system in pregnancy can cause fetal and neonatal morbidity and even death. Once pregnancy is detected, every effort should be made to discontinue aliskiren therapy. Similar drugs such as ACE inhibitors have been associated with fetal and neonatal injury when administered to pregnant women. The reported adverse fetal and neonatal effects include hypotension, neonatal skull hypoplasia and craniofacial deformation, fetal limb contractures, hypoplastic lung development, anuria, oligohydramnios, reversible or irreversible renal failure, and death.[5896] [10048] Prematurity, intrauterine growth retardation, and patent ductus arteriosus have also been reported, although it is not clear whether these occurrences were due to exposure to the drug. Inform women of reproductive age about the potential fetal risks of aliskiren exposure throughout pregnancy. While it was previously thought that adverse effects do not result from first-trimester drug exposure, a recent observational study based on Tennessee Medicaid data has reported that the risk of congenital malformations is significantly increased during first-trimester exposure to ACE inhibitors.[9113] Women taking aliskiren should tell their healthcare professionals if they are planning to become pregnant or think they might be pregnant. Pregnant women should only be prescribed drugs acting on the renin-angiotensin system if the expected benefits clearly exceed the potential risks. Rarely (probably less often than once per every thousand pregnancies), no alternative to this type of medications will be found.[10048] In these rare cases, the pregnant women should be apprised of the potential hazards to their fetus, and serial ultrasound examinations should be performed to assess the intraamniotic environment.[10048]

It is not known whether aliskiren is excreted in human milk. Aliskiren was secreted in the milk of lactating rats. Because of the potential for adverse effects on the nursing infant, a decision should be made whether to discontinue breast-feeding or discontinue the drug, taking into account the importance of the drug to the mother.[10048]

Contraindications last revised 5/24/2007 8:46:00 PM

Drug Interactions

Antihypertensive Agents

- Atorvastatin
- Ketoconazole
- Warfarin

NOTE: Aliskiren does not inhibit any CYP450 isozymes and it does not induce CYP3A4.

A compilation of four open-labeled studies examined the pharmacokinetic interactions in healthy subjects between aliskiren 300 mg and therapeutic doses of amlodipine, valsartan, hydrochlorothiazide (HCTZ), and ramipril.[10053] No statistically significant or clinically relevant pharmacokinetic interactions were found during coadministration with any of the test medications. A separate study involved healthy subjects and investigated the pharmacokinetic interactions between single oral doses of aliskiren 150 mg and therapeutic doses of lovastatin, atenolol, celecoxib, and cimetidine.[10054] Mean AUC and half-life for aliskiren were not significantly affected by lovastatin, atenolol, or celecoxib (< 10% difference between treatments). A non-significant 36% increase in Cmax was observed with celecoxib. A non-significant increase in bioavailability of aliskiren was observed during coadministration with cimetidine. The potential for drug interactions appears to be low since aliskiren does not affect cytochrome P450 enzyme activities, is minimally metabolized, and is not extensively protein bound.[10053] In addition, when aliskiren is coadministered with digoxin or metformin, the pharmacokinetics of aliskiren or the other agent are not affected.[10048]

Aliskiren can enhance the effects of antihypertensive agents and diuretics on blood pressure if given concomitantly.[10048] This additive effect may be desirable, but dosages must be adjusted accordingly. Patients with hyponatremia or hypovolemia may become hypotensive and/or develop reversible renal insufficiency when given aliskiren and diuretics concomitantly. When aliskiren is

administered in combination with furosemide, the AUC and Cmax of furosemide are reduced by approximately 30% and 50%, respectively; the pharmacokinetics of aliskiren are not affected.[10048] Patients should be monitored for loss of effect of furosemide when aliskiren is initiated. In addition, multiple doses of coadministered irbesartan and aliskiren reduces the Cmax of aliskiren by up to 50%.[10048] Therefore, blood pressure should be closley monitored in patients taking both of these medications. Combining aliskiren with antihypertensive agents that increase serum potassium such as angiotensin-converting enzyme inhibitors (ACE inhibitors) and angiotensin receptor antagonists (ARBs), may also increase the likelihood of inducing hyperkalemia. During clinical trials, when aliskiren was used in combination with an ACE inhibitor in patients with diabetes, the incidence of hyperkalemia was 5.5% compared to an incidence of 0.9% in patients not using a concomitant ACE inhibitor. Electrolytes should be routinely monitored in patients receiving aliskiren.[10048]
Coadministration of atorvastatin resulted in an approximate 50% increase in aliskiren Cmax and AUC after multiple doses; the pharmacokinetics of atorvastatin were not affected.[10048] Blood pressure should be monitored in patients taking both of these medications.
Administration of 200 mg of ketoconazole twice daily with aliskiren increased the plasma concentrations of aliskiren by 80%. Although a 400 mg dose of ketoconazole was not studied, it is expected that the higher dose would further increase plasma concentrations of aliskiren.[10048] Blood pressure should be monitored in patients taking both of these medications.
Coadministration of warfarin with aliskren decreses the absorption (Cmax) of warfarin by up to 12%. Patients in a small (N=15) pharmacokinetic crossover study were administered a single oral dose of 25 mg racemic warfarin twice, given on the 8th day of treatment with 150 mg aliskiren and repeated at the same time point during treatment with placebo. Collected blood samples did not reveal any significant effect on blood coagulation parameters such as partial thromboplastin time (aPTT), prothrombin time (PT), or international normalized ratio (INR). Aliskiren had no effect on the pharmacodynamic properties of warfarin over a period of 144 h after dosing.[10052] [10055] Nevertheless, blood coagulation markers should be closely monitored in patients taking both of these medications.

Interactions last revised 4/26/2007 11:44:00 AM

Adverse Reactions

- angioedema
- cough
- diarrhea
- dizziness
- headache
- hyperkalemia
- hypotension

During clinical evaluation, the safety of aliskiren was studied in over 6,460 patients, with more than 1,740 treated for longer than 6 months, and more than 1,250 treated out to one year. Discontinuations due to adverse events or uncontrolled hypertension were low in controlled trials, including 2.2% of patients treated with aliskiren vs. 3.5% of patients treated with placebo. Adverse events in published clinical trails were similar to those that occurred with placebo at doses up to 300 mg daily. The most common adverse events included headache, dizziness, and some gastrointestinal events. Doses above 300 mg did not improve blood pressure response but were associated with increased rates of GI adverse events. Aliskiren is considered safe and well tolerated up to 300 mg/day.
Angioedema of the face, extremities, lips, tongue, glottis, and larynx has been reported in patients taking aliskiren; it can occur at any time after treatment initiation.[10048] Whether or not this effect is more common in Black patients compared to non-Black patients is not yet known. If angioedema is suspected, aliskiren should be discontinued immediately and supportive care initiated.
Compared with ACE inhibitors, renin inhibitors have the potential to cause fewer side effects since they do not affect metabolism of bradykinin. ACE inhibition can result in the accumulation of kinins in the respiratory tract, often causing a persistent, nonproductive cough. During clinical trials, the incidence of cough was 1.1% in patients taking aliskiren vs. 0.6% in patients taking placebo.[10048] When compared to ACE inhibitors, the incidence of cough in patients taking aliskiren was approximately one-half to one-third the incidence of cough in patients taking ACE inhibitors.
Diarrhea was reported among the most common adverse events in 2.3% of patients receiving aliskiren 300 mg/day compared to only 1.2% of patients receiving placebo.[10048] In women or elderly patients > 65 years of age, an increase in the incidence of diarrhea was evident at a lower dose of 150 mg/day compared to a higher dose of 300 mg/day in younger men.[10048] Other reported GI adverse events include abdominal pain, dyspepsia, and gastroesophageal reflux, but were more likely to occur at doses approaching 600 mg daily.
When used as monotherapy, the incidence of hyperkalemia (i.e., serum potassium > 5.5 mEq/L) was 0.9% in patients receiving aliskiren vs. 0.6% of patients receiving placebo.[10048] However, when used in combination with an ACE inhibitor in patients with diabetes, the incidence of hyperkalemia was 5.5%.[10048] Electrolytes should be routinely monitored in patients receiving aliskiren.
During clinical trials, hypotension has been rarely reported with an incidence of 0.1% in patients receiving monotherapy and an incidence of < 1% in patients taking aliskiren in combination with other antihypertensives.[10048] It is possible that patients with activated renin-angiotesnin systems or those who are volume-depleted or salt-depleted (e.g., receiving diuretics) may experience symptomatic hypotension once aliskiren is initiated. If hypotension occurs, the patient should be placed in a supine position and administered IV normal saline when indicated. Hypotension does not contraindicate further treatment with aliskiren; it can usually be reinitiated without sequelae once the blood pressure has stabilized.
Other adverse events reported during clinical trials of aliskiren include rash (1% for aliskiren vs. 0.3% for placebo), elevated uric acid (0.4% vs. 0.1%), gout (0.2% vs. 0.1%), renal stones (0.2% vs. 0%), decreased hemoglobin/hematocrit, elevations in creatine kinase > 300% (1% vs. 0.5%), elevations in BUN and/or serum creatinine (7% vs. 6%), and a single episode of tonic-clonic seizures in 2 patients.[10048]
In an 8 week, controlled clinical trial, aliskiren was well tolerated with an adverse event rate similar to placebo at doses up to 600 mg.[10056] Adverse reaction rates for aliskiren 150 mg, 300 mg, and 600 mg were 26.8%, 36.2%, and 33.1%, respectively, compared with 32.1% with placebo. The comparator drug, irbesartan 150 mg, had an adverse event rate of 36.6%.

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Sotalol
Betapace AF™ | Betapace® | Sorine™
Classification:
- Autonomic Agents
  - Sympatholytics
    - Beta-blockers
- Cardiovascular Agents
  - Antiarrhythmics
    - Class III antiarrhythmics

Description, Mechanism of Action, Pharmacokinetics

Description: Sotalol is a hydrophilic, and nonselective beta-adrenergic blocking agent, with low lipid-solubility. It is used to treat ventricular and supraventricular arrhythmias. Sotalol is currently available in the U.S. as an oral agent. An intravenous formulation is pending FDA approval and has been included as a Class IIa recommendation (good/very good evidence provides support) for use in the ACLS treatment algorithm for stable monomorphic and polymorphic ventricular tachycardia.[2999] Sotalol is a unique beta-blocker which has both Vaughn Williams Classification class II and III antiarrhythmic properties. As a Class II nonselective beta-blocker, sotalol has no intrinsic sympathomimetic activity (ISA) or membrane-stabilizing activity (MSA). The Class III antiarrhythmic effects of sotalol, like amiodarone, prolong the action potential duration and increase cardiac tissue refractoriness. As a result, sotalol is used in the treatment of atrial arrhythmias or life-threatening ventricular arrhythmias, including sustained ventricular tachycardia. It should not be used for mild arrhythmias because it is known to be proarrhythmic, with an increased risk for torsade de pointes. In comparative studies, sotalol has been shown to be more effective in preventing recurrent arrhythmias than several other drugs. Thus, it could benefit patients in whom other treatments have failed. It has not been determined whether the survival rate is improved with sotalol use over use of an implanted defibrillator alone. Sotalol was originally FDA approved under the name Betapace® for the treatment of life-threatening ventricular arrhythmias in October 1992. The d-isomer of sotalol (virtually devoid of beta-blocking activity and considered a pure Class III antiarrhythmic) was investigated as an antiarrhythmic in high-risk patients after myocardial infarction, but the trial was terminated early due to a higher mortality rate with d-sotalol versus placebo, presumably due to increased arrhythmic deaths (SWORD trial).[2950] In February 2000, sotalol was approved as Betapace AF™ for the treatment of atrial fibrillation and atrial flutter. Although they are both sotalol, Betapace® should not be substituted for Betapace AF™ because of significant differences in indications, dosing, administration, safety information, and the patient package insert appropriate for patients with atrial fibrillation provided in the approved product labeling for Betapace AF™.

Mechanism of Action: Sotalol is a racemic mixture of isomers. The levorotatory isomer has all of the beta-blocking activity, and the dextrorotatory isomer possesses the Class III antiarrhythmic activity. Although significant beta-blockade occurs at oral doses as low as 25 mg, significant Class III effects are seen only at daily doses >= 160 mg. The beta-blocker activity of the drug increases sinus cycle length, decreases AV nodal conduction, and increases AV nodal refractoriness. The antiarrhythmic activity is exerted by a combination of Class II activity and additional Class III activity, which lengthens repolarization or the plateau phase of the action potential. In addition, sotalol prolongs the QT interval (a Class III effect), which must be carefully monitored to avoid predisposing patients to proarrhythmic events. In general, beta-blockers without intrinsic sympathomimetic activity (ISA) exert detrimental effects on LVH and the lipid profile, and cause sexual dysfunction.
Pharmacokinetics: Sotalol is administered orally. Bioavailability is almost 100%. Food and milk reduce the rate and extent of absorption by roughly 20%, but the medication may be taken with or without food clinically. Onset of action following oral administration occurs in approximately 1 hour and peaks in 2.5—4 hours. Sotalol has low lipid solubility and does not cross the blood-brain barrier to any extent. Sotalol does not appear to bind to plasma proteins. There does not appear to be a correlation between peak serum concentrations and maximal effects on the heart rate.

Sotalol is not metabolized and is excreted primarily by the kidneys. Patients with impaired renal function require dosage reductions (see Dosage, Patients with renal impairment section). The plasma half-life in patients with normal renal function is between 8—17 hours. Patients with renal impairment have an increased elimination half-life proportional to the degree of renal dysfunction, and half-life can be prolonged up to 6 days in patients with severe renal failure. Elderly patients have been documented to have a prolonged sotalol half-life relative to younger patients (11 vs. 7 hours). Age-associated decline in renal function may contribute to reduced renal clearance in elderly patients. Patients with hepatic impairment show no alteration in the clearance of sotalol versus healthy adults.

Description, Mechanism of Action, Pharmacokinetics last revised 6/14/2007 12:18:00 PM

Indications

- atrial fibrillation
- atrial flutter
- paroxysmal supraventricular tachycardia (PSVT) prophylaxis†
- ventricular tachycardia
- Wolff-Parkinson-White (WPW) syndrome†

† non-FDA-approved indication

Dosage

For the conversion to and maintenance of normal sinus rhythm in patients with atrial fibrillation or atrial flutter:

NOTE: Patients with atrial fibrillation (AF) should be anticoagulated according to usual medical practice prior to electrical or pharmacological cardioversion. Anticoagulant therapy may be continued after cardioversion according to medical guidelines for the treatment of patients with AF.

Oral dosage (Betapace AF™) for the initiation or titration of sotalol treatment:

Adults: Initial doses of sotalol must be individualized according to clinical response, CrCl, and QTc. Prior to initiating sotalol, the QTc must be determined. If the baseline QTc exceeds 450 msec or CrCl < 40 ml/min, then sotalol is contraindicated for the treatment of atrial arrhythmias. The initial dose in patients with normal renal function is 80 mg PO twice daily. The starting dose of sotalol is based on CrCl (see Patients with renal impairment). During initiation and titration, monitor the QT interval 2—4 hours after each dose. If the QT interval prolongs to >= 500 msec, the sotalol dose must be decreased or the drug discontinued. The dosage may be titrated to 120 mg PO twice daily in the case of recurrence. The maximum recommended dosage is 160 mg PO twice daily in those with normal renal function provided the QT interval is not excessively prolonged. Patients should be monitored by continuous ECG for >= 3 days after dosage titration or for at least 5—6 doses of sotalol if dosing is once daily.

Elderly: Elderly patients may have a prolonged drug half-life. Age-associated decline in renal function may contribute to reduced renal clearance in elderly patients. Assess CrCl to determine dosage (see Dosage for patients with renal impairment).

Children > 2 years: Based on pharmacokinetic data, the manufacturer suggests an initial dose of 90 mg/m2/day, given in 3 divided doses. May gradually increase dosage up to a maximum of 180 mg/m2/day. Adjust dosage at intervals >= 36 hours; monitor QT intervals. Alternatively, doses of 2—4 mg/kg/day PO (given in 2—3 divided doses) have been studied in children. This dose may be increased by 1—2 mg/kg/day every 3—4 days, up to a maximum of 8 mg/kg/day PO.[1531] [1532]

Children <= 2 years: Based on pharmacokinetic data, the manufacturer suggests that the initial pediatric dosage (see dosage for children > 2 years) be reduced by a age-specific factor. This factor is determined by plotting the child's age on a logarithmic scale provided by the manufacturer (refer to complete prescribing information).

Oral Dosage (Betapace AF™) for switching to sotalol from other antiarrhythmics:

Adults: Individualize dosage based on clinical response, CrCl, and QTc. Before initiating sotalol, the previous antiarrhythmic therapy should be withdrawn under careful monitoring for a minimum of (2—3) plasma half-lives for the discontinued drug. Sotalol treatment has been initiated in patients on intravenous lidocaine without ill effect. Because of unpredictable pharmacokinetics with amiodarone, sotalol should not be initiated following discontinuation of amiodarone therapy until the QTc interval has normalized.

Elderly: Elderly patients may have a prolonged drug half-life. Age-associated decline in renal function may contribute to reduced renal clearance in elderly patients. Assess CrCl to determine dosage (see Dosage for patients with renal impairment).

Oral Dosage (Betapace AF™) for maintenance sotalol therapy:

Adults: Individualize dosage based on clinical response, CrCl, and QTc. Continue the sotalol dosage from hospital discharge following the initial dosage titration. Renal function and QTc should be re-evaluated regularly or as medically warranted. If the QTc >= 520 msec at any time, sotalol dosage should be reduced and the patient should be carefully monitored until QTc returns to baseline levels. If the patient is receiving 80 mg PO once or twice daily and the QTc is >= 520 msec, sotalol should be discontinued. If renal function deteriorates, adjust the dose as described in the dosage guidelines for patients with renal impairment. Sotalol was found to be comparable to quinidine in maintaining sinus rhythm after 6 months of therapy following cardioversion in 183 patients. Sotalol was also observed to slow ventricular rate in the event of a relapse.[1201]

Elderly: Elderly patients may have a prolonged drug half-life. Age-associated decline in renal function may contribute to reduced renal clearance in elderly patients. Assess CrCl to determine dosage (see Dosage for patients with renal impairment).

Children: Individualize dosage based on clinical response, CrCl, and QTc. Adjust dosage at intervals >= 36 hours.

For the treatment of ventricular arrhythmias, such as sustained ventricular tachycardia that are deemed to be life-threatening :

NOTE: Initial doses of sotalol must be individualized according to CrCl and the QTc. Prior to initiating sotalol, the QTc must be determined. Sotalol is contraindicated if QT prolongation is present at baseline.

Intravenous dosage (Investigational in US†):

Adults: NOTE: The IV formulation is pending FDA approval for use in the U.S. Dosage cannot be recommended at this time.[2999]

Oral dosage (Betapace®) for the initiation or titration of sotalol treatment:

Adults: Initially, 80 mg PO twice per day in patient with normal renal function. Individualize dosage based on clinical response, CrCl, and QTc. The starting dose of sotalol is based on CrCl (see Patients with renal impairment). Dosage should be adjusted gradually in increments of 40—80 mg, at 3 days intervals as needed and tolerated. Dosage may be increased to 240—320 mg/day PO given in two divided doses. During initiation and titration, monitor the QTc between 2—4 hours after each dose. Sotalol should be used with

particular caution if the QT c > 500 msec. If the QTc prolongs to >= 550 msec, the sotalol dose should be decreased or the drug discontinued. Patients should be monitored by continuous ECG for >= 3 days after dosage titration or for at least 5—6 doses of sotalol if dosing is once daily. Dosage up to 640 mg/day should only be used if the benefits outweigh the risks, such as the risk of proarrhythmia.
Elderly: Elderly patients may have a prolonged drug half-life. Age-associated decline in renal function may contribute to reduced renal clearance in elderly patients. Assess CrCl to determine dosage (see Dosage for patients with renal impairment).
Children > 2 years: Based on pharmacokinetic data, the manufacturer suggests an initial dose of 90 mg/m2/day, given in 3 divided doses. May gradually increase dosage up to a maximum of 180 mg/m2/day. Adjust dosage at intervals >= 36 hours; monitor QT intervals. Alternatively, doses of 2—4 mg/kg/day PO (given in 2—3 divided doses) have been studied in children. This dose may be increased by 1—2 mg/kg/day every 3—4 days, up to a maximum of 8 mg/kg/day PO.[1531] [1532]
Children <= 2 years: Based on pharmacokinetic data, the manufacturer suggests that the initial pediatric dosage (see dosage for children > 2 years) be reduced by a age-specific factor. This factor is determined by plotting the child's age on a logarithmic scale provided by the manufacturer (refer to complete prescribing information).
Oral Dosage (Betapace®) switching to sotalol from other antiarrhythmics:
Adults: Individualize dosage based on clinical response, CrCl, and QTc. Before initiating sotalol, the previous antiarrhythmic therapy should be withdrawn under careful monitoring for a minimum of (2—3) plasma half-lives for the discontinued drug. Sotalol treatment has been initiated in patients on intravenous lidocaine without ill effect. Because of unpredictable pharmacokinetics with amiodarone, sotalol should not be initiated following discontinuation of amiodarone therapy until the QTc interval has normalized.
Elderly: Elderly patients may have a prolonged drug half-life. Age-associated decline in renal function may contribute to reduced renal clearance in elderly patients. Assess CrCl to determine dosage (see Dosage for patients with renal impairment).
Oral Dosage (Betapace®) for maintenance sotalol therapy:
Adults: Individualize dosage based on clinical response, CrCl, and QTc. Continue the sotalol dosage from hospital discharge following the initial dosage titration. Renal function and QTc should be re-evaluated regularly or as medically warranted. If the QTc >= 520 msec at any time, sotalol dosage should be reduced and the patient should be carefully monitored until QTc returns to baseline levels. If renal function deteriorates, adjust the dose as described in the dosage guidelines for patients with renal impairment.
Elderly: Elderly patients may have a prolonged drug half-life. Age-associated decline in renal function may contribute to reduced renal clearance in elderly patients. Assess CrCl to determine dosage (see Dosage for patients with renal impairment).
Children: Individualize dosage based on clinical response, CrCl, and QTc. Adjust dosage at intervals >= 36 hours.
For the maintenance of sinus rhythm in patients with refractory paroxysmal supraventricular tachycardia (i.e., paroxysmal supraventricular tachycardia (PSVT) prophylaxis†), including patients with Wolff-Parkinson-White (WPW) syndrome†:
Oral dosage:
Children > 2 years: Based on pharmacokinetic data, the manufacturer suggests an initial dose of 90 mg/m2/day, given in 3 divided doses. May gradually increase dosage up to a maximum of 180 mg/m2/day. Adjust dosage at intervals >= 36 hours; monitor QT intervals. Alternatively, doses of 2—4 mg/kg/day PO (given in 2—3 divided doses) have been studied in children. This dose may be increased by 1—2 mg/kg/day every 3—4 days, up to a maximum of 8 mg/kg/day PO.[1531] [1532]
Children <= 2 years: Based on pharmacokinetic data, the manufacturer suggests that the initial pediatric dosage (see dosage for children > 2 years) be reduced by a age-specific factor. This factor is determined by plotting the child's age on a logarithmic scale provided by the manufacturer (refer to complete prescribing information).
Maximum Dosage Limits:
•*Adults:* 320 mg/day PO for atrial fibrillation/atrial flutter (i.e., Betapace AF™). Up to 480—640 mg/day PO in life-threatening ventricular arrhythmias (i.e., Betapace®) provided benefits of higher dosage outweigh risks.
•*Elderly:* 320 mg/day PO for atrial fibrillation/atrial flutter (i.e., Betapace AF™). Up to 480—640 mg/day PO in life-threatening ventricular arrhythmias (i.e., Betapace®) provided benefits of higher dosage outweigh risks.
•*Adolescents:* Safe and effective use has not been established.
•*Children > 2 years:* 180 mg/m2/day PO is the maximum dosage recommended by the manufacturer; up to 8 mg/kg/day PO has been studied in children.[1531] [1532]
•*Children <= 2 years:* See full prescribing information for age-specific dosing chart.
Patients with hepatic impairment:
No dosage adjustment in hepatic impairment is needed; sotalol is not metabolized and is eliminated unchanged via the kidney.
Patients with renal impairment:
NOTE: Safe and effective use in children with renal impairment has not been established.
CrCl > 60 ml/min: No dosage adjustment needed, give appropriate dosage every 8—12 hours according to the indication (ventricular vs. atrial arrhythmia) and clinical response. The initial recommended adult dose is 80 mg PO twice daily for both indications.
CrCl 40—60 ml/min: Extend dosage interval to every 24 hours for adults. The initial recommended adult dose is 80 mg PO once every 24 hours.
CrCl < 40 ml/min: Use is contraindicated for the treatment of atrial arrhythmias (i.e., Betapace AF™) if CrCl < 40 ml/min. For adults with ventricular arrhythmias (i.e., Betapace®), if CrCL is < 30 ml/min use a sotalol dosage interval of 36—48 hours according to clinical response. Patients with CrCl < 10 ml/min should receive individualized dosages.
Intermittent hemodialysis:
See dosage adjustments for patients with CrCl < 40 ml/min. Use extreme caution in patients on hemodialysis, the half-life of sotalol is prolonged up to 69 hours in anuric patients. While sotalol is partially removed by hemodialysis, subsequent partial rebound in sotalol concentrations will occur once the dialysis session is completed. Both heart rate and QT interval, as well as efficacy (arrhythmia control) must be carefully monitored. Safe and effective use in children with renal impairment has not been established.
†non-FDA-approved indication

Indications...Dosage last revised 2/10/2004 3:08:00 PM

Administration Guidelines

NOTE: Due to a risk for proarrhythmia, the initiation or upward titration of sotalol dosage requires continual telemetry monitoring in

a hospitalized setting for a minimum of 3 days.
NOTE: Doses of sotalol must be individualized according to CrCl, the baseline QTc, and the indication for use.
NOTE: Although they are both sotalol, Betapace® should not be substituted for Betapace AF™ due to significant differences in indications, dosage, administration, safety information, and the patient package insert appropriate for patients with atrial fibrillation provided in the approved product labeling for Betapace AF™.
Oral Administration
•Sotalol may be administered with or without food.
•Patients on sotalol must be discharged with an adequate home supply to allow uninterrupted dosing.
•Betapace® should generally not be substituted for Betapace AF™ because of significant differences in indications, dosing, administration and safety information. The labeling for Betapace® discusses the use of sotalol for ventricular arrhythmias and Betapace AF™ labeling discusses the use of sotalol for atrial arrhythmias (e.g., atrial fibrillation and flutter).
Administration last revised 2/10/2004 2:39:00 PM

Contraindications/Precautions

- *abrupt discontinuation*
- *acute bronchospasm*
- *AV block*
- *bradycardia*
- *heart failure*
- *hypokalemia*
- *hypomagnesemia*
- *pulmonary edema*
- *QT prolongation*
- *torsade de pointes*
- acute myocardial infarction
- asthma
- breast-feeding
- bronchitis
- cardiogenic shock
- cerebrovascular disease
- children
- chronic obstructive pulmonary disease (COPD)
- depression
- diabetes mellitus
- dialysis
- driving or operating machinery
- elderly
- electrolyte imbalance
- emphysema
- females
- hyperthyroidism
- hypotension
- myasthenia gravis
- peripheral vascular disease
- pheochromocytoma
- pregnancy
- psoriasis
- pulmonary disease
- Raynaud's disease
- renal disease
- renal failure
- renal impairment
- sick sinus syndrome
- surgery
- thyroid disease
- thyrotoxicosis
- vasospastic angina
- ventricular arrhythmias
- ventricular dysfunction
- ventricular fibrillation
- ventricular tachycardia

• *Absolute contraindications are in italics.*

Abrupt discontinuation of sotalol can precipitate arrhythmias and possibly myocardial infarction. If the drug must be discontinued abruptly, the temporary use of an alternative beta-blocker may be considered. Patients should be advised not to discontinue treatment with sotalol abruptly; gradual dose reduction over 1 or 2 weeks is recommended.
Beta-blockers should be used with caution in patients with hyperthyroidism or thyrotoxicosis because the drug can mask tachycardia, which is a useful monitoring parameter in thyroid disease. Abrupt withdrawal of beta-blockers in a patient with hyperthyroidism can precipitate thyroid storm. However, certain beta-blockers are generally useful in the symptomatic treatment of hyperthyroid-related states, like thyrotoxicosis.
Sotalol is contraindicated in patients with sinus *bradycardia,* sick sinus syndrome or second or third degree *AV block* unless a functioning pacemaker is present, congenital or acquired *QT prolongation* syndromes, *hypokalemia*, *cardiogenic shock*, or uncontrolled *heart failure*. Although Betapace AF™ is specifically contraindicated in patients with *sick sinus syndrome,* the prescribing information for the Betapace® product indicates a warning, recommending that Betapace® be used with extreme caution in patients with symptomatic sick sinus syndrome.[4960] [5598] Patients with symptomatic sick sinus syndrome are generally managed with placement of a pacemaker to prevent sinus bradycardia, sinus pause, and/or sinus arrest. In general, beta-blockers should not be used in patients with *cardiogenic shock, acute pulmonary edema,* or acute systolic congestive heart failure, particularly in those with severely compromised left ventricular dysfunction, because the negative inotropic effect of these drugs can further depress cardiac output. In stable patients with heart failure, however, beta-blockers (e.g., bisoprolol, carvedilol, metoprolol) given in low doses have been documented to be beneficial. Sotalol should not be used in patients with *QT prolongation* or hypokalemia because it could precipitate *torsade de pointes*. Despite the fact that sotalol is a beta-blocker, sotalol is proarrhythmic and can induce ventricular arrhythmias or worsen preexisting ventricular arrhythmias. Like amiodarone, another class III antiarrhythmic, sotalol has been associated with QT prolongation which can lead to sustained ventricular fibrillation, sustained ventricular tachycardia, and/or torsade de pointes (see Adverse Reactions). Although it is sometimes difficult to distinguish between a patient's underlying malignant arrhythmia and a drug-induced arrhythmia, patients with an initially normal QT interval who subsequently suffer a proarrhythmic event generally do so as the result of antiarrhythmic therapy. Use of antiarrhythmic drugs has been associated with sudden death, and patients are continually at risk, not just during the initiation of therapy as was once believed. Risk factors for sotalol-induced arrhythmias include renal disease, electrolyte imbalance (e.g., *hypokalemia, hypomagnesemia*), and concomitant use of other drugs known to prolong the QT interval. Females and patients with a history of ventricular arrhythmias or ventricular tachycardia may also

have a higher incidence of proarrhythmic events (e.g., torsade de pointes).
Because of potential effects of beta-blockade on blood pressure and pulse, beta-blockers should be used with caution in patients with cerebrovascular insufficiency (cerebrovascular disease) or stroke. If signs or symptoms suggesting reduced cerebral blood flow develop following initiation of beta-blocker, alternative therapy should be considered.
Because sotalol exhibits beta-adrenergic blocking activity, effects on blood pressure and pulse are possible. In hypertensive patients, sotalol produces significant reductions in both systolic and diastolic blood pressures. In addition, patients receiving sotalol and other antihypertensive drugs should be monitored closely for hypotension.
Sotalol is relatively contraindicated in renal impairment or renal failure because of possible decreased clearance of the drug, since it is principally eliminated via renal processes. The use of sotalol is absolutely contraindicated for the treatment of atrial arrhythmias (Betapace AF™) when the CrCl is < 40 ml/min. When using Betapace® for the treatment of ventricular arrhythmias, dosage adjustment is recommended when the creatinine clearance is < 60 ml/min. Safe and effective use in pediatric patients with renal impairment has not been established. Use extreme caution in patients on hemodialysis, the half-life of sotalol is prolonged up to 69 hours in anuric patients. While sotalol is partially removed by hemodialysis, subsequent partial rebound in sotalol concentrations will occur once the dialysis session is completed. Both heart rate and QT interval, as well as efficacy (arrhythmia control) must be carefully monitored.
Beta-blocker monotherapy should be used with caution in patients with a pheochromocytoma or vasospastic angina (Prinzmetal's angina) because of the risk of hypertension secondary to unopposed alpha-receptor stimulation. In patients with pheochromocytoma, an alpha-blocking agent should be used prior to the initiation of any beta-blocker.
The necessity or desirability of withdrawing beta-blockers prior to major surgery is controversial; the risks versus benefits should be evaluated in individual patients. Patients receiving beta-blockers before or during surgery involving the use of general anesthetics with negative inotropic effects (e.g., ether, cyclopropane, or trichloroethylene) should be monitored closely for signs of heart failure. Severe, protracted hypotension and difficulty in restarting the heart have been reported after surgery in patients receiving beta-blockers. Gradual withdrawal of beta-blockers is sometimes recommended prior to general anesthesia to limit the potential for hypotension and heart failure, because of the reduced ability of the heart to respond to beta-adrenergically mediated sympathetic reflex stimuli. However, it may not be advisable to withdraw beta-blockers prior to elective surgery in many patients. The risk of precipitating adverse cardiac events (e.g., myocardial infarction, tachycardia) following preoperative withdrawal of beta-blockers may outweigh the risks of ongoing beta-blocker therapy, particularly in patients with co-existing cardiovascular disease. Consideration should be given to the type of surgery (e.g., cardiac vs. noncardiac), anesthetic strategy, and co-existing health conditions. The anesthetic technique may be modified to reduce the risk of concurrent beta-blocker therapy. If needed, the negative inotropic effects of beta-blockers may be cautiously reversed by sufficient doses of adrenergic agonists such as isoproterenol, dopamine, dobutamine, or norepinephrine. Vagal dominance, if it occurs, may be corrected with atropine (1—2 mg IV).
Sotalol (non-specific beta-blocker) is contraindicated in patients with a pulmonary disease such as *bronchial asthma* or during *acute bronchospasm* because bronchodilation can be inhibited by beta-blockade. Sotalol should be avoided where possible, or used with caution at the lowest effective dose in patients with nonallergic bronchospastic disease [e.g., chronic obstructive pulmonary disease (COPD), emphysema, bronchitis].
In general, beta-blockers have been shown to increase the risk of developing diabetes mellitus in hypertensive patients; however this risk should be evaluated relative to the proven benefits of beta-blockers in reducing cardiovascular events.[3498] Sotalol should be used with caution in patients with diabetes mellitus because it can mask signs of hypoglycemia such as tachycardia, palpitations, tremor, and feelings of anxiety (but not diaphoresis). Sotalol may also prolong or enhance hypoglycemia by interfering with glycogenolysis.
Sotalol is classified as FDA pregnancy risk category B. Adequate evaluation of the use of sotalol during pregnancy has not been completed. Sotalol has been shown to cross the placenta and can be found in amniotic fluid. One case of subnormal birth weight was reported with use of sotalol in a pregnant woman. All beta-blockers have the potential for causing fetal bradycardia. Thus, sotalol should be used during pregnancy only when the benefits outweigh the potential risk to the fetus.
Sotalol should be used with caution in breast-feeding mothers because the drug is distributed into breast milk. Concentrations in breast milk can be three times those in the maternal blood.
Beta-blockers may be associated with dizziness or drowsiness in some patients. Patients should be cautioned to avoid driving or operating machinery until the drug response is known.
Sotalol is relatively contraindicated in patients with Raynaud's disease or peripheral vascular disease because reduced cardiac output and the relative increase in alpha stimulation can exacerbate symptoms.
The relationship between depression and beta-blockers has not been definitively established. Beta-blockers should be used with caution in patients with major depression.
Beta-blockers may exacerbate conditions such as psoriasis.
Beta-blockers may potentiate muscle weakness and double vision in patients with myasthenia gravis.
Beta-blockers can be used safely in elderly patients, however these patients may have unpredictable responses to beta-blockers. The elderly may be less sensitive to the antihypertensive effects of the drug, however, reduced elimination (via renal excretion) may increase the potency of sotalol in this population. Elderly patients have been documented to have a prolonged sotalol half-life relative to younger patients (11 vs. 7 hours). Age-associated decline in renal function may contribute to reduced renal clearance in elderly patients; assess CrCl to determine dosage (see Dosage for patients with renal impairment). The elderly have age-related peripheral vascular disease and the relative increase in alpha stimulation can exacerbate symptoms. Geriatric patients are at increased risk of beta-blocker-induced hypothermia.
According to the manufacturer labeling for Betapace® and Betapace AF™, the safety and effectiveness of sotalol has not been established in children. However, sotalol has been used off-label to treat ventricular and atrial arrhythmias in children; limited data are available (see Dosage). The manufacturer provides some dosing recommendations based on pediatric pharmacokinetic data; wait at least 36 hours between dosage adjustments to allow monitoring of QT intervals. Safe and effective use in children with renal impairment has not been established.
Although sotalol can be used safely in the long-term treatment of ventricular arrhythmias following myocardial infarction, the manufacturer warns that the use of sotalol in the early phase following acute myocardial infarction (MI) is limited and may be of concern at high initial dosages. The manufacturer advises caution and careful dosage titration (especially in patients with markedly impaired ventricular function) for use of sotalol during the first 2 weeks post-MI. The manufacturer notes that sotalol (up to 320 mg/day PO) has been used without affecting mortality in one large study of patients following a recent acute MI. However one large trial (320 mg/day PO; non-titrated) and one smaller trial (320 mg PO twice daily) have observed an excess of early sudden deaths in post-MI patients receiving sotalol therapy. During investigation of the d-isomer of sotalol (virtually devoid of beta-blocking activity and considered a pure Class III antiarrhythmic) as an antiarrhythmic in high-risk patients post-MI, a higher mortality rate has been

observed with d-sotalol versus placebo, presumably due to increased arrhythmic deaths (SWORD trial).[2950]

Contraindications last revised 12/29/2006 2:29:00 PM

Drug Interactions

- Adenosine
- Alfuzosin
- Amoxapine
  - Antacids
  - Antidiabetic Agents
  - Antihypertensive Agents
- Arsenic Trioxide
- Astemizole
- Bepridil
  - Beta-agonists
  - Beta-blockers
- Cevimeline
- Chloroquine
- Ciprofloxacin
- Cisapride
- Clarithromycin
  - Class IA antiarrhythmics
  - Class III antiarrhythmics
- Clonidine
- Clozapine
- Cocaine
- Colesevelam
- Conivaptan
- Cyclobenzaprine
- Cyclopropane
- Dasatinib
- Digoxin
- Diltiazem
  - Diuretics
- Dolasetron
- Droperidol
- Encainide
  - Ergot Alkaloids
- Erythromycin
- Ethanol
- Flecainide
- Gatifloxacin
- Gemifloxacin
  - General Anesthetics
- Ginger, Zingiber officinale
- Glucagon
- Grepafloxacin
- Halofantrine
  - Halogenated anesthetics
- Haloperidol
- Hawthorn, Crataegus laevigata
- Lapatinib
- Levodopa
- Levofloxacin
- Levomethadyl
- Lidocaine
  - Local Anesthetics
- Maprotiline
- Mefloquine
- Methadone
  - Monoamine oxidase inhibitors (MAOIs)
- Moricizine
- Moxifloxacin
- Norfloxacin
- Octreotide
- Ofloxacin
- Olanzapine
- Ondansetron
- Paliperidone
- Palonosetron
- Pentamidine
  - Phenothiazines
- Pilocarpine
- Pimozide
- Propafenone
- Quetiapine
  - Radiopaque Contrast Agents
- Ranolazine
- Risperidone
- Sevelamer
- Sodium Phosphate Monobasic Monohydrate; Sodium Phosphate Dibasic Anhydrous
- Sparfloxacin
- Succinylcholine
- Sunitinib
  - Sympathomimetics
- Tacrolimus
- Telithromycin
- Terfenadine
- Theophylline, Aminophylline
  - Thyroid hormones
  - Tricyclic antidepressants
- Troleandomycin
- Vardenafil
- Verapamil
- Vorinostat
- Ziprasidone

NOTE: Most drug interactions with sotalol occur via enhanced pharmacological and electrophysiologic effects (beta-blockade, QT prolongation, AV blockade) with other drugs. Sotalol is primarily eliminated by renal excretion and does not induce or inhibit CYP 450 enzymes; therefore, sotalol is not expected to have drug interactions associated with hepatic metabolism.[5558]
Because the pharmacologic effects of sotalol include depression of AV nodal conduction and myocardial function,[5558] additive effects are possible when used in combination with adenosine [5001] or other antiarrhythmics or drugs that also significantly depress AV nodal conduction or myocardial function, especially in patients with pre-existing left ventricular dysfunction. The risk of additive inhibition of AV conduction is symptomatic bradycardia with hypotension or advanced AV block; whereas additive negative inotropic effects could precipitate overt heart failure in some patients. Using sotalol with other beta-blockers would be illogical as it would represent duplicate therapy; additive effects on AV nodal conduction and blood pressure would be expected.[5001]
Digoxin used concomitantly with sotalol can increase the possibility of proarrhythmia. Sotalol does not appear to interfere

substantially with digoxin serum levels. Proarrhythmic events were more common in sotalol-treated patients also receiving digoxin; it is not clear whether this represents an interaction or is related to the presence of CHF, a known risk factor for proarrhythmia, in the patients receiving digoxin.[5558] Despite potential for interactions, digoxin sometimes is intentionally used in combination with sotalol. Nevertheless, these combinations should be used cautiously, and therapy dosages may need adjustment in some patients.
There is limited experience when using class 1C antiarrhythmics in combination with sotalol.[5558] Pharmacologically, sotalol causes AV nodal conduction depression [5558] and additive effects are possible when used in combination with class 1C antiarrhythmic drugs including flecainide [5016], propafenone [5014], moricizine [1478], and encainide [5808].Patients should be monitored closely if class IC antiarrhythmic drugs are used in combination with sotalol, and the dose should be adjusted according to clinical response.
There is limited experience when using class IB antiarrhythmics in combination with sotalol.[5558] Propranolol has been shown to decrease lidocaine clearance and symptoms of lidocaine toxicity have been seen as a result of this interaction. The mechanism of this interaction is thought to be due to propranolol-induced decreased hepatic blood flow causing decreased elimination of lidocaine. This interaction is possible with other beta-blocking agents as most decrease hepatic blood flow. Monitoring of lidocaine concentrations is recommended during concomitant therapy.[5001]
Beta-blocking drugs may potentiate the rebound hypertension sometimes observed after discontinuation of clonidine; therefore, caution is advised when discontinuing clonidine in patients receiving sotalol.[5558] If a beta-blocker is to be substituted for clonidine, clonidine should be gradually tapered and the beta-blocker should be gradually increased over several days to avoid the possibility of rebound hypertension; administration of beta-blockers during withdrawal of clonidine can precipitate severe increases in blood pressure as a result of unopposed alpha stimulation.[5017] It is possible to administer clonidine and beta-blockers concurrently without sequelae, although hypotensive effects can be additive.
Conivaptan has been associated with hypokalemia (9.8%).[8569] Drug-induced hypokalemia increases the potential for proarrhythmic effects (e.g., torsade de pointes) due to sotalol [4960].
Diuretics should be used cautiously with sotalol and should be accompanied by close monitoring of electrolyte balance because hypokalemia and hypomagnesemia have been associated with an increased risk of proarrhythmia.[5558] Sotalol is contraindicated in patients with uncorrected hypokalemia (< 4 mEq/ml). No pharmacokinetic interaction has been observed between sotalol and hydrochlorothiazide.[5558]
Bepridil has been associated with QT prolongation and concomitant use with sotalol should be avoided where possible. Use sotalol with considerable caution along with other calcium-channel blockers with additional AV nodal-blocking activity such as verapamil and diltiazem. Sotalol should generally be administered with caution in conjunction with calcium-channel blocks, due to possible additive effects on AV conduction or ventricular function.[5558] Additionally, concomitant use of sotalol and calcium-channel blockers or other antihypertensive agents may have additive effects on blood pressure, possibly leading to hypotension.[5558] Patients treated with catecholamine-depleting agents, such as reserpine, other rauwolfia alkaloids, or guanethidine, together with sotalol should be carefully monitored because excessive reductions in resting sympathetic tone can produce hypotension or bradycardia, precipitating a syncopal episode.[5558]
The effects of beta-agonists can be reduced with concurrent use of sotalol, which is a non-selective beta-blocker. Increased beta-adrenergic agonist dosages may be required during concurrent administration with sotalol.[5558] Although sotalol is not used as an antihypertensive, its beta-blocking activities may interfere with the vasopressor actions of some sympathomimetics. Prior administration of a beta-blocker has been shown to potentiate phenylephrine's vasoconstricting effects. Phenylephrine has been postulated to occupy, but not stimulate, beta2-receptors in blood vessels. Sotalol therefore may occupy these receptors and effectively increase the quantity of the drug available for stimulation of alpha receptors. The effect of unopposed alpha vasoconstriction can result in hypertension and/or reflex bradycardia. The effect may be more likely to occur with non-selective beta-blockers.[5052] While taking beta-blockers, patients with a history of severe anaphylactic reaction to a variety of allergens may be more reactive to repeated challenge, either accidental, diagnostic, or therapeutic; such patients may be unresponsive to the usual doses of epinephrine used to treat allergic reactions.[5558]
Sotalol administration is associated with a well-established risk of QT prolongation and torsades de pointes (TdP).[4960] [4951] [5558] Drugs that prolong the QT interval should be avoided where possible or used with extreme caution in combination with sotalol. Ventricular tachycardia, including torsade de pointes and monomorphic ventricular tachycardia can occur with excessive prolongation of the QT interval. Examples of agents which may prolong the QT interval include: Class IA antiarrhythmics [4951] [4952] [5187] and other Class III antiarrhythmics [4951] [4952] [5187]. Before initiating sotalol, the previous Class I and Class III antiarrhythmic therapy should be withdrawn under careful monitoring for a minimum of (2—3) plasma half-lives for the discontinued drug. Class III antiarrhythmics (e.g., amiodarone, dofetilide) are associated with QT prolongation and ventricular arrhythmias; concurrent exposure with sotalol could increase the risk of drug-induced proarrhythmias. Because of unpredictable pharmacokinetics with amiodarone, sotalol should not be initiated following discontinuation of amiodarone therapy until the QTc interval has normalized. In addition to avoiding concurrent drug interactions, the potential for TdP can be reduced by avoiding the use of QT prolonging drugs in patients at substantial risk for TdP.[5162] Examples of general risk factors for TdP include congenital long QT syndrome, female sex, elderly patients, significant bradycardia, hypokalemia, hypomagnesemia, and underlying cardiac disease (e.g., arrhythmias, cardiomyopathy, acute myocardial ischemia).
Although beta-blocking agents are used to treat or reduce the signs and symptoms of cocaine intoxication and the subsequent cardiovascular manifestations of cocaine withdrawal, excessive alpha-agonism has been reported either secondary to cocaine or due to endogenous catecholamines. It has been suggested that when non-selective beta-blockers are used during cocaine intoxication, unopposed alpha stimulation ensues. In theory, the use of alpha-blocker and beta-blocker combinations or selective beta-blockers in low doses may not cause unopposed alpha stimulation in this situation.[5053] In addition, cocaine can reduce the therapeutic effects of beta-blockers.
Sotalol administration is associated with a well-established risk of QT prolongation and torsades de pointes (TdP).[4960] [4951] [5558] Drugs that prolong the QT interval should be avoided where possible or used with extreme caution in combination with sotalol. Ventricular tachycardia, including torsade de pointes and monomorphic ventricular tachycardia can occur with excessive prolongation of the QT interval. In addition to Class IA and Class III antiarrhythmic drugs previously mentioned, other drugs which have been established to have a causal association with QT prolongation and TdP include: astemizole [140], arsenic trioxide [4951] [4977], bepridil [4951] [4953], cisapride [4951], chloroquine [4951] [4955] [4956], clarithromycin [4951] [4964], droperidol [3610] [4951] [4963], erythromycin [228] [4951] [4978], grepafloxacin [5149], halofantrine [4951] [4968], haloperidol [42] [336] [4951] [5036], levomethadyl [4951] [5079] [5081] [5146], methadone [4951] [5048] [5049] [5050] [5051], pentamidine [168] [335] [4951] [5149], certain phenothiazines (chlorpromazine [4951], mesoridazine [4951] [5831], and thioridazine [4951] [5022]), pimozide [4951], probucol [5145], sparfloxacin [4951] [4958], and terfenadine [141] [231]. Drugs associated with a lower, but possible risk for QT prolongation and TdP based on varying levels of documentation (see separate drug monographs) include: alfuzosin [4988], amoxapine [5145], beta-agonists [4951] [5038] [5047], ofloxacin [7501], ciprofloxacin [4951] [5149] [5496]

[5507] [6579], clozapine [5146], cyclobenzaprine [5155] [5156], dasatinib [9211], dolasetron [5037], flecainide [331] [5484], gatifloxacin [5149] [5150] [5152], gemifloxacin [5154], halogenated anesthetics [5187] [5188] [5486] [5487] [5488], lapatinib [10040], levofloxacin [5149] [5150] [5151], local anesthetics, maprotiline [5145], moxifloxacin [5149] [5150] [5153], olanzapine [9575] [9576], ondansetron [8046], norfloxacin [6564], octreotide [4951], paliperidone [9784], palonosetron [5148], some phenothiazines (fluphenazine [5145], perphenazine [5145], prochlorperazine [5145], and trifluoperazine [5145]), propafenone [5014] [5146], quetiapine [5855] [9916] [9920] [9922], risperidone [4951] [5144], ranolazine [8747], sertindole [5187], sunitinib [8779], tacrolimus [4049] [4050] [4951], telithromycin [4880], tricyclic antidepressants when given in excessive doses or overdosage [5145] [5146], troleandomycin (based on interactions with macrolides) [5149], vardenafil [4942], vorinostat [9633], or ziprasidone [4959]. This list is not inclusive of all agents that can cause QT interval prolongation. Some of the drugs listed are contraindicated for use with other drugs known to cause QT prolongation such as sotalol. In addition to avoiding concurrent drug interactions, the potential for TdP can be reduced by avoiding the use of QT prolonging drugs in patients at substantial risk for TdP.[5162] Examples of general risk factors for TdP include congenital long QT syndrome, female sex, elderly patients, significant bradycardia, hypokalemia, hypomagnesemia, and underlying cardiac disease (e.g., arrhythmias, cardiomyopathy, acute myocardial ischemia).

Sodium phosphate monobasic monohydrate; sodium phosphate dibasic anhydrous is considered to be associated with an increased risk for QT prolongation. The need to coadminister sodium phosphate salt products with drugs known to prolong the QT interval such as sotalol should be done with a careful assessment of risks and benefits. Consider the risks of QT prolongation along with the risks for potential electrolyte imbalance before treatment with sodium phosphate salts.[8973] [8974]

Because thyroid hormones cause cardiac stimulation including increased heart rate and increased contractility,[5178] the effects of beta-blockers may be reduced by thyroid hormones. The reduction of effects may be especially evident when a patient goes from a hypothyroid to a euthyroid state or when excessive amounts of thyroid hormone is given to the patient. In addition, because liothyronine (T3) has more pronounced cardiovascular side effects when compared to levothyroxine (T4), the effects on beta-blockers may be more common in patients treated with liothyronine.[6268]

Hyperglycemia may occur during sotalol therapy and the symptoms of hypoglycemia may be masked; the dosage of insulin or antidiabetic drugs may require adjustment during concurrent therapy.[5558] Beta-blockers exert complex actions on the body's ability to regulate blood glucose.[6141] Beta-blockers can prolong hypoglycemia by interfering with glycogenolysis (secondary to blocking the compensatory actions of epinephrine) or can promote hyperglycemia (by inhibiting insulin secretion and decreasing tissue sensitivity to insulin). Furthermore, a prospective trial in non-diabetic patients with hypertension indicated that treatment with beta-blockers increased the risk of the development of diabetes by 28% at six years.[7335] Since insulin secretion is mediated via beta2-receptors, beta-blockers, particularly nonselective agents, can directly antagonize the major beneficial effect of sulfonylureas. The ability to decrease tissue sensitivity to insulin interferes with one of the therapeutic effects of metformin. Also, beta-blockers can blunt the tachycardic response and exaggerate the hypertensive response to hypoglycemia. Thus, while no pharmacokinetic interaction has been observed between beta-blockers and antidiabetic agents, patients receiving beta-blockers and antidiabetic agents concomitantly should be closely monitored for an inappropriate response. Selective beta-blockers, such as acebutolol, atenolol, or metoprolol can cause fewer problems with blood glucose regulation, although these agents can still mask the symptoms of hypoglycemia.[6141] While beta-blockers may have negative effects on glycemic control, they reduce the risk of cardiovascular disease and stroke in patients with diabetes.[7247] Furthermore, their use should not be avoided in patients with compelling indications for beta-blocker therapy (i.e., post-MI, heart failure, etc.) when no other contraindications are present. Decreased mortality has been shown in the post-MI and heart failure populations when beta-blockers are used, especially in patients with coexisting diabetes mellitus.[6141]

General anesthetics can potentiate the antihypertensive effects of beta-blockers and can produce prolonged hypotension.[5054] Patients receiving beta-blockers before or during surgery involving general anesthetics that possess negative inotropic effects (e.g., ether or cyclopropane) should be monitored closely for signs of heart failure. Severe, protracted hypotension and difficulty in restarting the heart have been reported after surgery on patients receiving beta-blockers.[5558]

Limited data suggest that bradycardia is worsened when monoamine oxidase inhibitors (MAOIs) are administered to patients receiving beta-blockers. Although the sinus bradycardia observed was not severe, until more data are available, clinicians should use MAOIs cautiously in patients receiving beta-blockers.[5055]

Whenever possible, concomitant use of beta-blockers and ergotamine or dihydroergotamine or other ergot alkaloids should be avoided, since non-selective beta-blockers have been reported to potentiate the vasoconstrictive action of ergotamine or dihydroergotamine by blocking the vasodilating property of epinephrine.[5018] [5585] [5623] The risk of peripheral ischemia, resulting in cold extremities or gangrene, has been reported to be increased when ergotamine or dihydroergotamine is coadministered with non-selective beta-blockers.[5589] [5590] [5591] [5592] However, the precise mechanism of these interactions remains elusive.[5591] Additionally, because of the potential to cause coronary vasospasm [5018] [5585] [5623], ergot alkaloids could antagonize the therapeutic effects of anti-anginal agents including beta-blockers; clinicians should keep in mind that such ergot alkaloids are contraindicated for use in patients with coronary heart disease or hypertension.

In vitro studies have demonstrated the positive inotropic effects of ginger, Zingiber officinale.[2217] It is theoretically possible that ginger could affect the action of antiarrhythmics, however, no clinical data are available.

Following hawthorn administration to guinea pigs, the cardiac action potential duration is increased and the refractory period is prolonged.[2367] Hawthorn, Crataegus laevigata appears to block delayed and inward rectifier potassium currents in ventricular cardiac cells, leading to prolongation of the cardiac action potential. This herb could interact with Class III antiarrhythmic agents and concurrent use should be avoided. However, no clinical data are available.

Coadministration of antacids with sotalol reduces the Cmax and AUC of sotalol by 26% and 20%, respectively. This interaction results in a 25% reduction in the bradycardic effect of sotalol (measured at rest).[5558] Antacid administration two hours after the sotalol dose does not alter sotalol pharmacokinetics or pharmacodynamics.[5558] Patients should be instructed to avoid using antacids containing aluminum hydroxide or magnesium hydroxide within 2 hours of taking sotalol.[5558]

Cevimeline may alter cardiac conduction and/or heart rate. Conduction disturbances are possible with concurrent use of beta-blockers and cevimeline.[5256]

Concurrent use of mefloquine and beta-blockers can result in ECG abnormalities or cardiac arrest.[5030]

Concomitant use of levodopa with hypotensive agents such as sotalol can result in additive hypotensive effects.[5251]

Because beta-blockers blunt sympathomimetic-mediated hepatic gluconeogenesis,[6270] beta-blockers can inhibit the hyperglycemic actions of glucagon. In addition, intravenous administration of glucagon has been shown to have positive inotropic and chronotropic effects. A transient increase in both blood pressure and pulse rate may occur following the administration of glucagon, especially in patients taking beta-blockers.[5358] Because glucagon has positive inotropic properties, it may be a useful alternative for treating beta-blocker-induced heart failure unresponsive to beta-agonists. Clinicians should be aware of these opposing pharmacologic

actions of glucagon and beta-blockers.
Sotalol, a non specific beta-blocker, can cause bronchospasm in patients requiring theophylline for bronchospastic disease [5558], and theophylline can antagonize some of the therapeutic cardiovascular actions of sotalol.
Acute alcohol consumption lowers blood pressure; ethanol may interact with antihypertensive agents by potentiating their hypotensive effect.[5944]
No pharmacokinetic interaction has been observed between sotalol and warfarin.[5558]
Conflicting data exists as to whether or not patients taking beta-blockers are at increased risk for anaphylaxis. Some consider patients taking beta-blockers to be at increased risk for anaphylactoid reactions and administer prophylactic corticosteroids/antihistamines prior to the administration of radiopaque contrast agents.[5423]
Beta-blockers can enhance the neuromuscular blocking activity of succinylcholine.[6950]
The manufacturer for colesevelam suggests monitoring serum drug concentrations and/or clinical effects when colesevelam is coadministered with drugs with a narrow therapeutic index.[7576] To minimize potential for interactions, consider administering oral antiarrhythmics such as sotalol at least 1 hour before or at least 4 hours after colesevelam.
Systemically administered pilocarpine (e.g., when used for the treatment of xerostomia or xerophthalmia) should be administered with caution in patients taking beta-blockers including sotalol because of the possibility of cardiac conduction disturbances.[9981] The risk of conduction disturbances with beta-blockers and ophthalmically administered pilocarpine is low.
When sevelamer is coadministered with oral drugs considered to have narrow therapeutic ranges (i.e., antiarrhythmics), the potential for reduced drug absorption could result in clinical significance, with the potential for loss of efficacy. To minimize this interaction, patients should be advised to separate the administration of antiarrhythmics by at least 1 hour before or 3 hours after sevelamer. In addition, patients should be monitored for changes in efficacy of the antiarrhythmics when these drugs are coadministered.[4827]

Interactions last revised 6/1/2007 1:58:00 PM

Adverse Reactions

- angina
- arrhythmia exacerbation
- asthenia
- bradycardia
- diabetes mellitus
- dizziness
- dyspnea
- elevated hepatic enzymes
- fatigue
- heart failure
- hyperglycemia
- hypoglycemia
- hypotension
- nausea/vomiting
- palpitations
- peripheral neuropathy
- QT prolongation
- torsade de pointes
- ventricular fibrillation
- ventricular tachycardia

Adverse reactions most often reported across sotalol doses studied during Betapace® premarketing trials in patients treated for ventricular arrhythmias included: fatigue (20%), sinus bradycardia (16%), and dyspnea (21%). In patients with a history of ventricular tachycardia or ventricular fibrillation, additional adverse effects have been reported, including angina (16%), palpitations (14%), dizziness (12%), and nausea/vomiting (10%). Discontinuation of sotalol was necessary in about 16—17% of patients treated for VT/VF in clinical trials, the most frequently reported side effects leading to discontinuation were fatigue (4%), bradycardia (3%), dyspnea (3%), proarrhythmia (3%), asthenia (2%), dizziness (2%), and hypotension (2%). During premarketing trials for Betapace AF™ during treatment of atrial fibrillation (AFIB) or atrial flutter (AFL), the most common reactions were similar to those reported during the VT/VF clinical trials. Dose-related reactions included: bradycardia, dyspnea, fatigue, and QT prolongation. In the AFIB/AFL trials, the most common adverse events leading to discontinuation of Betapace AF™ included: fatigue (4.6%), bradycardia (2.4%), proarrhythmia (2.2%), dyspnea (2%), and QT prolongation 1.4%). Arrhythmia exacerbation may occur during sotalol therapy.
Sotalol is associated with dose-related QT prolongation, which can lead to sustained ventricular fibrillation, sustained ventricular tachycardia, and/or torsade de pointes.[325] Torsade de pointes occurs in about 2.3% of patients, while the incidence of all proarrhythmic events is about 5.5%. Proarrhythmia typically occurs during the first month of therapy or after an increase in dosage. Patients with adverse renal function should receive lower doses to reduce the risk of drug accumulation and possible proarrhythmias. Careful monitoring of QT intervals and electrolyte balance is critical with sotalol therapy to minimize potentially lethal adverse events.
As with all beta-blockers, sotalol may worsen congestive heart failure due to systolic dysfunction. In premarketing studies, new or worsened congestive heart failure occurred in 3.3% of patients and led to discontinuation of therapy in about 1% of patients. The incidence was higher in patients presenting with sustained ventricular tachycardia/fibrillation (4.6%) or with a history of heart failure (7.3%).
In general, beta-blockers have been shown to increase the risk of developing diabetes mellitus in hypertensive patients; however this risk should be evaluated relative to the proven benefits of beta-blockers in reducing cardiovascular events.[3498] Because sotalol is a beta-blocker, it may prolong or enhance hypoglycemia by interfering with glycogenolysis. Sotalol may also mask signs of hypoglycemia, especially tachycardia, palpitations, and tremors; in contrast, diaphoresis and the hypertensive response to hypoglycemia are not suppressed with beta-blockade. Beta-blockers can occasionally cause hyperglycemia. This is thought to be due to blockade of beta2-receptors on pancreatic islet cells, which would inhibit insulin secretion.
Occasional reports of elevated hepatic enzymes have occurred during sotalol therapy; no causal relationship has been established.
One case of peripheral neuropathy, which resolved upon discontinuation of sotalol and recurred with rechallenge, has been reported.

Adverse Reactions last revised 5/24/2007 8:49:00 PM

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Isosorbide Mononitrate
Imdur® | Ismo® | Monoket®
Classification:
• Cardiovascular Agents
  • Antianginals
    • Nitrates
Description, Mechanism of Action, Pharmacokinetics

Description: Isosorbide-5-mononitrate, the long-acting metabolite of isosorbide dinitrate, is a vasodilatory agent used for the prophylactic management of angina pectoris. Isosorbide mononitrate is not subject to first-pass metabolism and therefore has improved bioavailability and a significantly longer half-life than isosorbide dinitrate. Isosorbide mononitrate (Ismo™) was approved by the FDA in December 1991. Monoket®, a second immediate-release isosorbide mononitrate product, was granted FDA approval in June 1993. An extended-release formulation (Imdur®) was approved by the FDA in August 1993.

Mechanism of Action: Similar to other nitrites and organic nitrates, isosorbide mononitrate is converted to nitric oxide (NO), a reactive free radical. Nitric oxide is also formed endogenously and is believed to be endothelial-derived growth factor. Among other properties, NO is believed to produce vasodilation. Nitric oxide, the active intermediate compound common to all agents of this class, activates the enzyme guanylate cyclase, thereby stimulating the synthesis of cyclic guanosine 3',5'-monophosphate (cGMP). This second messenger then activates a series of protein kinase-dependent phosphorylations in the smooth muscle cells, eventually resulting in the dephosphorylation of the myosin light chain of the smooth muscle fiber and the subsequent release, or extrusion, of calcium ions. The contractile state of smooth muscle is normally maintained by a phosphorylated myosin light chain (stimulated by an increase in calcium ions). Thus, the nitrite- or nitrate-induced dephosphorylation of the myosin light chain signals the cell to release calcium, thereby relaxing the smooth muscle cells and producing vasodilation.
It is believed that nitrates reduce myocardial oxygen demand by causing direct relaxation of vascular smooth muscle. This results in dilation of peripheral venous vessels, causing pooling of venous blood and decreased venous return to the heart, which decreases preload. Peripheral arteries are also dilated, although this effect occurs at dosages larger than those required to dilate veins. Arteriolar relaxation reduces systemic vascular resistance, systolic arterial pressure, and mean arterial pressure (afterload). Thus, nitrates reduce both venous filling pressures and arterial impedance, resulting in a reduction of left ventricular systolic wall tension. Nitrate-induced reduction of wall tension from reduced ventricular volume and pressure leads to a lowering of myocardial oxygen demand.
Nitrates can increase total coronary blood flow in patients with normal coronary arteries. However, in patients with ischemic heart disease, the drug may not increase total coronary blood flow but may simply redistribute blood to ischemic areas. This effect is believed to be due to the drug's preferential dilation of the larger conductive vessels of the coronary circulation, which, in the presence of coronary atherosclerosis, redirects the distribution of the coronary blood supply to ischemic areas.
Nitrates cause a transient reflex compensatory increase in heart rate and myocardial contractility, which normally would increase myocardial oxygen consumption, yet the nitrate-induced decrease in ventricular wall tension results in a net decrease in myocardial oxygen demand and amelioration of the pain of angina pectoris. In addition, isosorbide relaxes all other types of smooth muscle including bronchial, biliary, GI, ureteral, and uterine. Nitrites and nitrates are functional antagonists of acetylcholine, norepinephrine, and histamine.
In individuals who have little compensatory tachycardia response, syncope can result from the decrease in blood pressure that occurs following higher doses of nitrates and nitrites. Although this is not likely to occur with doses of nitrates that do not cause blood pressure reduction, patients should be sitting or lying down during and immediately after administration of isosorbide dinitrate.
Pharmacokinetics: Isosorbide-5-mononitrate is rapidly and completely absorbed from the GI tract and is not metabolized in the liver. Thus, the absolute bioavailability following oral administration is nearly 100%, and maximal serum concentrations are achieved in 30—60 minutes. Peak antianginal effects are evident in 1—4 hours. Less than 4% of an oral dose is plasma protein-bound, with isosorbide being only minimally distributed throughout the body. The drug is metabolized via glucuronidation to the mononitrate glucuronide and other inactive metabolites. At least 99% of the drug is metabolized prior to elimination in the urine. The plasma half-life of the drug is approximately 5 hours and is not affected by age or renal or hepatic impairment.

Description, Mechanism of Action, Pharmacokinetics last revised 8/25/2003 2:27:00 PM

Indications

• angina

Dosage
For the chronic treatment of angina pectoris due to coronary artery disease:
Oral dosage- Immediate-release tablets (Ismo™ or Monoket®):
Adults: 20 mg PO twice daily, with doses given 7 hours apart ('asymmetric' or 'eccentric' dosing, to allow a 12 hour nitrate-free interval). However, a starting dose of 5 mg may be appropriate in patients with small stature, which should be increased to at least 10 mg by day 2—3 of therapy. Doses > 20 mg twice daily have not been adequately studied.
Elderly: See adult dosage. In general, the initial dose for an elderly patient should start at the low end of the dosage range. Adjust dosage based on clinical response. Elderly patients may be more sensitive to hypotensive effects of nitrates.
Children: Safe and effective use has not been established.
Oral dosage- Extended-release tablets (Imdur®):
Adults: 30—60 mg PO once daily, preferably in the morning upon awakening. After several days, the dosage may be increased to

120 mg (given as a single 120 mg tablet or two 60 mg tablets) once daily. Rarely, up to 240 mg/day (once daily) may be needed.
Elderly: See adult dosage. In general, the initial dose for an elderly patient should start at the low end of the dosage range. Adjust dosage based on clinical response. Elderly patients may be more sensitive to hypotensive effects of nitrates.
Children: Safe and effective use has not been established.

Maximum Dosage Limits:

•*Adults:* 40 mg/day PO for immediate-release tablets (e.g., Ismo™, Monoket®); 240 mg/day PO for extended-release tablets (e.g., Imdur®).
•*Elderly:* 40 mg/day PO for immediate-release tablets (e.g., Ismo™, Monoket®); 240 mg/day PO for extended-release tablets (e.g., Imdur®).
•*Adolescents:* Safe and effective use has not been established.
•*Children:* Safe and effective use has not been established.

Patients with hepatic impairment:

No dosage adjustment needed.

Patients with renal impairment:

No dosage adjustment needed.

Intermittent hemodialysis:

Isosorbide mononitrate is significantly removed from the blood during hemodialysis (AUC is decreased by 30%); however, supplemental dosage is generally not needed following dialysis.

Indications...Dosage last revised 8/26/2003 5:21:00 PM

Administration Guidelines

NOTE: Isosorbide mononitrate should not be used to abort acute anginal attacks. The interdosing ('nitrate-free') interval sufficient to avoid tolerance to isosorbide mononitrate has not been completely defined. For immediate-release products (e.g., Ismo™, Monoket®), a twice daily dosage regimen with the two doses given 7 hours apart has been shown to avoid development of tolerance.

Oral Administration

•*All dosage forms*: Food may decrease the rate but not the extent of absorption. Administer with at least 4 ounces (120 ml) of fluid.
•*Extended-release tablets*: Swallow intact; do not crush or chew.

Administration last revised 8/26/2003 10:17:00 AM

Contraindications/Precautions

- *closed-angle glaucoma*
- *head trauma*
- *increased intracranial pressure*
- *intracranial bleeding*
- *nitrate hypersensitivity*
- abrupt discontinuation
- anemia
- breast-feeding
- cardiomyopathy
- children
- dehydration
- elderly
- GI disease
- glaucoma
- hyperthyroidism
- hypotension
- hypovolemia
- myocardial infarction
- orthostatic hypotension
- pregnancy
- syncope

• *Absolute contraindications are in italics.*

Isosorbide mononitrate should be used cautiously in patients with recent myocardial infarction because drug-induced hypotension and/or tachycardia can worsen or expand ischemic damage, and the effects of long-acting nitrates are difficult to terminate quickly. Patients with low filling (diastolic) pressure are particularly predisposed to this effect.
Isosorbide mononitrate should be used with caution in patients with hypotension because the drug can worsen hypotension, cause a paradoxical bradycardia, and/or exacerbate angina. Preexisting orthostatic hypotension, hypovolemia, or dehydration can worsen this effect. Nitrate-induced hypotension has resulted in fatalities. Elderly patients may be more sensitive to the hypotensive effects of nitrates. The elderly are at higher risk of falling due to syncope at therapeutic doses of nitrates. Elderly patients may have reduced baroceptor function; severe orthostatic hypotension may occur when vasodilators such as nitrates are administered. Nitrate therapy can also worsen angina due to hypertrophic cardiomyopathy, particularly in the elderly. In general, the initial dose of isosorbide mononitrate for an elderly patient should start at the low end of the adult dosing range, with subsequent dosage adjustment based on clinical response.
Isosorbide mononitrate should not be used in patients with increased intracranial pressure (e.g., recent *head trauma* or *intracranial bleeding*) because the drug's vasodilatory effects on the meningeal blood vessels can exacerbate these conditions.
Isosorbide mononitrate is contraindicated in patients with *closed-angle glaucoma* due to the risk of drug-induced increased intraocular pressure.
Isosorbide mononitrate is contraindicated in patients with severe anemia because the drug causes oxidation of hemoglobin to methemoglobin, which could exacerbate this condition.
Isosorbide mononitrate is absolutely contraindicated in patients who have known *nitrate hypersensitivity.*
Isosorbide mononitrate should be used cautiously in patients with hepatic disease because metabolism of the drug can be impaired,

resulting in an increased risk of methemoglobinemia.
When nitrates are to be discontinued following long-term or high-dose administration, avoid abrupt discontinuation to avoid potential for rebound angina.
Isosorbide mononitrate is generally classified as pregnancy risk category C. Although no adequate human studies have examined the effects of this drug on the fetus, and animal reproduction studies have shown adverse fetal effects for the initial isosorbide mononitrate product (Ismo™). Therefore, in making the decision to administer this drug during pregnancy, the potential risks to the fetus must be weighed against the potential benefits to the mother. The FDA ratings for the specific isosorbide mononitrate products vary, with Ismo™ classified as pregnancy category C. In contrast, Monoket® and Imdur® are specifically classified by the FDA as a pregnancy risk cateogy B drugs, as the animal studies did not show adverse fetal effects; however, no adequate and well-controlled studies in pregnant women are available. Because animal studies are not always predictive of human response, Imdur® and Monoket® should only be used during pregnancy when clearly needed.
It is not known whether isosorbide mononitrate is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when isosorbide mononitate is administered to a woman who is breast-feeding.
Isosorbide mononitrate is relatively contraindicated in patients with hyperthyroidism.
Extended-release isosorbide mononitrate products should be avoided in patients with GI disease such as hypermotility or malabsorption syndromes. This dosage form may not dissolve and may be excreted intact in these conditions.
The safety and effectiveness of isosorbide mononitrate in children have not been established.

Contraindications last revised 8/17/2005 3:38:00 PM

Drug Interactions

Antihypertensive Agents
- Ethanol
- Hawthorn, Crataegus laevigata
- Prilocaine
- Sildenafil

Sympathomimetics
- Tadalafil
- Vardenafil

Vasodilators

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]
The pharmacology of sympathomimetic drugs includes stimulatory effects on adrenergic receptors which can result in increases in heart rate and blood pressure.[6289] Concomitant use of nitrates such as isosorbide mononitrate with sympathomimetics, including epinephrine, phenylephrine, ephedra, or ephedrine, can result in antagonism of the antianginal effects of nitrates.[6124] [6288] In addition, the vasodilatory effects of nitrates [6124] [6288] can block the alpha-adrenergic effects of epinephrine [6234] [6290], possibly precipitating tachycardia and severe hypotension.
Nitrates amplify the vasodilatory effects of sildenafil or other phosphodiesterase inhibitors (e.g., vardenafil, tadalafil) if coadministered and result in severe hypotension.[6124] [6288] Coadministration of sildenafil [4923], tadalafil [4946], or vardenafil [4942] to patients who are concurrently using organic nitrates or nitrites in any form is considered contraindicated.
Hawthorn, *Crataegus laevigata* may lower peripheral vascular resistance [4713] and exhibit additive hypotensive effects with nitrates.
Patients treated with prilocaine who are receiving nitrates concurrently are at greater risk for developing methemoglobinemia.[5799] [6288]

Interactions last revised 7/23/2004 12:52:00 PM

Adverse Reactions

- cyanosis
- diaphoresis
- dizziness
- flushing
- headache
- hypotension
- methemoglobinemia
- nausea/vomiting
- orthostatic hypotension
- sinus tachycardia
- syncope
- tolerance

A persistent, throbbing headache can occur following isosorbide mononitrate administration. Although nitrate-induced headaches usually diminish quickly, acetaminophen or other analgesic agents may be given to alleviate the pain. Severe or prolonged headaches are rare but warrant prompt medical attention.
Orthostatic hypotension can occur following administration of nitrates, accompanied by dizziness, weakness, nausea/vomiting, and occasionally syncope. Hypotension, adverse cardiovascular effects, and syncope have been reported in patients receiving isosorbide mononitrate, but these effects occurred in fewer than 1% of the patients receiving the drug.
Hypersensitivity to the drug also can occur, resulting in cutaneous vasodilation, flushing, diaphoresis, sinus tachycardia, syncope, palpitations, and cardiovascular collapse. Patients should be sitting or lying down during and immediately after nitrate therapy.
Methemoglobinemia is a rare adverse reaction with nitrate products. Symptoms of methemoglobinemia include cyanosis (blue discoloration of the lips and mucous membranes), nausea/vomiting, coma, and shock. These symptoms are usually associated with

high doses/overdoses of nitrate products, but can be seen at normal therapeutic doses.
Tolerance to isosorbide mononitrate or attenuation of the drug's vasodilatory effects can develop when large or sustained dosages are given. This effect is probably related to both the size of the dose and the frequency of the dosing interval. If tolerance occurs, it is recommended that isosorbide mononitrate be administered in two doses, 7 hours apart, followed by a 17-hour, drug-free interval. This interval is crucial because it allows plasma concentrations of isosorbide mononitrate to decrease, preventing drug tolerance and avoiding the development of attenuation of the drug's antianginal effects.

Adverse Reactions last revised 7/1/2002

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Clopidogrel
Plavix®
Classification:
- Hematological Agents
  - Platelet Inhibitors

Description, Mechanism of Action, Pharmacokinetics

Description: Clopidogrel is an oral antiplatelet agent with a structure and mechanism of action similar to ticlopidine. It is associated with a lower incidence of adverse cutaneous, gastrointestinal, or hematologic adverse reactions than ticlopidine. Unlike ticlopidine, clopidogrel does not require routine hematologic monitoring. Overall tolerability associated with use of clopidogrel appears to be similar to that of aspirin; however, gastrointestinal bleeding may occur less often with clopidogrel. Conversely, clopidogrel appears to possess a slightly higher incidence of neutropenia than aspirin, although severe neutropenia is rare with either drug. Clopidogrel was approved by the FDA for reduction of atherosclerotic events in November 1997. Several of the potential uses of clopidogrel are discussed below.
•Arterial thromboembolism prophylaxis in patients with established cardiovascular disease: Clopidogrel is used to reduce atherosclerotic events (stroke, myocardial infarction, and vascular death) in patients with a history of recent stroke, recent myocardial infarction (MI), or established peripheral vascular disease. The CAPRIE study shows that it is more effective than aspirin in reducing atherosclerotic events in high risk patients.[1637] The CAPRIE study included three types of patients, those with recent MI, recent stroke, or symptomatic peripheral arterial disease. In these populations clopidogrel has been shown to reduce atherosclerotic events. In the CHARISMA trial, patients with a history of or at risk for cardiovascular disease (n > 15,000) were randomized to 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 cardiovascular death compared with aspirin alone (rate of 6.8% in the combination group vs. 7.3% in the aspirin only group, p=0.22); 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 an increased risk of severe bleeding. Data from a sub-group analysis should be interpreted with caution; the data indicate that combination antiplatelet therapy in patients with established cardiovascular disease reduces the risk of recurrent MI, stroke, or cardiovascular death (rate of 6.9% in the combination therapy group vs. 7.9% in the aspirin only group; RR 0.88, 95% CI 0.77—0.998, p=0.046). However, in patients without established cardiovascular disease but who have risk factors including diabetes mellitus, hypertension, or hypercholesterolemia, combination antiplatelet therapy is not associated with a difference in clinical outcomes and may be associated with an increased risk of cardiovascular death. 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 combination therapy in patients without established cardiovascular disease.[8833] [9091]
•Acute coronary syndrome (ACS): In the acute coronary syndrome (ACS) population, clopidogrel has been shown to decrease cardiovascular events.[686] [687] The CURE study evaluated the efficacy and safety of the combination of clopidogrel plus aspirin in patients with ACS without ST-segment elevation (unstable angina or non-Q-wave acute myocardial infarction); clopidogrel plus aspirin reduced cardiovascular events (combined endpoint: cardiovascular death, non-fatal MI, or stroke).[686] Several additional studies have demonstrated a benefit of long-term combination clopidogrel/aspirin therapy in reducing cardiovascular events in patients with ACS undergoing percutaneous coronary intervention (PCI).[687] [4335] Accordingly, the 2006 AHA/ACC guidelines for secondary prevention for patients with coronary and other atherosclerotic vascular disease recommend that in patients with ACS, including patients undergoing PCI with stent placement, clopidogrel should be used with aspirin for up to 12 months.[9219] In patients with a sirolimus drug eluting stent (DES), the current recommendation is to continue clopidogrel for at least 3 months and for up to 12 months after stent placement; in patients with a paclitaxel DES, the current recommendation is to continue clopidogrel

for at least 6 months and for up to 12 months after stent placement.[9219] The ACC and AHA strongly encourage a full 12 months of dual antiplatelet therapy in patients with DES.[9219] [9914] In addition, premature discontinuation is discouraged, including the temporary discontinuation of clopidogrel and aspirin for elective surgery. The recommendation of the AHA and ACC is to postpone elective surgery until at least 12 months after DES placement when possible.[9914] Observational evidence indicates that 6 months of clopidogrel in combination with aspirin after placement of a DES may not be sufficient. In one study, after receiving clopidogrel for 6 months following DES or bare metal stent (BMS) placement, patients discontinued clopidogrel and were followed for an additional 7—18 months; the rate of cardiac death or MI was significantly higher in patients with DES vs. BMS during this time period (4.9% vs. 1.3%, respectively), which minimized the overall benefit of DES vs. BMS for the total 18 months of follow-up.[9765] In a second study in patients with DES receiving clopidogrel for 6 months, subsequent discontinuation of clopidogrel was associated with a higher rate of death than in those patients continuing clopidogrel for 24 months (2% in patients continuing clopidogrel vs. 5.3% in patients stopping clopidogrel, P=0.03); similar results were found for death or MI (3.1% in patients continuing clopidogrel vs. 7.2% in patients stopping clopidogrel, P=0.02).[9766] Neither of these studies evaluated the additional risks of treatment (e.g., bleeding) with extended therapy. It should be noted that an FDA panel met in December 2006 to discuss these findings, and a consensus on the extended use of clopidogrel in DES patients was not met. Furthermore, randomized clinical trials are needed before the optimal duration of clopidogrel therapy in DES patients can be determined. Clopidogrel is preferred to ticlopidine for ACS due to its improved safety profile and shorter onset of action.[2998] Although the risk of major bleeding is increased with clopidogrel in ACS, the risk of hemorrhagic stroke or life-threatening bleeding is not increased.[686]

•***ST-segment elevation myocardial infarction (STEMI):*** In patients with ST-segment elevation MI (STEMI), clopidogrel added to standard therapy (e.g., aspirin with or without fibrinolytic therapy) has been shown to improve rates of patency of the related infarcted artery and reduce recurrent MI, ischemia, stroke, and death, without increasing the risk of minor or major bleeding. These outcomes have been demonstrated in patients regardless of whether or not they undergo angioplasty or percutaneous coronary intervention (PCI).[9236] [9237] The FDA approved clopidogrel for the treatment of acute ST segment elevation myocardial infarction (STEMI) on August 16, 2006.

•***Stroke prophylaxis in patients with noncardioembolic TIA or stroke:*** For patients with a history of noncardioembolic TIA or stroke, the American College of Chest Physicians (ACCP) recommends clopidogrel as one of several first-line antiplatelet regimens; other first-line regimens include low-dose aspirin or aspirin; dipyridamole combination therapy (Grade 1A recommendation).[7011] [7012]

•***Cardioembolic stroke prophylaxis in patients with atrial fibrillation:*** Although warfarin remains the treatment of choice for stroke prophylaxis in patients with atrial fibrillation, clopidogrel has been investigated for use in this population. The Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events (ACTIVE) has been initiated to determine the benefits of clopidogrel with aspirin for the prevention of cardioembolic stroke in patients with atrial fibrillation. One arm of the trial, ACTIVE W, which randomized patients that were eligible and willing to take warfarin to either aspirin (75—100 mg/day) plus clopidogrel (75 mg/day) or warfarin (goal INR 2—3), was stopped early (after a median of 1.28 years) as aspirin plus clopidogrel was found to be inferior to warfarin; in addition, minor but not major bleeding was more common in patients receiving combination antiplatelet therapy.[9199] A second arm of the study, ACTIVE A is ongoing and has randomized patients ineligible or unwilling to take warfarin to either aspirin or aspirin plus clopidogrel. The role of combination antiplatelet therapy in patients ineligible or unwilling to take warfarin therapy is not yet known.

Mechanism of Action: Clopidogrel is a thienopyridine compound which acts to antagonize adenosine diphosphate (ADP). Clopidogrel is inactive *in vitro* and requires hepatic activation to exert its antiplatelet effect. The active metabolite selectively and irreversibly inhibits ADP-induced platelet aggregation. It prevents binding of adenosine diphosphate (ADP) to its platelet receptor. Thus, ADP-mediated activation of the glycoprotein GPIIb/IIIa complex is impaired. Because the glycoprotein GPIIb/IIIa complex is the major receptor for fibrinogen, impaired activation of the GPIIb/IIIa complex prevents fibrinogen binding to platelets which ultimately inhibits platelet aggregation. Because the active metabolite of clopidogrel irreversibly modifies the platelet ADP receptor; platelets exposed to the drug are affected for the remainder of their lifespan. In platelet aggregation studies, clopidogrel 75 mg once daily produced inhibition of ADP-induced platelet aggregation equivalent to that of ticlopidine 250 mg twice daily. The active metabolite of clopidogrel also inhibits platelet aggregation induced by agonists other than ADP by blocking the amplification of platelet activation by released ADP; the active metabolite does not inhibit phosphodiesterase.

Pharmacokinetics: Clopidogrel is administered orally; it is inactive *in vitro* and requires hepatic biotransformation to an active metabolite. Previously, hepatic activation was thought to be mediated by the CYP P450 1A subfamily [5476]; however, more recent *in vivo* [5477] and *in vitro* [5163] evidence indicate that hepatic activation is mediated by the CYP 3A subfamily. The uncharacterized active metabolite is labile and highly reactive. The pharmacokinetic profile of clopidogrel is described using the pharmacologically inactive primary metabolite, a carboxylic-acid derivative. The carboxylic-acid derivative represents roughly 85% of the circulating metabolites in plasma.

Following oral administration, clopidogrel is rapidly absorbed and undergoes extensive first-pass metabolism in the liver. Absorption is at least 50% and is not significantly affected by food. Peak plasma concentrations (roughly 3 mg/L) of the primary circulating metabolite occur at about one hour following multiple dosing of 75 mg/day. Plasma concentrations of the parent drug are undetectable 2 hours after an oral dose. Plasma concentrations of the main circulating metabolite increase proportionally with clopidogrel doses in the range of 50—150 mg. Clopidogrel and the main circulating metabolite bind reversibly *in vitro* to human plasma proteins (98% and 94%, respectively). Approximately 50% of radiolabeled clopidogrel is eliminated in urine and about 46% via the feces over a period of 5 days. The half-life of the carboxylic acid derivative is roughly 8 hours.

Dose dependent inhibition of platelet aggregation can be seen two hours after a single oral dose. With repeated doses of 75 mg/day, maximum inhibition of platelet aggregation is achieved within 3—7 days. At steady state, platelet aggregation is inhibited by 40—60%. Bleeding time prolongation is not significantly affected by age, renal impairment, or gender. Platelet aggregation and bleeding time gradually return to baseline about 5 days after discontinuation of clopidogrel.

Description, Mechanism of Action, Pharmacokinetics last revised 2/23/2007 1:00:00 PM

Indications

- acute myocardial infarction
- stroke prophylaxis

- arterial thromboembolism prophylaxis
- myocardial infarction prophylaxis
- percutaneous coronary intervention (PCI)
- thrombosis prophylaxis
- transient ischemic attack (TIA)
- unstable angina

Dosage

For arterial thromboembolism prophylaxis (i.e., myocardial infarction prophylaxis, stroke prophylaxis, thrombosis prophylaxis):

•for patients with stable coronary artery disease, congestive heart failure, or atherosclerosis as documented by recent stroke, transient ischemic attack (TIA), recent myocardial infarction, or established peripheral arterial disease:

NOTE: For patients with a history of noncardioembolic TIA or stroke, the American College of Chest Physicians (ACCP) recommends clopidogrel, low-dose aspirin, or aspirin; dipyridamole combination therapy as first-line treatments (Grade 1A recommendation).[7011] [7012] In patients who can not tolerate aspirin or have an aspirin allergy, clopidogrel should be used. The use of aspirin plus clopidogrel is not recommended as the combination is not associated with an added benefit, but is associated with an increased risk of bleeding.[9239]

NOTE: Results of the large CHARISMA study indicate that in patients at risk for cardiovascular disease, combination therapy of clopidogrel plus low-dose aspirin versus aspirin alone does not reduce the risk of recurrent myocardial infarction, stroke, or cardiovascular death. Furthermore, combination therapy is associated with an increase in moderate bleeding.[8833] [9091]

Oral dosage:

Adults: 75 mg PO once daily. Per the American College of Chest Physicians (ACCP), in those patients with stable coronary artery disease or congestive heart failure who are considered to be at high-risk for a myocardial infarction, clopidogrel 75 mg PO once daily should be administered in combination with aspirin.[9241]

Elderly: See adult dosage.

Children: Safe and effective use has not been established.

•for patients with acute coronary syndrome (unstable angina or non-Q-wave acute myocardial infarction), including patients who are to be managed medically, and for those undergoing percutaneous coronary intervention (PCI) or CABG:

NOTE: In the CURE study, most patients with acute coronary syndrome (ACS) also received heparin acutely, and the use of GPIIb/IIIa inhibitors were not permitted for 3 days prior to study randomization. Although the risk of major bleeding is increased with clopidogrel in ACS, the risk of hemorrhagic stroke or life-threatening bleeding is not increased.[686]

Oral dosage:

Adults: The FDA-approved regimen is a 300 mg PO loading dose, then 75 mg PO once daily in combination with aspirin.[2998] Per the 2006 AHA/ACC guidelines for secondary prevention in patients with coronary or other atherosclerotic vascular disease, clopidogrel should be given to all patients with ACS for up to 12 months; aspirin (75—162 mg/day PO) should be continued indefinitely.[9219] In patients with an aspirin allergy, clopidogrel monotherapy can be used.[9242] In patients undergoing PCI, the clopidogrel 300 mg loading dose should be administered at least 6 hours before the procedure. A 600 mg loading dose has also been used; however the safety and efficacy compared to 300 mg is less established. A higher loading dose will more rapidly achieve a higher level of antiplatelet activity.[4464] [4465] [9238] The 2006 AHA/ACC guidelines recommend that in patients that have had a bare metal stent placed after PCI, clopidogrel should be given for a minimum of 1 month, with aspirin initially given at a higher dose (325 mg/day PO) for 1 month. In patients that have had a sirolimus-eluting stent placed, clopidogrel should be given for a minimum of 3 months, with aspirin given at a higher dose for 3 months; for patients that have had a paclitaxel-eluting stent placed, clopidogrel should be given for a minimum of 6 months, with aspirin given at a higher dose for 6 months. However, the ACC and AHA strongly encourage the use of both aspirin and clopidogrel for a full 12 months following stent placement.[9219] [9914] Furthermore, premature discontinuation of dual antiplatelet therapy by other clinicians is discouraged, even in the setting of elective surgery. It is recommended by these organizations that elective surgery be delayed for 12 months following a drug-eluting stent placement (and at least for 1 month following bare metal stent placement). If the surgery can not be delayed, continuing aspirin in high-risk patients should be considered.[9914] If CABG is planned, withhold clopidogrel for at least 5—7 days prior to the procedure to minimize potential for bleeding.[2998] A loading dose of clopidogrel 300 mg PO can be administered 6 hours after CABG followed by 75 mg PO once daily for 9—12 months. Clopidogrel should be administered in combination with aspirin.[9241]

Elderly: See adult dosage.

Children: Safe and effective use have not been established.

•for patients with ST-segment elevation MI (STEMI):

Oral dosage:

Adults: 75 mg PO once daily in combination with aspirin, with or without a 300 mg PO loading dose, is the recommended dose. Clopidogrel can be administered with or without thrombolytics. Additionally, per the American College of Chest Physicians (ACCP), clopidogrel 300 mg PO followed by 75 mg PO once daily is recommended for patients that can not tolerate or have an allergy to aspirin.[9242] In patients with ST-segment elevation MI (STEMI), 75 mg PO once daily in addition to aspirin 75—162 mg PO per day with or without either a fibrinolytic agent or anticoagulant has been shown to improve rates of patency of the related infarcted artery and reduce recurrent MI, ischemia, stroke, and death, without increasing the risk of minor or major bleeding. This benefit is not known to pertain to patients who receive primary angioplasty.[9236] [9238] In the CLARITY-TIMI 28 trial, approximately 3500 patients < 75 years were randomized to receive a clopidogrel 300mg PO loading dose followed by 75 mg PO daily or placebo in addition to a fibrinolytic agent, aspirin, and an anticoagulant (if indicated). Approximately 94% of the patients underwent angiography; in these patients, clopidogrel or placebo was continued through the day of angiography. In patients not undergoing angiography, clopidogrel or placebo was continued for 8 days or until hospital discharge, whichever occurred first. The median number of doses of study drug administered was four. PCI, which occurred from days 2—8 (median 3.5 days) after enrollment, was performed in approximately 57% of patients. The primary efficacy endpoint (occluded infarct-related artery at angiography plus death or recurrent infarction prior to angiography; or death or reinfarction by day 8 or hospital discharge in those patients not undergoing angiography) occurred in 15% of patients receiving clopidogrel vs. 21.7% of patients receiving placebo (36% relative reduction; $P<0.001$). All patients were offered open-label clopidogrel after angiography or PCI. The odds of cardiovascular death, recurrent MI, or recurrent ischemia occurring at 30 days was reduced by 20% in patients treated with clopidogrel (from 14.1 to 11.6%, $P=0.03$).[9236] In the COMMIT study, aspirin plus clopidogrel or placebo was administered to patients until hospital discharge or for 4 weeks, whichever occurred first; a loading dose of clopidogrel was not administered. Approximately 54% of the patients received a fibrinolytic agent and 75% received an anticoagulant. Approximately 3% of the patients in this study underwent an elective PCI. The mean duration of clopidogrel or placebo in survivors was 14.9 days. Death, reinfarction, and stroke were

reduced in patients that received clopidogrel (9.2% for clopidogrel vs. 10.1% for placebo, P=0.002); additionally, death from any cause was reduced in patients receiving clopidogrel (7.5% for clopidogrel vs. 8.1% for placebo, P=0.03). It should be noted that in this study, the rates of efficacy or bleeding were not different in patients > 70 years of age versus those <= 70 years of age.[9237]
Elderly: See adult dosage. NOTE: The safety and efficacy of a 300 mg loading dose in combination with aspirin and fibrinolytics in elderly patients >= 75 years of age is not known.[9236]
Children: Safe and effective use have not been established.

Maximum Dosage Limits:

•*Adults:* 75 mg/day PO chronic treatment (up to 600 mg PO for single loading dose).
•*Elderly:* 75 mg/day PO chronic treatment (up to 600 mg PO for single loading dose).
•*Adolescents:* Safe and effective use has not been established.
•*Children:* Safe and effective use has not been established.

Patients with hepatic impairment:

No specific guidelines are available. Clopidogrel is extensively metabolized by the liver and dosage reductions may be needed in moderate to severe hepatic disease. Use caution in patients with severe hepatic disease, who may have bleeding diatheses.

Patients with renal impairment:

Although no dosage adjustment is recommended, the manufacturer warns that clopidogrel should be used with caution in patients with severe renal impairment. Experience is limited in this patient population.

Indications...Dosage last revised 2/23/2007 1:00:00 PM

Administration Guidelines

Oral Administration

•Clopidogrel is administered with or without food.

Administration last revised 7/10/2006 10:14:00 AM

Contraindications/Precautions

- *bleeding*
- *GI bleeding*
- *intracranial bleeding*
- *retinal bleeding*
- *retroperitoneal bleeding*
- breast-feeding
- children
- elderly
- hepatic disease
- peptic ulcer disease
- pregnancy
- renal disease
- renal failure
- renal impairment
- surgery
- trauma

• *Absolute contraindications are in italics.*

Clopidogrel is contraindicated in any patient with active pathological *bleeding* such as *GI bleeding*, *retinal bleeding*, *retroperitoneal bleeding,* or *intracranial bleeding*. As with other antiplatelet agents, clopidogrel should be used with caution in patients who may be at risk of increased bleeding from trauma, surgery, or other pathological conditions (especially gastrointestinal or intraocular). If a patient is to undergo elective surgery and an antiplatelet effect is not desired, clopidogrel should be discontinued 7 days prior to the surgery. Clopidogrel prolongs bleeding time and is associated with a 2% incidence of GI bleeding. Thus, this drug should be used with caution in individuals who have lesions with a propensity to bleed, such as patients with peptic ulcer disease. In addition, drugs that might induce such lesions (such as aspirin or other NSAIDs) should be used with caution in patients taking clopidogrel (see Drug Interactions). If symptoms of bleeding occur during clopidogrel therapy, blood cell counts and/or other appropriate testing should be promptly considered.

Clopidogrel should be used with caution in patients with hepatic disease. A bleeding diathesis may exist in these patients, especially in those with severe liver disease, which may increase the risk of bleeding associated with clopidogrel. In addition, severe hepatic disease may impair the conversion of clopidogrel, the prodrug, to its active form.
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.

Clopidogrel is classified as FDA pregnancy risk category B. Reproduction studies performed in rats and rabbits at doses up to 500 and 300 mg/kg/day (respectively, 65 and 78 times the recommended daily human dose on a mg/m2 basis), revealed no evidence of impaired fertility or fetotoxicity due to clopidogrel. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of a human response, clopidogrel should be used during pregnancy only if clearly needed.
It is not known whether clopidogrel or its metabolites are excreted in human milk. However, studies have shown that clopidogrel and/or its metabolites are excreted in rat milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue breast-feeding or to discontinue the drug, taking into account the importance of the drug to the mother.
Of the total number of subjects in controlled clinical studies, approximately 50% of patients treated with clopidogrel were elderly (i.e., 65 years of age and over). Approximately 16% of patients treated with clopidogrel were 75 years of age and over. In the CURE

trial, the percent of patients experiencing thrombotic events increased with age regardless of treatment group. The percent of patients experiencing thrombotic events in patients < 65 years of age was 5.2% for the clopidogrel plus aspirin group vs. 7.6% for the aspirin plus placebo group. In patients aged 65—74 years, the percent of patients experiencing thrombotic events was 10.2 % for the clopidogrel plus aspirin group vs. 12.4% for the aspirin plus placebo group; in patients >= 75 years of age, 17.8% of patients in the clopidogrel plus aspirin group vs. 19.2% of patients in the aspirin plus placebo group experienced thrombotic events. In addition, the incidence of major bleeding increased with age in both treatment groups; however, the incidence of bleeding was higher in patients treated with combination clopidogrel and aspirin. In patients < 65 years of age, the incidence of major bleeding events was 2.5% in the clopidogrel plus aspirin group vs. 2.1% in the aspirin plus placebo group. In patients aged 65—74 years, the incidence of major bleeding rose to 4.1% in the clopidogrel plus aspirin group vs. 3.1% in the aspirin plus placebo group; in patients >= 75 years of age, the incidence of bleeding was 5.9% in the clopidogrel plus aspirin group vs. 3.6% in the aspirin plus placebo group. If bleeding is a potential concern and combination therapy is desired, elderly patients should be encouraged to use a low dose of aspirin with clopidogrel.
Safe and effective use of clopidogrel has not been established in children.

Contraindications last revised 2/11/2005 2:54:00 PM

Drug Interactions

- Alosetron
- Amiodarone
  - Anticoagulants
  - Antineoplastic Agents
  - Anti-retroviral protease inhibitors
- Antithymocyte Globulin
- Aprepitant
- Atorvastatin
  - Azole antifungals
  - Barbiturates
- Bosentan
- Carbamazepine
- Clarithromycin
- Conivaptan
- Dalfopristin; Quinupristin
- Danazol
- Delavirdine
- Diltiazem
- Doxercalciferol
- Echinacea
- Efavirenz
- Erythromycin
- Feverfew, Tanacetum parthenium
- Fish Oil, Omega-3 Fatty Acids
- Fluoxetine
- Fluvastatin
- Fluvoxamine
- Fosphenytoin
- Garlic, Allium sativum
- Ginger, Zingiber officinale
- Ginkgo, Ginkgo biloba
- Green Tea
- Horse Chestnut, Aesculus hippocastanum
- Imatinib, STI-571
- Methylsulfonylmethane, MSM
- Mifepristone, RU-486
- Nefazodone
  - Nonsteroidal antiinflammatory drugs (NSAIDs)
- Pentoxifylline
- Phenytoin
  - Photosensitizing Agents
  - Platelet Inhibitors
- Prasterone, Dehydroepiandrosterone, DHEA
- Ramelteon
- Rifabutin
- Rifampin
- Rifapentine
  - Salicylates
- Strontium-89 Chloride
- Tamoxifen
  - Thrombolytic Agents
- Tolbutamide
- Torsemide
- Troleandomycin
- Verapamil
- Zafirlukast

NOTE: At high concentrations *in vitro*, clopidogrel inhibits the activity of cytochrome P450 2C9. Clopidogrel requires hepatic biotransformation to an active metabolite; the activation is thought to be mediated by the CYP3A4 isoenzyme (see Pharmacokinetics).[5163]
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.

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]

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]

Clopidogrel, an inactive thienopyridine prodrug, is metabolized in the liver by CYP3A4 isoenzymes to an active metabolite.[5163] Amiodarone is an inhibitor of CYP3A4 isoenzymes [5629] and theoretically may decrease the hepatic metabolism of clopidogrel to its active metabolite. A potential interaction between clopidogrel and amiodarone resulting in ineffective inhibition of platelet aggregation has been reported.[4950]

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

Clopidogrel requires hepatic biotransformation to an active metabolite; the activation is thought to be mediated by the CYP3A4 isoenzyme (see Pharmacokinetics).[5163] Bosentan may induce the CYP3A4 metabolism of clopidogrel to its active metabolite. Patients should be monitored for potential increased antiplatelet effects when clopidogrel is used in combination with CYP3A4 inducers such as bosentan. In addition, clopidogrel may inhibit CYP2C9 metabolism of bosentan. At high concentrations *in vitro*, clopidogrel inhibits the activity of CYP2C9.[5163] It is prudent to monitor for potential adverse effects of bosentan during coadministration with clopidogrel. Excessive bosentan dosage may result in hypotension or elevated hepatic enzymes. It is important to review all the medications taken concurrently with bosentan. According to the manufacturer, coadministration of bosentan with a potent CYP2C9 inhibitor plus a CYP3A4 inhibitor is not recommended; large increases in bosentan plasma concentrations are expected with such combinations.[5226]

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

At high concentrations *in vitro*, clopidogrel inhibits the activity of cytochrome P450 2C9.[5165] Thus, clopidogrel could increase plasma concentrations of drugs metabolized by this isoenzyme, such as alosetron [5112], ethotoin, fluvastatin [4718], many NSAIDs [4718], tamoxifen [4718], tolbutamide [4718], torsemide [4718], and warfarin [4718]. Although there are no *in vivo* data with which to predict the magnitude or clinical significance of these potential interactions, caution should be used when any of these agents is coadministered with clopidogrel.

Because phenytoin and fosphenytoin are metabolized by cytochrome P450 2C9 [4718], concomitant therapy with clopidogrel at high concentrations could increase their plasma concentrations and cause symptoms of toxicity. Phenytoin concentrations should be monitored more closely when initiating clopidogrel therapy. In addition, clopidogrel is metabolized by CYP 3A; phenytoin and fosphenytoin induce cytochrome P450 3A4 isozymes.[4718] Therefore, the therapeutic effectiveness of clopidogrel should be monitored when used concomitantly with phenytoin or fosphenytoin.

No clinically significant pharmacodynamic interactions were observed when clopidogrel was coadministered with atenolol or nifedipine.[5165] The pharmacodynamic activity of clopidogrel was not significantly affected by the coadministration of estrogen, or by coadministration with a hepatic enzyme inducer (phenobarbital) or inhibitor (cimetidine).[5165] The pharmacokinetics of digoxin or theophylline were not modified by concomitant administration of clopidogrel.[5165]

Ginkgo biloba can produce clinically-significant antiplatelet effects.[1900] Therefore, *Ginkgo biloba* should be used cautiously in patients taking platelet inhibitors such as clopidogrel [5165] to minimize the potential for additive risk of bleeding. A compound found in *Ginkgo biloba*, ginkgolide-B, may act as a selective antagonist of platelet activating factor (PAF). Although a review of *Ginkgo biloba* in 1992 stated that no known drug interactions exist,[1705] spontaneous hyphema has been reported in an elderly male who began taking ginkgo while stabilized on daily aspirin. After ginkgo was stopped, no further bleeding was noted despite continuing the aspirin therapy.[1706] Other clinical data exist[1707] that describe spontaneous subdural hematomas associated with chronic *Ginkgo biloba* ingestion.

Additive platelet effects may occur if clopidogrel is given in combination with ginger, Zingiber officinale, or garlic, Allium sativum. Ginger inhibits thromboxane synthetase (platelet aggregation inducer) and is a prostacyclin agonist.[5200] Garlic produces clinically significant antiplatelet effects.[2223]

Because clopidogrel inhibits platelet aggregation, a potential additive risk for bleeding exists if clopidogrel is given in combination with other drugs that affect hemostasis.[5164] Clopidogrel should be used cautiously in patients with thrombocytopenia following the administration of myelosuppressive antineoplastic agents, antithymocyte globulin [6303], strontium-89 chloride [4694], or other drugs that cause significant thrombocytopenia due to the increased risk of bleeding.

Aspirin, and other agents that affect platelet activity including platelet inhibitors, could decrease the efficacy of photosensitizing

agents used in photodynamic therapy.[6359] [6625]
Drug interactions with Horse chestnut, Aesculus hippocastanum are not well documented. Coumarin compounds with the potential for anticoagulant activity have been isolated from the herb.[5279] [5875] It is possible that the use of horse chestnut may increase the risk of bleeding if co-administered with anticoagulants (e.g., enoxaparin, heparin, warfarin), thrombolytic agents, or platelet inhibitors (e.g., aspirin, clopidogrel, and others).[5875] [6504] Reparil® Dragees (Madaus AG, Germany) a drug derived from horse chestnut and containing aescin (escin), is labeled with a precaution that the action of anticoagulants may be potentiated by aescin.[6505] Caution and careful monitoring of clinical and/or laboratory parameters are warranted if horse chestnut is coadministered with any of these agents.
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]
Green tea has demonstrated antiplatelet and fibrinolytic actions in animals.[6434] [6440] It is possible that the use of green tea may increase the risk of bleeding if coadministered with clopidogrel. Caution and careful monitoring of clinical and/or laboratory parameters are warranted if green tea is coadministered with platelet inhibitors.
Prasterone, dehydroepiandrosterone, DHEA appears to have anti-platelet effects,[2459] which may prolong bleeding times and increase the risk of bleeding in patients taking platelet inhibitors including clopidogrel. In addition, DHEA is converted to androgens and estrogens within the human body and thus may affect hemostasis via androgenic or estrogenic effects. Estrogens increase the production of clotting factors VII, VIII, IX, and X.[4744] Androgens, such as testosterone, increase the synthesis of several anticoagulant and fibrinolytic proteins. Because of these potential and varied effects on coagulation, patients receiving DHEA concurrently with other platelet inhibitors should be monitored for side effects or the need for dosage adjustments.
Fish oil, omega-3 fatty acids have platelet aggregation inhibition properties.[6320] Caution is advised in combining fish oil, omega-3 fatty acids with platelet inhibitors due to a theoretical risk of bleeding. However, clinically significant bleeding events have not yet been reported in study patients.
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).
Ramelteon should be administered with caution in patients taking CYP2C9 inhibitors, such as clopidogrel.[8143] [4718] The AUC and Cmax of ramelteon has been elevated > 150% when administered with other CYP2C9 inhibitors. The patient should be monitored closely for toxicity even though ramelteon has a wide therapeutic index.
Doxercalciferol is converted in the liver to 1,25-dihydroxyergocalciferol, the major active metabolite, and 1-alpha, 24-dihydroxyvitamin D2, a minor metabolite. Although not specifically studied, cytochrome P450 enzyme inhibitors including clopidogrel may inhibit the 25-hydroxylation of doxercalciferol, thereby decreasing the formation of the active metabolite and thus, decreasing efficacy. Patients should be monitored for a decrease in efficacy if clopidogrel is coadministered with doxercalciferol.[7566] [6904]
Clopidogrel is metabolized by CYP3A4. The effects of echinacea on CYP3A4 are complex. *In vitro* data suggest that echinacea can inhibit the CYP3A4 isoenzyme; however, the clinical significance of these data are not yet known, as some authors have reported the *in vivo* activity in humans to be minor. Other limited *in vivo* data indicate that echinacea inhibits intestinal CYP3A4, but induces hepatic CYP3A4. In 6 subjects administered echinacea plus intravenous midazolam a probe for CYP3A4), the systemic clearance of midazolam increased by 34% and the AUC decreased to 75%. However, when oral midazolam was administered, the oral availability increased leading to no change in the overall clearance of oral midazolam. The overall effects on orally administered drugs metabolized by CYP3A4 are unknown and may be negligible. It may be prudent to closely monitor for changes in efficacy or toxicity when echinacea is coadministered with drugs that are metabolized by CYP3A4, including clopidogrel, until more data are available.[7213] [7566] [8894]
Increased effects from concomitant anticoagulant drugs including increased bruising or blood in the stool have been reported in patients taking methylsulfonylmethane, MSM.[9832] [9834] Although these effects have not been confirmed in published medical literature or during clinical studies, clinicians should consider using methylsulfonylmethane, MSM with caution in patients who are taking anticoagulants or antiplatelets including clopidogrel until data confirming the safety of these drug combinations are available. During one of the available, published clinical trials in patients with osteoarthritis, those patients with bleeding disorders or using anticoagulants or antiplatelets were excluded from enrollment.[9832] Patients who choose to consume methylsulfonylmethane, MSM while receiving clopidogrel should be observed for increased bleeding.

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Adverse Reactions

- abdominal pain
- agranulocytosis
- anaphylactoid reactions
- angioedema
- aplastic anemia
- bleeding
- bronchospasm
- colitis
- confusion
- diarrhea
- dyspepsia
- elevated hepatic enzymes
- maculopapular rash
- myalgia
- neutropenia
- ocular hemorrhage
- pancreatitis
- pancytopenia
- peptic ulcer
- platelet dysfunction
- pneumonitis
- prolonged bleeding time
- pruritus
- purpura

- erythema multiforme
- fever
- gastritis
- GI bleeding
- glomerulonephritis
- hallucinations
- hepatic failure
- hepatitis
- hypotension
- intracranial bleeding
- rash (unspecified)
- retinal hemorrhage
- retroperitoneal bleeding
- serum sickness
- Stevens-Johnson syndrome
- stomatitis
- thrombotic thrombocytopenic purpura (TTP)
- toxic epidermal necrolysis
- vasculitis

Clopidogrel has been evaluated for safety in over 42,000 patients, including over 9,000 patients treated for >= 1 year. In the CAPRIE study, 9599 patients received clopidogrel and 9586 patients received aspirin for an average of 1.6 years.[1637] Overall tolerability of clopidogrel was similar to that of aspirin; 13% of patients in both groups withdrew early from the treatment regimen due to adverse events. Adverse events that were reported with a higher incidence in clopidogrel-treated patients than in aspirin-treated patients were diarrhea (3.3% vs. 1.6%), purpura (5.3% vs. 3.7%), maculopapular rash (4.2% vs. 3.5%), and pruritus (3.3% vs. 1.6%). The frequency of severe rash (unspecified) and severe diarrhea among patients receiving clopidogrel (0.23% and 0.26%, respectively) was twice as high as that reported among aspirin-treated patients, although these events were uncommon. Adverse events reported in >= 2.5% of the study population, but at a higher incidence with aspirin compared with clopidogrel, included abdominal pain (7.1% vs. 5.6%) and dyspepsia (6.1% vs. 5.2%). Most of these adverse effects were mild and transient.
Due to drug-induced platelet dysfunction, bleeding may occur at any site. In the CAPRIE study,[1637] clopidogrel was associated with a lower incidence of severe GI bleeding than aspirin (0.49% vs. 0.71%), including fewer hospitalizations for GI bleeding (0.7% vs. 1.1%) and fewer GI ulcers (0.7% vs. 1.2%). The incidence of severe intracranial bleeding was not significantly different between clopidogrel and aspirin (0.31% vs. 0.43%). Similarly, in CLARITY, major bleeding was similar between the 2 treatment groups (1.3% for clopidogrel plus aspirin vs. 1.1% for aspirin plus placebo); the incidence of fatal bleeding and intracranial hemorrhage was similar between the 2 groups. Additionally, the overall rate of noncerebral major bleeding or cerebral bleeding in the COMMIT trial was low and similar in the clopidogrel plus aspirin vs. aspirin only groups. Bleeding events reported during worldwide marketing or post-marketing experience with clopidogrel have also included ocular hemorrhage, prolonged bleeding time, retinal hemorrhage and retroperitoneal bleeding. In the CURE study, the incidence of major bleeding increased with age; however, the incidence of bleeding was higher in patients treated with combination clopidogrel and aspirin than in patients treated with aspirin alone. In patients < 65 years of age, the incidence of major bleeding events was 2.5% in the clopidogrel plus aspirin group vs. 2.1% in the aspirin plus placebo group. In elderly patients aged 65—74 years, the incidence of major bleeding rose to 4.1% in the clopidogrel plus aspirin group vs. 3.1% in the aspirin plus placebo group; in patients >= 75 years of age, the incidence of bleeding was 5.9% in the clopidogrel plus aspirin group vs. 3.6% in the aspirin plus placebo group. If bleeding is a potential concern and combination therapy is desired, elderly patients should be encouraged to use a low dose of aspirin with clopidogrel.
Severe neutropenia (absolute neutrophil count < 450/mm3) was reported in 0.04% of clopidogrel-treated patients and 0.02% of aspirin-treated patients. Ticlopidine, an antiplatelet agent similar to clopidogrel, has been associated with a 0.8—1% incidence of severe neutropenia. Although use of clopidogrel does not require routine hematologic monitoring, the possibility of myelotoxicity should be considered in a patient who demonstrates fever or other signs of infection while receiving the drug. Other hematological effects that have been reported during clopidogrel therapy include: agranulocytosis, aplastic anemia, and pancytopenia. Fever has been reported during post-marketing experience with clopidogrel.
Thrombotic thrombocytopenic purpura (TTP) has been reported rarely in patients receiving clopidogrel, sometimes after short exposure (< 2 weeks). Eleven cases of TTP were reported between March 1998 and March 2000; in all but one case, TTP developed within 14 days of beginning clopidogrel therapy. One patient died, eight had complete resolution of TTP after discontinuing clopidogrel and treatment with plasma exchange, and two had relapses up to seven months after the onset of TTP, with recovery after plasma exchange. It should be noted that almost half the patients with clopidogrel-induced TTP had received cholesterol-lowering drugs. In one of the patients, TTP appeared to be induced by atorvastatin, and one patient had a recurrence during treatment with atorvastatin that responded quickly to plasma exchange. In this series of patients, clopidogrel-induced TTP differed from ticlopidine-induced TTP in that it occurred sooner, was prone to recurrence, and required up to 30 plasma exchanges before clinical improvement occurred.[2754] TTP is a serious condition that can be fatal and requires urgent treatment including plasmapheresis (plasma exchange). Thrombocytopenia, microangiopathic hemolytic anemia (schistocytes seen on peripheral smear), neurological findings, renal dysfunction, and fever characterize TTP. In world-wide post-marketing experience, TTP has been reported at a rate of about four cases per million patients exposed or about 11 cases per million patient-years. The rate in the general population is approximately four cases per million person-years.
Other adverse effects that have been reported during worldwide marketing or post-marketing experience include acute hepatic failure, anaphylactoid reactions, angioedema, bronchospasm, colitis, confusion, elevated hepatic enzymes, erythema multiforme, fever, gastritis, glomerulonephritis, hallucinations, hepatitis, hypersensitivity reactions, hypotension, interstitial pneumonitis, lichen planus, myalgia, pancreatitis, peptic ulcer (both gastric and duodenal), serum sickness, Stevens-Johnson syndrome, stomatitis, toxic epidermal necrolysis, and vasculitis.

Adverse Reactions last revised 5/14/2007 7:52:00 AM

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Fexofenadine
Allegra®
Classification:
• Antihistamines
  • H1-blockers
    • Non-sedating H1-blockers
Description, Mechanism of Action, Pharmacokinetics

Description: Fexofenadine is an H1-receptor antagonist. It is the active metabolite of another H1-antagonist, terfenadine. Both fexofenadine and terfenadine are non-sedating, however, unlike terfenadine, fexofenadine does not cause QT prolongation when given in doses up to 800 mg/day or when administered concomitantly with ketoconazole or erythromycin. However, one case report documented ventricular tachycardia associated with QT prolongation during fexofenadine therapy in a patient with a history of prolonged QT interval.[2482] Fexofenadine was first approved by the FDA in July 25, 1996 for the treatment of seasonal allergic rhinitis in adults and children 12 years and older. The drug received subsequent approval for children as young as 6 years old in February 2000. The development and submission of Allegra™ to the FDA was completed in 2.8 years, compared to the industry average of 14 years. In France and the UK, the trade name is Telfast. Fexofenadine was approved for the treatment of chronic idiopathic urticaria in adults and children aged 6 and older in February 2000. In October 2006, the FDA approved a new liquid formulation (Allegra® Oral Suspension) for the treatment of seasonal allergic rhinitis in children 2—11 years of age and for the treatment of chronic idiopathic urticaria in children 6 months to 11 years of age.

Mechanism of Action: Similar to other H1-blockers, fexofenadine does not prevent the release of histamine as do cromolyn and nedocromil, but competes with free histamine for binding at the H1-receptor. This competitive antagonism blocks the effects of histamine on H1-receptors in the GI tract, uterus, large blood vessels, and bronchial smooth muscle. Blockade of H1-receptors also suppresses the formation of edema, flare, and pruritus that result from histaminic activity. At higher concentrations, H1-receptor antagonism becomes relatively irreversible. Fexofenadine is lipophilic compared to first generation antihistamines and does not readily cross the blood-brain barrier. CNS depression is minimal compared with other H1-antagonists. Although fexofenadine is a metabolite of terfenadine which has been associated with QT prolongation and ventricular tachycardias (torsades de pointes), pre-marketing trials with fexofenadine demonstrated no significant prolongation of the QT interval; doses up to 800 mg/day have been studied.
Pharmacokinetics: Fexofenadine is administered orally and is rapidly absorbed (peak in 2—3 hours). The absolute bioavailability of fexofenadine is unknown. The onset of antihistamine effectiveness (evaluated by wheal and flare studies) is about 1 hour and persists for up to 12 hours. Protein binding ranges from 60—70%; fexofenadine is primarily bound to albumin and alpha1-acid glycoprotein. Based on radiolabeled studies, approximately 80% and 11% of a dose was recovered in the feces and urine, respectively. Approximately 5% of the total administered dose is metabolized. Because the absolute bioavailability has not been determined, it is unknown if the fecal component represents unabsorbed drug or biliary excretion of the drug. Therefore, it is unknown if either renal excretion and/or metabolism plays a significant role in systemic drug elimination. The mean elimination half-life is approximately 14.4 hours in normal volunteers receiving 60 mg twice daily.
•***Special Populations:*** The pharmacokinetics of fexofenadine is altered by renal disease and age, but not hepatic disease or gender. Peak plasma concentrations were 87% and 111% greater in patients with mild (CrCl 41—80 ml/min) to severe (CrCl 11—40 ml/min) renal impairment, respectively. Mean elimination half-lives were 59% and 72% longer, respectively, than in normal volunteers. Peak plasma concentrations in dialysis patients (CrCl <= 10 ml/min) were 82% greater and half-life was 31% longer than in normal volunteers. The effect of hemodialysis on the removal of fexofenadine is unknown. Hemodialysis did not effectively remove fexofenadine from blood (up to 1.7% removed) following terfenadine oral administration. In older subjects (> 65 years old), peak plasma levels of fexofenadine were 99% greater than those observed in younger subjects (< 65 years old). Mean elimination half-lives were similar to those observed in younger subjects. The AUC of fexofenadine following a 60 mg oral dose is 56% higher in children aged 7—12 years than for adults. Relative to adults receiving a 60 mg dose, fexofenadine plasma exposure is similar in children receiving a 30 mg dose of fexofenadine. Estimated oral clearances were on average 44% and 36% lower in children 6—12 years and 2—5 years, respectively, compared to adults in a population pharmacokinetic analysis. The pharmacokinetics of fexofenadine hydrochloride in patients with hepatic disease did not differ substantially from that observed in healthy subjects. No clinically significant gender-related differences were observed in the pharmacokinetics of fexofenadine.

Description, Mechanism of Action, Pharmacokinetics last revised 10/20/2006 4:11:00 PM

Indications

• allergic rhinitis
• urticaria

Dosage
For the treatment of allergic rhinitis:
Oral dosage (immediate-release tablets or capsules, and oral suspension):
Adults, including the elderly, adolescents, and children >= 12 years: 60 mg PO twice daily or 180 mg PO once daily.
Children 2—11 years: 30 mg PO twice daily. During controlled trials of patients 6—11 years of age, 60 mg twice daily was not more beneficial than 30 mg twice daily.
Children < 2 years and infants: Safe and effective use has not been established.
For the treatment of chronic idiopathic urticaria:
Oral dosage (immediate-release tablets or capsules, and oral suspension):
Adults, including the elderly, adolescents, and children >= 12 years: 60 mg PO twice daily or 180 mg PO once daily.
Children 2—11 years: 30 mg PO twice daily.
Children < 2 years and infants >= 6 months: 15 mg PO twice daily.
Infants < 6 months: Safe and effective use has not been established.
Maximum Dosage Limits:

•*Adults:* 180 mg/day PO.
•*Elderly:* 180 mg/day PO.
•*Adolescents:* 180 mg/day PO.
•*Children 2—11 years:* 60 mg/day PO.
•*Children < 2 years:* 30 mg/day PO for chronic idiopathic urticaria; not recommended for allergic rhinitis.
•*Infants >= 6 months:* 30 mg/day PO for chronic idiopathic urticaria; not recommended for allergic rhinitis.
•*Infants < 6 months:* Safe and effective use has not been established.

Patients with hepatic impairment:

No dosage adjustment is recommended. The pharmacokinetics of fexofenadine are not substantially different in patients with hepatic disease.

Patients with renal impairment:

CrCl < 80 ml/min: Reduce starting dose to 60 mg PO once daily for adults, elderly and adolescents >= 12 years. Reduce to 30 mg PO once daily for children 2—11 years old, and reduce to 15 mg PO once daily for children < 2 years and infants >= 6 months of age.

Intermittent hemodialysis:

The effect of hemodialysis on the removal of fexofenadine is unknown. Hemodialysis did not effectively remove fexofenadine from blood (up to 1.7% removed) following terfenadine oral administration.

Indications...Dosage last revised 10/20/2006 4:11:00 PM

Administration Guidelines

Oral Administration

•*All oral formulations:* Avoid grapefruit, orange, and apple juice before or after drug administration to avoid potential reduction bioavailability.
•*Tablets or capsules:* Administer orally with water. May be administered without regard to meals.
•*Oral Suspension:* Shake well prior to each use. Measure dosage using a calibrated measuring device. Keep in a tightly closed container away from children. Store at room temperature between 20 and 25 degrees C (68 and 77 degrees F).

Administration last revised 4/9/2007 11:09:00 PM

Contraindications/Precautions

- *neonates*
- *terfenadine hypersensitivity*
- breast-feeding
- children
- driving or operating machinery
- elderly
- pregnancy
- renal disease
- renal failure
- renal impairment

• *Absolute contraindications are in italics.*

Do not use fexofenadine in patients with a history of *terfenadine hypersensitivity* due to the similarity in chemical structure.
Fexofenadine should be used cautiously in patients with renal impairment associated with renal disease or renal failure. Peak plasma concentrations were 87% and 111% greater in patients with mild (CrCl 41—80 ml/min) to severe (CrCl 11—40 ml/min) renal impairment, respectively. Mean elimination half-lives were 59% and 72% longer, respectively, than in normal volunteers. Peak plasma concentrations in dialysis patients (CrCl <= 10 ml/min) were 82% greater and half-life was 31% longer than in normal volunteers. Patients with mild to severe renal impairment should be given half the initial dose due to reduced clearance of fexofenadine.
It is unknown if the elderly respond differently than younger adults to fexofenadine; however, renal function may decline with age. Because of the potential toxicity associated with the use of fexofenadine in those with renal dysfunction, the drug should be used cautiously in geriatric patients. Lower initial dosages may be advisable until the effects of the drug are known.
Fexofenadine is classified as pregnancy category C. Results of animal studies have revealed an absence of mutagenicity or infertility. Teratogenicity was not observed in rats given approximately 15 times the maximum daily oral dose in humans based on an AUC comparison. Decreased pup weight gain and survival occurred in rats given 3 times the maximum daily oral dose in humans. There have been no adequate and well-controlled studies on the use of fexofenadine in human pregnancy. Fexofenadine should be used during pregnancy only when the benefits of therapy outweigh the risks.
It is unknown if fexofenadine is excreted into human breast milk. Fexofenadine should be used during breast-feeding only when the benefits of therapy outweigh the risks.
The incidence of drowsiness was 1.3% in patients receiving fexofenadine monotherapy (vs placebo 0.9%). Patients should be warned about undertaking hazardous tasks (e.g., driving or operating machinery) while taking fexofenadine, although the risk is relatively low.
The safety and effectiveness of fexofenadine for the treatment of allergic rhinitis in children younger than 2 years of age has not been established. The safety and effectiveness of the drug for the treatment of chronic idiopathic urticaria in infants less than 6 months has not been established. Antihistamines generally should not be used in *neonates* due to the possibility of paradoxical CNS stimulation.

Contraindications last revised 4/17/2007 7:55:00 PM

Drug Interactions

Antacids
- Erythromycin
- food
- grapefruit juice
- Ketoconazole
- Rifampin
- St. John's Wort, Hypericum perforatum

NOTE: Fexofenadine is a substrate for P-glycoprotein transport.[4718]
Most food does not interact significantly with fexofenadine; the drug may be administered with or without food.[6196] However, some fruit juices appear to impair the absorption of fexofenadine. Apple juice, orange juice, and grapefruit juice have been reported to decrease the AUC and Cmax of fexofenadine by roughly 60—70%, but individual variability in the changes have been noted in various studies.[6328] According to the manufacturer, the bioavailability of fexofenadine is estimated to be reduced by 36% during coadministration with grapefruit or orange juice.[6196] The mechanism of the interaction is proposed to be an inhibition of intestinal P-glycoprotein transport systems by the juices, resulting in decreased systemic drug absorption. Histamine-induced skin evaluations indicate that the size of wheal and flare reactions are significantly greater when fexofenadine is coadministered with either grapefruit or orange juice compared to water.[6196] The clinical significance of these observations is unknown. To maximize the effects of fexofenadine, the manufacturer recommends that fexofenadine be taken with water (see Dosage).[6196] Since fexofenadine effectiveness may be reduced, it is prudent for patients to avoid coadministration with grapefruit, orange, or apple juices.
Unlike terfenadine, fexofenadine has not been associated with QT prolongation or ventricular arrhythmias when coadministered with erythromycin or ketoconazole.[6196] In two separate studies of 24 healthy subjects, fexofenadine 120 mg twice daily (twice the recommended dose) was coadministered with erythromycin 500 mg every 8 hours or ketoconazole 400 mg once daily for seven days. No differences in adverse events or QTc interval were observed when subjects were administered fexofenadine alone or in combination with potent CYP 3A4 inhibitors, erythromycin or ketoconazole. Erythromycin increased steady-state fexofenadine peak concentrations by 82% and increased AUC by 109%.[6196] Ketoconazole increased steady-state fexofenadine peak concentrations by 135% and increased AUC by 164%.[6196] Fexofenadine had no effect on the pharmacokinetics of erythromycin or ketoconazole.[6196] The mechanism of these interactions has been evaluated using *in vitro*, *in situ*, and *in vivo* animal models.[6196] These studies indicate that ketoconazole or erythromycin coadministration enhances fexofenadine gastrointestinal absorption. This observed increase in the bioavailability of fexofenadine may be due to transport-related effects, such as p-glycoprotein. *In vivo* animal studies also suggest that in addition to enhancing absorption, ketoconazole decreases fexofenadine gastrointestinal secretion, while erythromycin may also decrease biliary excretion. According to the manufacturer, the associated changes in fexofenadine plasma levels following erythromycin or ketoconazole were within the range of plasma levels achieved in adequate and well-controlled clinical trials.[6196] Given the magnitude of the increases in AUC, it is prudent to use caution and monitor patients receiving fexofenadine and erythromycin or ketoconazole until additional data are available.
Coadministration with antacids (containing aluminum or magnesium) within 15 minutes decreases the AUC and Cmax of fexofenadine by 41% and 43%, respectively.[6196] Separate administration is recommended.
Although fexofenadine is considered a 'non-sedating' H1-blocker,[6196] sedation has been noted in individual patients receiving fexofenadine or other second generation, non-sedating H1-blockers. For this reason, it would be prudent to monitor for drowsiness during concurrent use with other CNS depressants such as tricyclic antidepressants, barbiturates, benzodiazepines, opiate agonists, antipsychotics, ethanol, other H1-blockers, and anxiolytics, sedatives, and hypnotics.
Rifampin may decrease plasma concentrations of fexofenadine and potentially reduce its antihistaminic effects. A 6-day course of rifampin (600 mg/day) has been reported to increase the oral clearance of fexofenadine (single dose) by 2 to 3-fold in 24 healthy subjects.[6329] Rifampin does not alter the renal clearance or half-life of fexofenadine. In theory, rifampin may activate P-glycoprotein transport in the small intestine, and thereby decreases the oral absorption of fexofenadine (a substrate of P-glycoprotein transport). Although the therapeutic range of fexofenadine is broad, monitor for potential decreased therapeutic effects of fexofenadine if rifampin is initiated.
Conflicting studies have shown that St. John's Wort may increase, decrease, or not change the plasma concentrations and AUC of fexofenadine. Results vary between single and multiple dose studies. The mechanisms proposed have included CYP3A4 induction and/or altered P-glycoprotein efflux transport of fexofenadine. The clinical importance of this theoretical interaction has not been established; further study is needed.[6067] [6330]

Interactions last revised 12/30/2005 10:37:00 AM

Adverse Reactions

- anaphylactoid reactions
- angioedema
- back pain
- cough
- diarrhea
- dizziness
- drowsiness
- dysmenorrhea
- dyspepsia
- fatigue
- fever
- headache
- infection
- insomnia
- myalgia
- nausea/vomiting
- pharyngitis
- pruritus
- QT prolongation
- rash (unspecified)
- restlessness
- rhinorrhea
- urticaria

The most common adverse reactions associated with fexofenadine therapy include viral infection (e.g., cold, flu), nausea/vomiting, dysmenorrhea, drowsiness, dyspepsia, and fatigue. These adverse reactions were more common in fexofenadine-treated patients than in placebo-treated patients and occurred in greater than 1% of patients. In a study of 570 patients 12 years of age and older, adverse reactions which were more common in those receiving fexofenadine 120 or 180 mg daily versus placebo, and occurred in greater than 2% of patients included back pain, headache, and upper respiratory infection. Adverse reactions reported in greater than 2% of patients in a placebo controlled pediatric study (age 6—11 years) included cough, fever, otitis media, pain (unspecified), and upper respiratory tract infection. Other adverse events which have been reported in clinical trials of patients 12 years of age and older include dizziness, myalgia, pharyngitis (nasal), and unspecified pain in extremity. Adverse effects reported with oral suspension or capsule content administration in greater than 2% of patients in placebo-controlled pediatric studies (age 6 months to 5 years) included vomiting (5.8%), pyrexia (3.9%), cough (3.6%), otitis media (3.6%), diarrhea (3%), rhinorrhea (1.9%), upper respiratory tract infections (1.9%), and somnolence (1.1%). Pyrexia and upper respiratory infection occurred less frequently in the fexofenadine groups than the placebo groups. Vomiting was reported in 12% of subjects receiving fexofenadine 30 mg/day and 4.2% of those receiving 60 mg/day, with an incidence of 8.6% in the placebo group.
Fexofenadine is a metabolite of terfenadine. Terfenadine has been associated with QT prolongation and ventricular tachycardias (torsades de point) and was withdrawn from the U.S. market after ten years of post-marketing experience. Pre-marketing trials with fexofenadine in greater than 900 patients demonstrated no significant prolongation of the QT interval at doses of 60—240 mg PO twice daily. One case report documented ventricular tachycardia associated with QT prolongation during therapy with fexofenadine in a patient with a history of prolonged QT interval.[2482] No cases of cardiac arrhythmias are reported in the fexofenadine or Allegra-D® product information. No QT prolongation was evident with the maximum fexofenadine dosage studied (400 mg PO twice daily for seven days in healthy subjects).
Events that have been reported during controlled clinical trials involving seasonal allergic rhinitis and chronic idiopathic urticaria patients with frequencies < 1%, similar to placebo, and have been rarely reported during post-marketing surveillance of fexofenadine include: insomnia, nervousness (restlessness), and sleep disorders or paranoia. In rare cases, rash (unspecified), urticaria, pruritus and hypersensitivity reactions (anaphylactoid reactions) with manifestations such as angioedema, chest tightness, dyspnea, flushing and systemic anaphylaxis have been reported.

Adverse Reactions last revised 10/20/2006 4:11:00 PM

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Donepezil
Aricept® | Aricept® ODT
Classification:
- Neurological Agents
  - Alzheimer's Agents
    - Cholinesterase inhibitors

Description, Mechanism of Action, Pharmacokinetics

Description: Donepezil (formerly known as E2020) was the first piperidine-type reversible cholinesterase (ChE) inhibitor. Donepezil is used for the symptomatic management of mild to moderate forms of Alzheimer's disease. Prior to approval of donepezil, tacrine, an acridine-type cholinesterase (ChE) inhibitor, was the only agent approved for this disease, however, the acridine-type ChEs are associated with hepatotoxicity. Donepezil has not been associated with hepatotoxicity.[1343] Donepezil has limited peripheral adverse reactions because of its greater affinity for CNS cholinesterase than tacrine. The long elimination half-life of donepezil allows for once daily dosing and is another advantage. Clinical efficacy of donepezil in mild to moderate Alzheimer's disease is similar to other available ChE inhibitors (e.g., rivastigmine and tacrine) based on the Clinical Global Impression of Change (CGIC) scale and the Alzheimer's Disease Assessment Scale-Cognitive Subscale score (ADAS-cog). Donepezil does not alter the long-term prognosis of Alzheimer's disease, but delays the time until institutionalization of the patient, which may be cost-effective. In addition, one large multicenter study has shown that the use of donepezil may also improve global function, cognition and behavior in those patients with moderate to severely advanced Alzheimer's disease (i.e., sMMSE score of 5—17) who do not yet require total nursing care.[3575] Although rigorous data to demonstrate consistent improvements in quality of life of these patients with ChE-inhibitor therapy are not yet available, many clinicians choose to treat and continue medication as long as improvement or stability in the dementia exists, based on periodic, objective examination. In addition to the head-to-head studies against other ChE-inhibitors; phase III trials of donepezil for Lewy Body dementia (LBD) and mild cognitive impairment (MCI) are in progress. Additionally, Eisai and Pfizer may file an NDA with the FDA in late 2002 or in 2003 for an additional indication for vascular dementia, pending further study. Two Phase III trials for cerebrovascular dementia have been completed, but further studies should delineate the most

effective dosage. Initial FDA approval for donepezil tablets for mild to moderate Alzheimer's disease was granted November 26, 1996. In October, 2004, a rapid disintegration tablet (Aricept® ODT) and an oral solution of Aricept® were approved by the FDA. On October 13, 2006, the drug received approval for the treatment of severe Alzheimer's disease dementia.

Mechanism of Action: Patients with Alzheimer's disease show behavioral consequences (e.g., decline in memory and learning) that are partially related to cholinergic deficits. CNS structural defects noted on biopsy or postmortem exam include cholinergic lesions in the nuclei projecting from the forebrain nucleus up to the cerebral cortex and the hippocampus, which is the specific region involved with the function of memory. The cholinergic system is known to be important in attentional processing and as a modulator of excitatory amino acid (EAA) neurotransmission. Although there is presently no 'cure' for Alzheimer's disease, therapy with cholinesterase inhibitors is designed to offset the loss of presynaptic cholinergic function and slow the decline of memory and the ability to perform functions of daily living. This mechanism requires that intact cholinergic neurons be present. As Alzheimer's disease progresses, fewer intact cholinergic neurons remain, and cholinesterase inhibitors become less effective. There is considerable evidence indicating that, as in Alzheimer's disease, the central cholinergic system is also impaired in vascular dementia (VaD) and in patients with Alzheimer's disease with cerebrovascular disease ('mixed' dementia), as well as other conditions.
Donepezil selectively inhibits acetylcholinesterase, the enzyme responsible for the destruction of acetylcholine, and improves the availability of acetylcholine. Donepezil binds to AChE via hydrogen bonding and is easily hydrolyzed by body water, thus the duration of enzyme inhibition at the receptor level is very short, and referred to as 'reversible'. However, donepezil's long half-life provides a long duration of drug availability for binding at the receptor sites. Donepezil has much greater affinity for acetylcholinesterase (AChE) in the CNS than for butylcholinesterase (BChE) in the periphery, unlike the organophosphates, acridines, carbamates, physostigmine, and the quaternary ammonium anti-ChEs (ambenonium, neostigmine, pyridostigmine) which have similar affinity for both enzymes. There is no evidence to suggest that the underlying disease process of dementia is affected by administration of donepezil.
Pharmacokinetics: Donepezil is administered orally. Following oral administration, the drug is well absorbed with a relative bioavailability of 100%. Peak plasma concentrations are reached in 3—4 hours. The time of day nor administration with food has an effect on the rate or extent of absorption. After multiple dosing, donepezil accumulates in plasma by 4—7 fold and steady state is reached within 15 days. Donepezil is approximately 96% bound to human plasma proteins, primarily to albumin (about 75%) and alpha1-acid glycoprotein (about 21%) over the concentration range of 2—1000 ng/ml.
Donepezil is metabolized to four major metabolites, two of which are known to be active, and several minor metabolites. Metabolism occurs via hepatic cytochrome P450 isoenzymes 2D6 and 3A4 and by glucuronidation. Approximately 57% and 15% of an administered dose is excreted in the urine and feces, respectively as metabolites. About 17% of a donepezil dose is recovered in urine as unchanged drug. Elimination half-life is about 70 hours.
Donepezil pharmacokinetics do not appear to be influenced by age, race or gender. The influence of renal impairment (CrCl < 22 ml/min) on donepezil elimination has only been assessed in a limited number of patients; pharmacokinetics of donepezil do not appear to be appreciably altered in moderate or severe renal impairment. In those patients with stable alcoholic cirrhosis, donepezil clearance is reduced by roughly 20%.

Description, Mechanism of Action, Pharmacokinetics last revised 10/19/2006 3:05:00 PM

Indications

- Alzheimer's disease
- dementia

Dosage
For the treatment of symptoms of mild to severe Alzheimer's disease dementia, or for the symptoms of dementia† associated with other causes [e.g., Pick's disease†, dementia of Lewy bodies (DLB)†, or subcortical vascular dementia†]:
Oral dosage:
Adults: Initially, 5 mg PO once daily. Steady state is not reached until 15 days of any given dosage. Upward titration should not occur until at least 4—6 weeks; then may increase to 10 mg PO once daily if needed for the treatment of mild to moderate Alzheimer's disease. The effective dose for severe Alzheimer's disease is 10 mg PO daily. There was no statistically consistent benefit of 10 mg/day over 5 mg/day in clinical trials for those with mild to moderate symptoms. However, some patients may gain additional benefit from 10 mg/day. Periodic evaluation after initiation and during continuation of therapy may be helpful to the clinician in deciding treatment duration (i.e., continue treatment if improvement or stability in functional, cognitive or behavioral status continues).
Maximum Dosage Limits:
•*Adults:* 10 mg/day PO.
•*Elderly:* 10 mg/day PO.
•*Adolescents:* Not indicated.
•*Children:* Not indicated.
Patients with hepatic impairment:
Donepezil elimination may be slightly reduced in patients with hepatic impairment, however, it appears no specific dosage adjustments are needed. Adjust dosage to patient response and tolerance.
Patients with renal impairment:
CrCl >= 22 ml/min: No dosage adjustment needed.
CrCl < 22 ml/min: Based on limited study in patients with severe renal impairment, it appears that no dosage adjustment is needed.
†non-FDA-approved indication

Indications...Dosage last revised 10/19/2006 3:05:00 PM

Administration Guidelines

Oral Administration
•Donepezil is administered once daily in the evening, just prior to retiring.
•All oral dosage forms are considered interchangeable.
•All dosage forms may be administered with or without food.
•*Orally-disintegrating tablets:* Place tablet in mouth on tongue, allow to dissolve, then swallow. Aricept ODT® tablets do not need to be administered with water or other liquids.
•*Oral solution:* Measure dose with a calibrated oral syringe or other calibrated container.

Administration last revised 1/12/2005 4:09:00 PM

Contraindications/Precautions

- *breast-feeding*
- *children*
- *GI bleeding*
- *jaundice*
- abrupt discontinuation
- anticholinergic medications
- asthma
- AV block
- bladder obstruction
- bradycardia
- cardiac arrhythmias
- cardiac disease
- chronic obstructive pulmonary disease (COPD)
- diarrhea
- GI disease
- GI obstruction
- head trauma
- hepatic disease
- hypotension
- ileus
- increased intracranial pressure
- Parkinson's disease
- peptic ulcer disease
- pregnancy
- pulmonary disease
- renal failure
- renal impairment
- seizure disorder
- seizures
- sick sinus syndrome
- surgery
- syncope
- urinary tract obstruction
- vomiting

• *Absolute contraindications are in italics.*

Treatment should be initiated and supervised by a physician experienced in the diagnosis and treatment of Alzheimer's dementia and the elderly. Diagnosis should be made according to current guidelines. Therapy with donepezil should only be started if a caregiver is available who will regularly monitor drug intake by the patient. The use of donepezil has not been investigated in patients with severe Alzheimer's dementia, other types of dementia, or in patients with other types of memory impairment (eg. age related cognitive decline). Avoid abrupt discontinuation of therapy where possible to limit sudden decline in cognitive function or increase in behavioral disturbances. The long half-life of donepezil makes cognitive changes due to abrupt discontinuation less of a concern than with other cholinesterase inhibitors.
Although patients with Alzheimer's disease and other dementias commonly lose weight, cholinesterase inhibitors, including donepezil, have been associated with weight loss in these patients. During therapy, weight must be monitored.
Donepezil should be used with caution in patients with cardiac disease sick sinus syndrome, severe cardiac arrhythmias, or cardiac conduction disturbances (e.g., sino-atrial block, AV block). An increase in vagal tone induced by the cholinomimetic may produce bradycardia or heart block in patients both with and without known underlying cardiac conduction abnormalities. Hypotension or syncope may also be exacerbated. However, data from unpublished trials indicate that donepezil infrequently induces bradycardia, even in the presence of other medications that may also lower heart rate.
Because donepezil potentiates the actions of acetylcholine, an increase in gastric acid secretion should be expected. Gastrointestinal disorders such as nausea and vomiting may occur particularly when initiating treatment and/or increasing the donepezil dose. Although donepezil did not show an increased incidence of ulcers relative to placebo in clinical trials, care should be exercised in treating patients with active peptic ulcer disease or patients pre-disposed to these conditions. Patients with a history of peptic ulcer disease or those receiving NSAIDs concurrently should be monitored closely for symptoms of active or occult GI disease. Other GI symptoms, such as diarrhea, can be increased by the use of cholinesterase inhibitors. Cholinergic effects may also exacerbate conditions involving GI obstruction or ileus. Discontinue use in cases of active *GI bleeding*.
Donepezil should be used cautiously in patients with hepatic disease. The clearance of donepezil was decreased by 20% in 10 patients with stable alcoholic cirrhosis as compared to healthy subjects. Dosage reduction may be necessary in some patients. There is no data available on the use of donepezil in the patient with acute *jaundice*.
Donepezil has only been evaluated in a limited number of patients with renal impairment/renal failure. Data from 4 patients suggests that the elimination of donepezil is not appreciably altered versus adults with normal renal function.
Donepezil should be used with caution in patients with asthma, chronic obstructive pulmonary disease (COPD), or other obstructive-type pulmonary disease. Although donepezil is relatively specific for CNS cholinesterase, it does have weak affinity for peripheral cholinesterase which may increase bronchoconstriction and bronchial secretion. Respiratory signs and symptoms should be monitored in patients with pulmonary disease as safety has not been demonstrated.
Cholinomimetics may induce or exacerbate urinary tract obstruction/bladder obstruction. Although this has not been observed with donepezil, caution is recommended in treating patients predisposed to these disorders. The relatively weak peripheral cholinergic effects of donepezil could potentially cause bladder outflow obstruction.
Because of their mechanism of action, cholinesterase inhibitors have the potential to interfere with the activity of anticholinergic medications.
Cholinomimetics may induce or exacerbate seizures. Seizures have rarely been observed with donepezil in post-market use, and

have not been causally related to the medication. Caution is recommended in treating patients predisposed to seizure disorder (e.g., head trauma, increased intracranial pressure, or unstable metabolic conditions). However, seizure activity may also be a manifestation of Alzheimer's disease. Increased cholinergic effects of donepezil in the CNS may also exacerbate symptoms of Parkinson's disease.
Donepezil is classified as FDA pregnancy category C. It is not known whether the drug will cause harm to the fetus or influence reproductive capacity. Safe use during pregnancy or *breast-feeding* has not been established.
There is no accepted use for donepezil in *children*.
Donepezil is an acetylcholinesterase inhibitor and therefore is likely to exaggerate muscle relaxation under anesthesia. If used during surgery, extended respiratory depression could result from prolonged neuromuscular blockade.

Contraindications last revised 9/23/2004 11:38:00 AM

Drug Interactions

- Amantadine
- Amiodarone
- Amoxapine

Antimuscarinics
Anti-retroviral protease inhibitors
Barbiturates

- Bosentan
- Carbamazepine

Cholinesterase Inhibitors

- Cimetidine
- Clarithromycin
- Clozapine
- Conivaptan
- Cyclobenzaprine
- Dalfopristin; Quinupristin
- Delavirdine
- Dexamethasone
- Digoxin
- Diltiazem
- Disopyramide
- Efavirenz
- Erythromycin
- Fluoxetine
- Fluvoxamine
- Fosphenytoin
- Gefitinib

General Anesthetics

- Imatinib, STI-571
- Itraconazole
- Ketoconazole

Local Anesthetics

- Maprotiline
- Modafinil
- Nefazodone

Neuromuscular blockers

- Nevirapine

Nonsteroidal antiinflammatory drugs (NSAIDs)

- Olanzapine
- Orphenadrine
- Oxcarbazepine

Parasympathomimetics

- Paroxetine

Phenothiazines

- Phenytoin
- Propafenone
- Quinidine
- Ranolazine
- Rifabutin
- Rifampin
- Rifapentine

Sedating H1-blockers

- Sertraline
- St. John's Wort, Hypericum perforatum
- Telithromycin

Tricyclic antidepressants

- Troglitazone
- Verapamil
- Voriconazole

NOTE: Donepezil is metabolized by CYP 450 isoenzymes 2D6 and 3A4.[4718] [6382]
Other cholinesterase inhibitors (e.g., galantamine [5234], rivastigmine [6380], tacrine [6381]) can produce additive pharmacodynamic effects if used concomitantly with donepezil [6382]. This is also true of parasympathomimetics such as bethanechol. Concurrent use is unlikely to be tolerated by the patient and should be avoided.
The therapeutic benefits of donepezil may be diminished when co-administered with the antimuscarinics [6338], the functional antagonists of the cholinesterase inhibitors [6002]. Atropine has been used to offset bradycardia in cholinesterase inhibitor overdose. Other drugs known to exhibit anticholinergic properties that could potentially interfere with the cholinesterase inhibitor activity include: amantadine, amoxapine, clozapine, cyclobenzaprine, disopyramide, sedating H1-blockers, maprotiline, olanzapine, orphenadrine, the antipsychotic phenothiazines, and tricyclic antidepressants. When concurrent use cannot be avoided, monitor the patient for reduced donepezil efficacy. In addition to anticholinergic effects, desipramine may potentially inhibit the metabolism of donepezil by inhibiting the hepatic CYP2D6 isoenzyme.[4718]
The elimination of donepezil may be increased by concurrent administration of certain *in vitro* inducers of the hepatic isoenzymes CYP2D6 and CYP3A4.[6382] Inducers of one or both of these isoenzymes include: barbiturates (e.g., phenobarbital) [4718], carbamazepine [4718], dexamethasone [4718], efavirenz (may induce or inhibit) [5172], fosphenytoin [5265], modafinil [4718], nevirapine [4718], oxcarbazepine [4718], phenytoin [4718], rifamycins [6382] (e.g., rifabutin, rifapentine, rifampin), St. John's wort, Hypericum perforatum [4718], and troglitazone [5399]. The clinical effect of these interactions on the efficacy of donepezil has not been determined. Observe patients for evidence of reduced donepezil efficacy if any of these agents are prescribed concurrently.
Ketoconazole has been shown, *in vitro*, to inhibit the metabolism of donepezil by inhibiting CYP3A4. In a 7-day cross-over study in 18 subjects, ketoconazole (200 mg daily) increased mean donepezil (5 mg daily) concentrations (AUC and Cmax) by 36%.[6382] The clinical relevance of this interaction is not known, but elevated donepezil concentrations could result in greater incidence of dose-related toxicity. However, the clinical effect of such an interaction on the response to donepezil has not been determined.
While donepezil is metabolized by CYP3A4 and CYP2D6 [4718] [6382] and coadministration with inhibitors of these enzymes could increase donepezil concentrations, potentially resulting in dose-related toxicity. Pharmacokinetic studies have shown that donepezil is

not affected by the concurrent administration of cimetidine, which is a non-specific inhibitor of hepatic CYP450 microsomal enzymes.[6382]
Donepezil is metabolized by CYP3A4.[4718] [6382] Coadministration with CYP3A4 inhibitors, such as anti-retroviral protease inhibitors [4718], may increase donepezil concentrations, potentially resulting in dose-related toxicity. However, the clinical effect of such an interaction on the response to donepezil has not been determined.
Donepezil is metabolized by CYP3A4.[4718] [6382] Coadministration with CYP3A4 inhibitors, such as clarithromycin [4718], may increase donepezil concentrations, potentially resulting in dose-related toxicity. However, the clinical effect of such an interaction on the response to donepezil has not been determined.
Donepezil is metabolized by CYP3A4.[4718] [6382] Coadministration with CYP3A4 inhibitors, such as dalfopristin; quinupristin [5221], may increase donepezil concentrations, potentially resulting in dose-related toxicity. However, the clinical effect of such an interaction on the response to donepezil has not been determined.
Donepezil is metabolized by CYP3A4.[4718] [6382] Coadministration with CYP3A4 inhibitors, such as delavirdine [4718], may increase donepezil concentrations, potentially resulting in dose-related toxicity. However, the clinical effect of such an interaction on the response to donepezil has not been determined.
Donepezil is metabolized by CYP3A4.[4718] [6382] Coadministration with CYP3A4 inhibitors, such as diltiazem [4718], may increase donepezil concentrations, potentially resulting in dose-related toxicity. However, the clinical effect of such an interaction on the response to donepezil has not been determined.
Donepezil is metabolized by CYP3A4.[4718] [6382] Coadministration with CYP3A4 inhibitors, such as erythromycin [4718], may increase donepezil concentrations, potentially resulting in dose-related toxicity. However, the clinical effect of such an interaction on the response to donepezil has not been determined.
Donepezil is metabolized by CYP3A4.[4718] [6382] Coadministration with CYP3A4 inhibitors, such as itraconazole [4718], may increase donepezil concentrations, potentially resulting in dose-related toxicity. However, the clinical effect of such an interaction on the response to donepezil has not been determined.
Donepezil is metabolized by CYP3A4.[4718] [6382] Coadministration with CYP3A4 inhibitors, such as nefazodone [4718], may increase donepezil concentrations, potentially resulting in dose-related toxicity. However, the clinical effect of such an interaction on the response to donepezil has not been determined.
Donepezil is metabolized by CYP3A4.[4718] [6382] Coadministration with CYP3A4 inhibitors, such as verapamil [4718], may increase donepezil concentrations, potentially resulting in dose-related toxicity. However, the clinical effect of such an interaction on the response to donepezil has not been determined.
Donepezil is metabolized by CYP3A4.[4718] [6382] Coadministration with CYP3A4 inhibitors, such as voriconazole [4718], may increase donepezil concentrations, potentially resulting in dose-related toxicity. However, the clinical effect of such an interaction on the response to donepezil has not been determined.
Quinidine has been shown, *in vitro*, to inhibit the metabolism of donepezil by inhibiting the hepatic CYP2D6 isoenzyme.[4718] Other inhibitors of CYP2D6 metabolism include amiodarone [4718], propafenone [4718], some of the SSRI-type antidepressants [4718]. This list may not be inclusive of all agents that may exhibit potent inhibition of CYP2D6. The clinical effect of these interactions on the response to donepezil have not been determined.
Local anesthetics can antagonize the effects of cholinesterase inhibitors by inhibiting neuronal transmission in skeletal muscle, especially if large doses of local anesthetics are used.[6156]
Muscle relaxation produced by succinylcholine can be prolonged when the drug is administered with a cholinesterase inhibitor, like donepezil. If used during surgery, extended respiratory depression could result from prolonged neuromuscular blockade. Other neuromuscular blockers may interact with donepezil in a similar fashion. Cholinesterase inhibitors are therefore also likely to exaggerate muscle relaxation under general anesthetics.[6382]
Nonsteroidal antiinflammatory drugs (NSAIDs) may cause additive pharmacodynamic GI effects with Alzheimer's disease (AD) agents that inhibit cholinesterase (e.g., donepezil [6382], galantamine [5234], rivastigmine [6380], or tacrine [6381]), leading to GI intolerance. Patients receiving concurrent NSAIDs should be monitored closely for symptoms of active or occult gastrointestinal bleeding. While NSAIDs appear to suppress microglial activity, which in turn may slow inflammatory neurodegenerative processes important for the progression of AD [4040], there are no clinical data at this time to suggest that NSAIDs alone [6384] [6386] or as combined therapy with AD agents result in synergistic effects in AD.
The increase in vagal tone induced by some cholinesterase inhibitors may produce bradycardia, hypotension, or syncope.[7719] The vagotonic effect of these drugs may theoretically be increased when given with other medications known to cause bradycardia such as digoxin. *In vitro* tests indicate that donepezil is not likely to interfere with the protein binding of digoxin. The metabolism of donepezil is not significantly affected by digoxin.[6382]
In vitro tests indicate that donepezil is not likely to interfere with the protein binding of warfarin.[6382] Donepezil also exhibits a low rate of binding to hepatic oxidative enzymes and is unlikely to inhibit the hepatic metabolism of other medications at therapeutic doses.[6382]
Bosentan is a potent inducer of CYP3A4 hepatic isoenzymes.[5226] Theoretically, bosentan can increase the hepatic clearance of donepezil (CYP3A4 substrate) [4718]; however, this interaction has not been studied.
Gefitinib may inhibit cytochrome P450 2D6 at clinical doses.[5012] Caution is recommended when administering gefitinib with other CYP2D6 substrates, such as donepezil [4718], that have a narrow therapeutic range or where large increases in serum concentrations may be associated with severe adverse reactions.
Imatinib, STI-571 is a potent inhibitor of cytochrome P450 3A4 and 2D6. The clinical effect of these interactions on the response to donepezil have not been determined.[4718]
Telithromycin, a ketolide antibiotic, can compete with donepezil for metabolism by CYP3A4. This can result in increased concentrations of donepezil if the two drugs are coadministered.[4880] [4718]
Clinicians should be aware of the potential for inhibition of donepezil metabolism via CYP2D6 by selected SSRIs, which may result in the need for dosage adjustment or selection of alternative therapy should side effects occur.[6382] Fluoxetine [4718], paroxetine [4718], and sertraline [4718], are potent inhibitors of the hepatic CYP2D6 isoenzyme, and concurrent use of these drugs with donepezil may lead to increased plasma levels of donepezil.[6382] An increased incidence of cholinergic-related side effects may occur. At least 2 case reports of an interaction with paroxetine have been published; the patients exhibited cholinergic-induced GI side effects and/or the appearance of insomnia, agitation, confusion and combativeness when paroxetine was added to donepezil therapy. The side effects subsided with the downward titration of the donepezil dosage or the discontinuation of both treatments.
Both fluoxetine and fluvoxamine another SSRI, inhibit the hepatic CYP3A4 isoenzyme and may decrease the metabolism of donepezil through this pathway.[4718] Citalopram and escitalopram do not appear to inhibit other CYP hepatic isoenzymes (e.g., 3A4, 2C9, or 2E1), based on *in vitro* studies, to any clinically significant degree and appear least likely of the SSRIs to decrease donepezil

metabolism.[4718] [4996] [4997]
Conivaptan is a potent inducer of CYP3A4 hepatic isoenzymes.[8659] Theoretically, conivaptan can increase the hepatic clearance of donepezil (CYP3A4 substrate) [4718]; however, this interaction has not been studied.
Donepezil is metabolized by CYP 450 isoenzymes 2D6 and 3A4.[4718] [6382] Ranolazine inhibits both of these metabolic pathways (CYP2D6 and CYP3A4 inhibitor).[8747] The clinical effects of these interactions on the response to donepezil have not been determined. According to the manufacturer for ranolazine, lower doses of CYP2D6 substrates may be required during coadministration with ranolazine.[8747] Use ranolazine and donepezil with caution, monitoring the clinical response to donepezil therapy. Consider using a lower dose of donepezil during coadministration with ranolazine.

Interactions last revised 5/24/2007 10:32:00 AM

Adverse Reactions

- abdominal pain
- agitation
- anorexia
- arthralgia
- AV block
- bradycardia
- depression
- diaphoresis
- diarrhea
- dizziness
- drowsiness
- dyspepsia
- ecchymosis
- fatigue
- GI bleeding
- headache
- hypotension
- increased urinary frequency
- insomnia
- muscle cramps
- nausea/vomiting
- nightmares
- seizures
- syncope
- weight loss

Donepezil is generally well-tolerated at dosages of 5 mg/day. At 10 mg/day, the discontinuation rate due to intolerable side effects approaches 13%. Many cholinergic side effects are dose-related and are more likely to be apparent during the initiation of therapy or during upward dosage titration. Slow titration over 1 week while advancing the dosage should help limit common adverse reactions. Adverse effects may respond to dosage reduction to the previously tolerated dosage level. In clinical trials for mild to moderate Alzheimer's disease, the following reactions were the most common: Anorexia, fatigue, diarrhea, muscle cramps, and nausea/vomiting. These side effects occurred in >= 5% of donepezil treated patients who received 10 mg/day PO and at twice the frequency of placebo. Nausea/vomiting and diarrhea were the most common reasons for discontinuing therapy. In clinical trials for severe Alzheimer's disease, adverse effects which occurred in at least 2% of those receiving donepezil and with an incidence twice that of placebo included anorexia (2% vs 1%), nausea (2% vs < 1%), diarrhea (2% vs 0%), and urinary tract infection (2% vs 1%). Hepatotoxicity has not been noted with donepezil as it has for tacrine.
Other frequently reported adverse reactions associated with donepezil therapy include headache, pain (various locations), syncope, ecchymosis, weight loss, arthralgia, insomnia, dizziness, depression, abnormal dreams or nightmares, drowsiness, dyspepsia, and increased urinary frequency. Weight loss usually averages 1—1.5 kg in those patients receiving cholinesterase inhibitors. These adverse reactions were reported during controlled clinical trials in at least 2% of patients receiving donepezil for mild to moderate Alzheimer's disease and at a higher frequency than in placebo-treated patients. Some side effects may respond to dosage reduction. Other adverse reactions occurring in at least 1% of patients receiving donepezil for mild to moderate Alzheimer's disease and at a frequency similar to placebo include abnormal crying, aggression, aphasia, ataxia, atrial fibrillation, bloating, blurred vision, bone fracture, bronchitis, cataract, chest pain (unspecified), dehydration, delusions, diaphoresis, dyspnea, epigastric pain, eye irritation, fecal incontinence, GI bleeding, hot flashes, hypertension, hypotension, increased libido, influenza, irritability, nervousness, nocturia, paresthesia, pruritus, restlessness, sore throat, toothache, tremor, urinary retention, urinary incontinence, urticaria, vasodilation, and vertigo.
Adverse reactions which occurred in at least 2% of patients in controlled trials receiving donepezil for severe Alzheimer's disease and at a rate higher than placebo include infection, headache, pain, fever, chest pain (unspecified), hypertension, hemorrhage, syncope, diarrhea, nausea/vomiting, anorexia, ecchymosis, increased creatine phosphokinase, dehydration, hyperlipidemia, insomnia, hostility, nervousness, hallucinations, somnolence, dizziness, depression, confusion, emotional lability, eczema, and urinary incontinence. Adverse reactions resulting in discontinuation of treatment included anorexia, diarrhea, nausea, and urinary tract infection. It should be taken into consideration when evaluating potential adverse reactions that some of these effects are also inherent to the condition being treated.

Adverse reactions occurring in at least 1% of patients in controlled trials receiving donepezil for severe Alzheimer's disease and primarily observed at a frequency similar to placebo include abdominal pain, asthenia, fungal infection, flu syndrome, hypotension, bradycardia, ECG abnormality, heart failure, constipation, gastroenteritis, fecal incontinence, dyspepsia, anemia, weight loss, peripheral edema, increased lactic dehydrogenase, increased alkaline phosphatase, arthritis, agitation, anxiety, tremor, convulsion, wandering, abnormal gait, pharyngitis, pneumonia, cough, bronchitis, rash, skin ulcer, pruritus, urinary tract infection, cystitis, hematuria, and glycosuria.
Post-marketing reports of adverse reactions temporally associated with donepezil include abdominal pain, agitation, cholecystitis, confusion, seizures/convulsions, hallucinations, hemolytic anemia, hyponatremia, neuroleptic malignant syndrome, pancreatitis, and rash (unspecified). There is inadequate data to determine a causal relationship to donepezil therapy.
An increase in vagal tone induced by donepezil may produce sinus bradycardia or heart block (AV block) in patients both with and without known underlying cardiac conduction abnormalities. Low blood pressure or syncope may also be exacerbated. However, data from unpublished trials indicate that donepezil infrequently induces bradycardia, even in the presence of other medications that may also lower heart rate.

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Darifenacin
Enablex®
Classification:
- Autonomic Agents
  - Anticholinergics
    - Antimuscarinics
- Genitourinary Agents
  - Bladder Antispasmodics

Description, Mechanism of Action, Pharmacokinetics

Description: Darifenacin hydrobromide is a competitive, selective M3 muscarinic receptor antagonist used orally in the treatment of overactive bladder (OAB) and its symptoms. Both M2 and M3 receptors are located in the detrusor muscle; even though M2 receptors are much more prevalent, it appears that M3 receptors are more important in mediating direct detrusor contractions. The M3 receptor is also involved in gastrointestinal smooth muscle function, salivary production, and iris sphincter function. Because M3 receptors are prevalent in gastrointestinal smooth muscle, the use of M3 selective antagonists, including darifenacin, has been investigated in the treatment of abdominal pain due to irritable bowel syndrome (IBS); however, preliminary results have been disappointing.[7488] Treatment with darifenacin for OAB results in significant reductions in the frequency of urinary incontinence, reductions in the number of micturitions per day, and improvements in the frequency and severity of symptoms including urgency. In addition, darifenacin has been shown to be as effective as oxybutynin in reducing the incidence of urinary incontinent episodes and symptoms of urgency. The most commonly reported adverse effects of darifenacin are dry mouth and constipation; the rates of

discontinuation due to these side effects in clinical trials is low indicating that such adverse effects are mild. *In vitro,* darifenacin is more selective for M3 receptors in the bladder than the salivary gland and when compared with oxybutynin, the incidence of dry mouth is significantly lower in patients treated with darifenacin (13% for darifenacin vs. 36% for oxybutynin, $p<0.05$).[7477] CNS side-effects are uncommon with darifenacin therapy. Similar to solifenacin, extended-release oxybutynin, and extended-release tolterodine, darifenacin is administered once daily. However, a disadvantage of darifenacin is the potential for significant drug interactions; darifenacin is metabolized by both CYP2D6 and CYP3A4 and many interactions involving drug metabolism are expected. Darifenacin (Enablex®) was FDA-approved for the treatment of OAB and its symptoms on December 22, 2004.

Mechanism of Action: Darifenacin is a competitive muscarinic receptor antagonist; darifenacin has a greater affinity for the M3 receptor than for other known muscarinic receptors. Darifenacin has a 9-fold greater affinity for M3 when compared to M1, a 12-fold greater affinity for M3 when compared to M5, and a 59-fold greater affinity for M3 when compared to M2 and M4 receptors. In general, muscarinic receptors play an important role in several cholinergically mediated functions including contractions of the urinary bladder smooth muscle and stimulation of salivary secretion. Both M2 and M3 receptors are found in the human detrusor muscle; even though there are a greater number of M2 receptors located in the detrusor muscle, it appears that M3 receptors are primarily responsible for bladder function and direct contraction of the detrusor muscle. In addition, M3 receptors are involved in contraction of the gastrointestinal smooth muscle, saliva production, and iris sphincter function; however, *in vitro,* darifenacin is more selective for M3 receptors in the bladder than the salivary gland.[7477] Adverse effects such as dry mouth, constipation, and abnormal vision may be mediated through effects on M3 receptors in these organs, although the severity and incidence of these side effects appears to be lower with darifenacin than traditional antimuscarinics. Darifenacin has been shown to increase bladder capacity and diminish the frequency of unstable detrusor contractions in patients with involuntary detrusor contractions.

Pharmacokinetics: Darifenacin is administered orally. The mean oral bioavailability at steady-state is estimated to be 15% and 19% for 7.5 mg and 15 mg tablets, respectively. After oral administration, peak plasma concentrations of darifenacin are reached approximately 7 hours after multiple dosing and steady state plasma concentrations are achieved by the sixth day of dosing. Darifenacin is 98% protein-bound, primarily to alpha-1-acid-glycoprotein, with a volume of distribution of 163 L.
Darifenacin is extensively metabolized by the liver after oral dosing; the three main routes of metabolism are monohydroxylation in the dihydrobenzofuran ring, dihydrobenzofuran ring opening, and N-dealkylation of the pyrrolidine nitrogen. Metabolism is mediated by CYP2D6 and CYP3A4. A subset of individuals (approximately 7% of Caucasians and 2% of African Americans) are poor metabolizers of CYP2D6 mediated drugs (PM). Individuals with normal CYP2D6 activity are referred to as extensive metabolizers (EM). In PMs, darifenacin metabolism will be mediated principally by CYP3A4. Exposure to darifenacin is substantially higher in PMs when compared to EMs; PM:EM ratios for Cmax and AUC following darifenacin 15 mg once daily are 1.9 and 1.7, respectively. Approximately 60% of an orally administered dose is recovered in the urine and 40% in the feces with 3% of the dose excreted in the urine as unchanged drug. Estimated darifenacin clearance is 40 L/h for EMs and 32 L/hr for PMS. The elimination half-life of darifenacin following chronic dosing is 13—19 hours.

•***Special Populations:*** While no dosage adjustment is necessary in elderly patients, clearance of darifenacin decreases with age (6% per decade relative to a median age of 44), with exposure of darifenacin 12—19% higher in volunteers aged 45—65 years compared to younger volunteers aged 18—44 years. While no dosage adjustment is necessary based on gender, darifenacin Cmax and AUC were 57—79% and 61—73% higher in females than in males, respectively. The pharmacokinetics of darifenacin are affected by moderate hepatic impairment (Child Pugh B); protein binding is affected and after adjusting for plasma protein binding, unbound darifenacin exposure is 4.7-fold higher in patients with moderate hepatic impairment. Mild hepatic impairment (Child-Pugh A) had no effect on the pharmacokinetics of darifenacin. Subjects with severe hepatic impairment (Child Pugh C) have not been studied.

Description, Mechanism of Action, Pharmacokinetics last revised 1/28/2005 3:48:00 PM

Indications

- overactive bladder (OAB)
- urinary incontinence

Dosage

For the treatment of an overactive bladder (OAB) with symptoms of urinary frequency, urinary urgency, or urge-related urinary incontinence:

Oral dosage (extended-release tablets):

Adults, including the elderly: Initially, 7.5 mg PO once daily. The dose may be increased to 15 mg PO once daily after 2 weeks based on individual response. In patients receiving other drugs that are potent CYP3A4 inhibitors (see Drug Interactions), the daily dose of darifenacin should not exceed 7.5 mg.

Adolescents and Children: Safe and effective use has not been established.

Maximum Dosage Limits:

•*Adults:* 15 mg/day PO.

•*Elderly:* 15 mg/day PO.

•*Adolescents:* Safe and effective use has not been established.

•*Children:* Safe and effective use has not been established.

Patients with hepatic impairment:

For patients with moderate liver impairment (Child-Pugh class B), do not exceed 7.5 mg PO once daily. In patients with severe hepatic impairment (Child-Pugh class C), the use of darifenacin is not recommended.

Patients with renal impairment:

Specific guidelines for dosage adjustments in renal impairment are not available; it appears that no dosage adjustments are needed.

Indications...Dosage last revised 1/28/2005 3:48:00 PM

Administration Guidelines

Oral Administration
•Darifenacin is administered without regard to meals.
•Darifenacin tablets are extended-release and should be swallowed whole; they should not be chewed, divided, or crushed.

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Contraindications/Precautions

- *GI obstruction*
- *ileus*
- *pyloric stenosis*
- *toxic megacolon*
- *urinary retention*
- anticholinergic medications
- autonomic neuropathy
- breast-feeding
- children
- closed-angle glaucoma
- contact lenses
- driving or operating machinery
- elderly
- gastroesophageal reflux disease (GERD)
- hepatic disease
- myasthenia gravis
- pregnancy
- prostatic hypertrophy
- renal disease
- ulcerative colitis
- urinary tract obstruction

• *Absolute contraindications are in italics.*

Darifenacin is contraindicated in patients who have demonstrated *hypersensitivity* to the drug or its ingredients.
Patients receiving darifenacin in combination with other anticholinergic medications may experience an increased frequency or severity of dry mouth, constipation, blurred vision, or other anticholinergic effects (see Drug Interactions).
Patients should be advised to use caution when driving or operating machinery while receiving darifenacin until the effects of the drug are known. Anticholinergic drugs in general can cause blurred vision, dizziness, or somnolence in some patients. However, in clinical trials of darifenacin, central nervous system related side effects were minimal; changes in EEGs and cognitive function and the incidence of blurred vision were comparable to placebo and tolterodine. Dizziness and somnolence were reported with an incidence of <= 2% in the largest phase III study of darifenacin.[7477] Continued precautions with driving or other tasks are not expected**.**
Due to the anticholinergic effects, darifenacin is contraindicated in patients with *urinary retention*. Anticholinergics may precipitate urinary retention in patients with preexisting urinary tract obstruction or prostatic hypertrophy, so caution is warranted. Use with caution in other patients with significant renal disease.
Darifenacin may increase intraocular pressure and aqueous outflow resistance in patients with closed-angle glaucoma so caution is advised in patients with treated disease; darifenacin should not be prescribed to patients with *uncontrolled closed-angle glaucoma*. Darifenacin is not contraindicated in patients with chronic open-angle glaucoma. The anticholinergic effects of darifenacin may make the eyes dry and this can cause irritation for wearers of contact lenses.
Darifenacin has a direct antispasmodic effect on smooth muscle that can delay gastric emptying, so it should not be used when there is *GI obstruction, pyloric stenosis,* or *ileus* present. Darifenacin would not be recommended for use in the setting of *toxic megacolon* or severe ulcerative colitis. In general, gastroesophageal reflux disease (GERD) may be aggravated by the use of anticholinergic medications.
Moderate hepatic disease (Child Pugh B) can alter the disposition of darifenacin; the total daily dose of darifenacin should not exceed 7.5 mg in patients with moderate hepatic disease (see Dosage). Darifenacin has not been studied in patients with severe hepatic disease (Child Pugh C) and its use in these patients is not recommended.
Anticholinergics in general may exacerbate the clinical symptoms of patients with myasthenia gravis or autonomic neuropathy.
Darifenacin is classified in FDA pregnancy risk category C. There are no studies of darifenacin in pregnant women; however, darifenacin, at a dose of 50 mg/kg in rats (59 times the AUC at maximum recommended human doses), caused a delay in the ossification of the sacral and caudal vertebrae. In addition, in rabbits, a dose of 30 mg/kg (28 times the AUC at maximum recommended human doses), increased post-implantation loss; in addition, dilated ureters and/or kidney pelvis' was observed in their offspring. Finally, dystocia was observed in rams at a dose equivalent to 17 times the AUC at the maximum recommended human dose with slight developmental delays in the pups. Because animal reproduction studies are not always predictive of human response, darifenacin should only be used in pregnancy if the potential benefit justifies the potential risk to the fetus.
Darifenacin is excreted into the milk of lactating rats. It is not known whether or not this drug is excreted into human milk; caution is advised when darifenacin is administered to a woman who is breast-feeding. Darifenacin should be used during breast-feeding only if the potential benefit justifies the potential risk to the baby.
Per the manufacturer, the safe and effective use of darifenacin in children has not been established.
During phase III clinical trials, 30% of patients were 65 years of age or older. Clearance of darifenacin decreases with age (6% per decade relative to a median age of 44) with exposure of darifenacin 12—19% higher in volunteers aged 45—65 years compared to younger volunteers aged 18—44 years. No overall difference in safety or efficacy was observed; dosage adjustments in elderly patients are not recommended. However, elderly patients may be more sensitive to the anticholinergic effects of drugs regardless of drug exposure. Monitor elderly patients for increased anticholinergic effects and consider dosage adjustments if these effects are

experienced.

Contraindications last revised 1/28/2005 3:48:00 PM

Drug Interactions

- Amantadine
- Amiodarone
- Amoxapine
- Amprenavir

  Antimuscarinics
- Aprepitant
- Atazanavir

  Barbiturates
- Bosentan
- Bupropion
- Caffeine
- Carbamazepine
- Chloroquine

  Cholinesterase inhibitors
- Cimetidine
- Cisapride
- Citalopram
- Clarithromycin
- Clozapine
- Conivaptan
- Cyclobenzaprine
- Dalfopristin; Quinupristin
- Delavirdine
- Digoxin
- Diltiazem
- Disopyramide

  Diuretics
- Dronabinol, THC
- Duloxetine
- Efavirenz
- Erythromycin
- Escitalopram
- Ethanol
- Flecainide
- Fluconazole
- Fluoxetine
- Fluvoxamine
- Fosamprenavir
- Fosphenytoin
- Gefitinib
- grapefruit juice
- Green Tea
- Guarana
- Haloperidol
- Hydroxychloroquine
- Imatinib, STI-571
- Indinavir
- Itraconazole
- Ketoconazole
- Lopinavir; Ritonavir
- Maprotiline
- Memantine
- Metoclopramide
- Miconazole
- Midazolam
- Mifepristone, RU-486
- Nabilone
- Nefazodone
- Nelfinavir
- Norfloxacin
- Olanzapine

  Opiate Agonists
- Orphenadrine

  Parasympathomimetics
- Paroxetine

  Phenothiazines
- Phenytoin
- Propafenone
- Propoxyphene
- Quinacrine
- Quinidine
- Quinine
- Rifabutin
- Rifampin
- Rifapentine
- Risperidone
- Ritonavir
- Saquinavir

  Sedating H1-blockers
- Sertraline
- Tegaserod
- Terbinafine
- Topiramate

  Tricyclic antidepressants
- Troleandomycin
- Verapamil
- Voriconazole
- Zafirlukast
- Zileuton

NOTE: Darifenacin is extensively metabolized in the liver; CYP2D6 and CYP3A4 are the primary mediators of metabolism. The metabolism of darifenacin may be affected by CYP3A4 and CYP2D6 inducers and inhibitors.[7474]
Amiodarone, an inhibitor of both CYP3A4 and CYP2D6, may decrease the metabolism of darifenacin and increase serum concentrations. Patients should be monitored for increased anticholinergic effects if these drugs are used concomitantly; dosage adjustments may be necessary.[4718] [7474] [5629]
Sedating H1-blockers are associated with moderate anticholinergic effects which could be additive when coadministered with darifenacin.[5983] [7474] In addition, several of the sedating H-1 blockers including chlorpheniramine, diphenhydramine, and promethazine are CYP2D6 inhibitors and thus could decrease the metabolism of darifenacin.[4718] [7474] Patients should be monitored for increased anticholinergic effects if these drugs are coadministered; dosage adjustments may be necessary.
Tricyclic antidepressants are associated with moderate anticholinergic effects which could be additive when coadministered with darifenacin.[5983] [7474] Caution should be exercised when darifenacin is used in combination with medications that are predominantly metabolized by CYP2D6 (i.e., tricyclic antidepressants) and have a narrow therapeutic window. The mean Cmax and AUC of imipramine were increased 57% and 70%, respectively, in the presence of steady-state darifenacin 30 mg once daily. In

addition, a 3.6-fold increase in the mean AUC and Cmax of imipramine's active metabolite, desipramine, was noted.[7474] Patients should be monitored for increased adverse effects, including anticholinergic effects, when these drugs are coadministered; dosage adjustments may be necessary.
Most phenothiazines are associated with moderate anticholinergic effects which could be additive when coadministered with darifenacin.[5983] Several of the phenothiazines including chlorpromazine, perphenazine, promethazine, and thioridazine are CYP2D6 inhibitors and thus could decrease the metabolism of darifenacin.[4718] [7474] In addition, caution should be exercised when darifenacin is used in combination with medications that are predominantly metabolized by CYP2D6 with narrow therapeutic windows such as thioridazine as the serum concentrations of thioridazine could be greatly increased in the presence of darifenacin.[7474]
Darifenacin is extensively metabolized in the liver; CYP2D6 and CYP3A4 are the primary mediators of metabolism.[7474]
Caution should be exercised when darifenacin is used in combination with medications that are predominantly metabolized by CYP2D6 with narrow therapeutic windows, such as flecainide, as the serum concentrations of such drugs could be greatly increased in the presence of darifenacin.[7474]
The mean Cmax and AUC of darifenacin 30 mg once daily at steady state were 42% and 34% higher, respectively, in the presence of cimetidine.[7474] Monitor patients receiving these two drugs concomitantly for increased anticholinergic effects; dosage adjustments may be necessary.
Antiretroviral protease inhibitors may decrease the metabolism of darifenacin leading to a possible increase in adverse anticholinergic effects. For instance, ritonavir inhibits CYP2D6 and is a potent inhibitor of CYP3A4.[4718] The manufacturer of darifenacin recommends that a maximum dose of 7.5 mg daily of darifenacin be administered when used concomitantly with potent CYP3A4 inhibitors including ritonavir, lopinavir; ritonavir, and nelfinavir.[7474] While such dosage restrictions are not recommended with other protease inhibitors (e.g., amprenavir, atazanavir, fosamprenavir, indinavir, and saquinavir), CYP3A4 is inhibited by these drugs and it may be prudent to monitor patients for increased anticholinergic effects when coadministered with darifenacin; dosage adjustments may be necessary.[4718] [7474] [5747]
Delavirdine is an inhibitor of both CYP2D6 and CYP3A4;[5206] if delavirdine is used concomitantly with darifenacin, monitor patients for increased anticholinergic effects and adjust the dosage of darifenacin if necessary.
Some of the selective serotonin reuptake inhibitors (SSRIs) may inhibit the CYP-mediated metabolism of darifenacin. For instance, fluoxetine is an inhibitor of both CYP3A4 and CYP 2D6.[4718] Fluvoxamine is an inhibitor of CYP3A4.[4718] Other SSRIs, including citalopram, escitalopram, paroxetine, and sertraline, inhibit CYP2D6.[4718] When using any of these drugs, patients should be monitored for increased anticholinergic effects. If such effects occur, dosage adjustments should be considered.
Bupropion, an inhibitor of CYP2D6 may inhibit the metabolism of darifenacin.[4718] In addition, bupropion is associated with moderate anticholinergic effects which could be additive when coadministered with darifenacin.[4781] [7474] Patients should be monitored for increased anticholinergic effects or other adverse effects when these two drugs are coadministered. Dosage adjustments may be necessary.
Erythromycin is an inhibitor of CYP3A4 and may inhibit the metabolism of darifenacin.[7474] A maximum dose of 7.5 mg daily of darifenacin is not necessary per the manufacturer; however, patients should be monitored for increased anticholinergic effects when these drugs are coadministered. In addition, because darifenacin antagonizes GI muscarinic cholinergic receptors, [7474] it decreases gastrointestinal motility. Darifenacin, therefore, may potentially antagonize the actions of drugs that enhance gastrointestinal motility, like erythromycin [5987].
Because darifenacin antagonizes GI muscarinic cholinergic receptors, [7474] it can antagonize the action of drugs that enhance gastrointestinal motility.[6824] Use with caution in patients receiving cisapride [7044], erythromycin (when erythromycin is being administered to enhance GI motility) [5987], metoclopramide [5688], or tegaserod [5691]. Avoid chronic administration of antimuscarinics along with prokinetic agents under most circumstances. The clinical significance of these potential interactions is uncertain.
Antimuscarinic drugs can raise intragastric pH. This effect may decrease the oral bioavailability of ketoconazole or itraconazole.[4700] [4699] In addition, the daily dose of darifenacin should not exceed 7.5 mg when coadministered with ketoconazole or itraconazole. When darifenacin 7.5mg once daily was coadministered with ketoconazole 400 mg, Cmax, and AUC concentrations of darifenacin increased significantly.[7474] Darifenacin should be used cautiously in patients receiving these drugs.
Per the manufacturer of darifenacin, the daily dose of darifenacin should not exceed 7.5 mg when coadministered with the following potent CYP3A4 inhibitors: clarithromycin, erythromycin, itraconazole, ketoconazole, lopinavir; ritonavir, nefazodone, nelfinavir, and ritonavir.[7474] The manufacturer does not necessitate a dosage adjustment when darifenacin is coadministered with less potent CYP3A4 inhibitors including erythromycin, fluconazole, diltiazem, and verapamil.[7474] Other examples of CYP3A4 inhibitors include amiodarone [5629], other antiretroviral protease inhibitors[4718] [5747], aprepitant [7438], conivaptan [8569], dalfopristin; quinupristin [5221], delavirdine [4718], efavirenz (inducer or inhibitor) [5172], fluoxetine [4718], fluvoxamine [4718], grapefruit juice [5822], mifepristone, RU-486 [4718], norfloxacin [6789], other systemic azole antifungals (miconazole, and voriconazole) [4718], troleandomycin [4718], zafirlukast [4948], and zileuton [5415]. This list is not inclusive of all CYP3A4 inhibitors. Patients should be monitored for increased adverse anticholinergic effects of darifenacin when drugs that inhibit CYP3A4 are coadministered; the dosage of darifenacin should be adjusted if warranted.
Rifampin [4718], rifabutin [4718], rifapentine [5213], carbamazepine [4718], barbiturates (e.g., phenobarbital or primidone) [4718], phenytoin [4718] (or fosphenytoin which is metabolized to phenytoin [5265]), and bosentan [5226] may induce the CYP3A4 metabolism of darifenacin and thereby reduce its oral bioavailability. In addition to CYP3A4, rifampin also induces CYP2D6 and may further affect the bioavailability of darifenacin.[4718] The dosage requirements of darifenacin may be increased in patients receiving concurrent enzyme inducers.
The dosage of darifenacin does not need to be adjusted when coadministered with CYP2D6 inhibitors. However, clinicians should monitor patients for increased anticholinergic effects when CYP2D6 inhibitors are coadministered with darifenacin; the dosage of darifenacin should be adjusted, if necessary. Examples of CYP2D6 inhibitors include amiodarone [4718], bupropion [4718], chloroquine [4718], chlorpheniramine [4718], chlorpromazine [4718], cimetidine [4718], delavirdine, diphenhydramine [4718], duloxetine [4718], gefitinib [5012], haloperidol [4718], hydroxychloroquine {6134], imatinib, STI-571 [4718], perphenazine [4718], promethazine [4718], propafenone [4718], propoxyphene [4718], quinacrine [4718], quinidine [4718], quinine [4718], risperidone [4718] ritonavir [4718], some SSRIs[4718], terbinafine [4718], and thioridazine. This list is not inclusive of all CYP2D6 inhibitors.
Oral formulations of digoxin can produce higher serum concentrations when administered concurrently with antimuscarinics (e.g., propantheline) because of decreased GI motility induced by the antimuscarinic agent.[4999] [7704] This interaction has mostly occurred in the literature with slowly-dissolving, large-particle formulations of digoxin tablets; the manufacture of oral digoxin products today, utilizing liquid formulations and/or smaller particle sizes, theoretically reduces the potential for absorption interactions. However, there is wide variability expected in individual responses to many digoxin-drug interactions.[4999] [7704]

Other pharmacodynamic and pharmacokinetic systemic interactions are possible between digoxin and select antimuscarinic agents. Both trospium (a selective antimuscarinic) and digoxin are eliminated by active renal tubular secretion;[4999] [5974] coadministration has the potential to increase serum concentrations of trospium or digoxin due to competition for the drug elimination pathway. Darifenacin (30 mg daily) coadministered with digoxin (0.25 mg daily) resulted in a 16% increase in digoxin exposure.[7474] Anticholinergics, because of their ability to cause tachycardia [6824], can also antagonize the beneficial actions of digoxin in atrial fibrillation/flutter. Routine therapeutic monitoring should be continued when an antimuscarinic agent is prescribed with digoxin until the effects of combined use are known.
Darifenacin 30 mg daily coadministered with a single, oral dose of midazolam 7.5 mg resulted in a 17% increase is midazolam exposure.[7474]
Pharmacologically, parasympathomimetic drugs enhance muscarinic/cholinergic function. Because darifenacin is an antimuscarinic,[7474] the muscarinic actions of parasympathomimetics, including both direct cholinergic receptor agonists and cholinesterase inhibitors could be antagonized when used concomitantly with darifenacin. However, successful treatment of both dementia with donepezil 10 mg/day and urinary incontinence with tolterodine 6 mg/day has been reported.[5975] In addition, preliminary evidence indicates that chronic anticholinergic use in patients with Alzheimer's Disease may possibly have an adverse effect on cognitive function. Therefore, the effectiveness of drugs used in the treatment of Alzheimer's such as memantine, may be adversely affected by chronic antimuscarinic therapy.[5976] Furthermore, the adverse effects of antimuscarinic drugs such as dry mouth, urinary hesitancy, or blurred vision, may be enhanced with the use of memantine; dosage adjustments of darifenacin may be required when memantine is coadministered.[6137]
Depending on the specific agent, additive anticholinergic effects may be seen when drugs with antimuscarinic properties like darifenacin are used concomitantly with other antimuscarinics.[7474] Other commonly used drugs with moderate to significant anticholinergic effects include amantadine [4771], amoxapine [5288], bupropion [4781], clozapine [4989], cyclobenzaprine [5155], disopyramide [4954], maprotiline [5491], olanzapine [5517], orphenadrine [5982], sedating H1-blockers [5983], most phenothiazines [5983], and most tricyclic antidepressants [5983]. Clinicians should note that additive antimuscarinic effects may be seen not only on GI smooth muscle, but also on bladder function and temperature regulation. While CNS-related side effects such as drowsiness and blurred vision are not typically noted with darifenacin, they may occur in some patients. Such effects could be additive with other anticholinergics, depending on the interacting agent.
Consuming > 400 mg/day caffeine has been associated with the development of urinary incontinence. Although conflicting data exists, daily consumption of alcohol may also be a risk factor for incontinence. Both caffeine and ethanol may aggravate bladder symptoms and counteract the effectiveness of darifenacin to some degree. Patients may wish to limit their intake of caffeinated drugs, dietary supplements (e.g., guarana), or beverages (e.g., green tea, other teas, coffee, colas) and alcoholic beverages.[5985]
Diuretics can increase urinary frequency, which may aggravate bladder symptoms.[5985]

Oligohidrosis and hyperthermia have been reported in post-marketing experience with topiramate.[4285] Use caution when topiramate is prescribed with agents known to predispose patients to similar heat-related disorders such as antimuscarinics.
Opiate agonists should be used cautiously with antimuscarinics since additive depressive effects on GI motility or bladder function may be seen.[5986] Opioids increase the tone and decrease the propulsive contractions of the smooth muscle of the gastrointestinal tract. Prolongation of the gastrointestinal transit time may be the mechanism of the constipating effect.[6365] Opiate analgesics combined with antimuscarinics can cause severe constipation or paralytic ileus, especially with chronic use.
Concurrent use of oral cannabinoids, such as dronabinol, THC or nabilone, with anticholinergics such as darifenacin may result in pronounced tachycardia and drowsiness.[7185] [9044]

Interactions last revised 6/30/2006 4:02:00 PM

Adverse Reactions

- abdominal pain
- asthenia
- constipation
- diarrhea
- dizziness
- drowsiness
- dyspepsia
- headache
- nausea/vomiting
- urinary retention
- xerosis
- xerostomia

During three phase III fixed-dose trials of darifenacin, adverse events were reported in 54% of patients receiving darifenacin 7.5 mg daily, in 66% of patients receiving darifenacin 15 mg daily, and in 49% of patients receiving placebo. In all placebo-controlled trails combined, the incidence of serious adverse events for 7.5 mg of darifenacin, 15 mg of darifenacin, and placebo was similar. The two most commonly reported adverse events in clinical trials of darifenacin (15 or 30 mg daily) were xerostomia (18.7—35.3% of patients receiving darifenacin vs. 8—9% of patients receiving placebo) and constipation (14.8—21.3% of patients receiving darifenacin vs. 6—8% of patients receiving placebo). The rates of discontinuation due to these 2 adverse events was low (< 1% for xerostomia and 0.6—1.2% for constipation) indicating a mild severity of such reactions. In addition, similar to other newer anticholinergics used in the treatment of overactive bladder, the incidence of xerostomia is lower with darifenacin when compared to oxybutynin; in crossover studies of darifenacin 15 mg or 30 mg daily compared with oxybutynin 5 mg three times daily, the incidence of xerostomia was 13% for darifenacin and 36% for oxybutynin ($p<0.05$).[7477] Other gastrointestinal-related adverse events reported in patients treated with darifenacin with a frequency greater than placebo include dyspepsia (2.7—8.4% vs. 2.6% in darifenacin and placebo patients, respectively), abdominal pain (2.4—3.9% vs. 0.5% in darifenacin and placebo patients, respectively), nausea/vomiting (1.5—4.1% vs.1.5% in darifenacin and placebo patients, respectively), and diarrhea (0.9—2.1% vs 1.8% in darifenacin and placebo patients, respectively).
Urinary tract infection was reported in 3.7—4.7% of darifenacin-treated patients compared to 2.6—3.1% of placebo-treated patients during clinical trials. In addition, acute urinary retention was reported in a total of 16 patients treated with darifenacin during phase I—III clinical trials; seven of these cases were reported as severe events. It should be noted that four of these patients were taking a

higher than recommended dosage of darifenacin (30 mg daily) for overactive bladder; the remaining severe cases were reported in a patient with irritable bowel syndrome, a patient with benign prostatic hypertrophy, and a patient with detrusor hyperactivity secondary to a stroke.
During Phase III clinical trials, xerosis was reported at an incidence of 1.5—2.1%. While the incidence was low, xerosis was reported more commonly in darifenacin-treated patients than placebo (0.5%).
Central nervous system (CNS) related side effects were uncommon during clinical trials of darifenacin; the most commonly reported CNS side effects were drowsiness and dizziness (<= 2% of patients). In the largest phase III study, no patients reported blurred vision, a common CNS side effect seen with antimuscarinics. Furthermore, darifenacin had no adverse effect on cognitive function in elderly patients (aged 65—84 years).[7477] Asthenia and headache were reported more commonly in darifenacin-treated patients during clinical trials. The incidence of asthenia was 1.5—2.7% in darifenacin-treated patients vs. 1.3% of placebo-treated patients; headache was reported in 6.7% of darifenacin-treated patients compared to 5.5% placebo-treated patients.
To determine the effects of darifenacin therapy on the QT interval and heart rate, 179 healthy adults aged 18—65 (18% poor metabolizers and 82% extensive metabolizers) were treated with either 15 mg or 75 mg of darifenacin daily, moxifloxacin 400 mg daily, or placebo for 6 days. At the doses studied, darifenacin did NOT cause a prolongation in the QT interval while moxifloxacin treatment caused a mean increase from baseline of about 7 msec. Changes in heart rate were also small; 3.1 bpm for the patients treated with darifenacin 15 mg daily and 1.3 bpm for patients treated with 75 mg of darifenacin daily. During Phase II and III clinical trials, the median change in heart rate after exposure to darifenacin was no different than placebo.
Flu-like symptoms (3%) and accidental injury (3%) were reported in patients receiving darifenacin during a 12-week, phase III study at a frequency greater than placebo (2.4% for both effects). Other adverse events reported during phase III, placebo-controlled trials in >= 1% of patients regardless of causality were abnormal vision, back pain, dry skin, hypertension, peripheral edema, weight gain, arthralgia, bronchitis, pharyngitis, rhinitis, sinusitis, rash, pruritus, and vaginitis.

Adverse Reactions last revised 1/28/2005 3:48:00 PM

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Ranitidine
Wal-Zan | Zantac®
Classification:
- Antihistamines
  - H2-blockers
- Gastrointestinal Agents
  - Antiulcer Agents
    - H2-blockers

Description, Mechanism of Action, Pharmacokinetics

Description: Ranitidine is an antagonist at histamine H2-receptors. The actions and indications for ranitidine differ little from other H2-blockers; however, compared to cimetidine ranitidine is 5—12 times more potent as a histamine receptor antagonist and has less affinity for the cytochrome P450 hepatic enzyme system. As a result, it is much less likely than cimetidine to interact with other drugs, although drug interactions with ranitidine do exist. Similar to other H2-receptor antagonists, the main use of ranitidine is in the treatment of various gastrointestinal disorders. However, for the symptomatic acute and chronic treatment of gastroesophageal reflux disease (GERD), proton pump inhibitors (PPIs) are considered to be more effective than H2- blockers.[2667] PPIs are also preferred over H2-blockers in currently recommended treatment regimens for the eradication of *Helicobacter pylori* gastrointestinal infection.[2661] Ranitidine (Zantac®) was approved by the FDA in June 1983. A non-prescription (OTC) formulation (75 mg tablets) was approved in December 1995. Glaxo also produces a formulation of ranitidine in combination with bismuth citrate (Tritec® - see separate monograph), used in regimens to treat *H. pylori*, which was FDA-approved in 1996. The Zantac® EFFERdose® granules for oral solution were discontinued by the manufacturer in January 2003; EFFERdose® tablets are still available. A 25-mg strength of EFFERdose® was approved by the FDA in April 2004 for the treatment of GERD in children and infants >= 1 month of age.

Mechanism of Action: Ranitidine competitively inhibits the binding of histamine to receptors on gastric parietal cells (designated as the H2 receptor), thus reducing basal and nocturnal gastric acid secretion. The drug also decreases the amount of gastric acid released in response to stimuli such as food, caffeine, insulin, betazole, or pentagastrin. Ranitidine reduces the total volume of gastric juice, thereby indirectly decreasing pepsin secretion. Ranitidine has little to no effect on serum gastrin and does not impair intrinsic factor secretion. The drug does not appear to alter gastric motility, gastric emptying, esophageal pressures, biliary secretions, or pancreatic secretions. Ranitidine is not an antimuscarinic anticholinergic. Ranitidine may aid in gastromucosal healing, and it may protect the mucosa from the irritant effects caused by aspirin and nonsteroidal antiinflammatory agents. Other actions of ranitidine include an increase in gastric bacterial flora (e.g., nitrate-reducing organisms). The clinical significance of this effect is not known. H2-blockers, as single agents, do not erradicate *H. pylori* infection.
After bolus ranitidine doses of 100 mg IV or greater, small and transient increases in prolactin serum concentrations have been noted. Ranitidine does not affect serum concentrations or release of gonadotropin, TSH, or GH. Ranitidine may impair the release of vasopressin. Ranitidine has no effect on serum cortisol, aldosterone, androgen, or estrogen levels.
Pharmacokinetics: Ranitidine is administered either orally or parenterally. Intramuscular (IM) administration results in a bioavailability of 90—100% versus intravenous (IV) administration. Due to first-pass elimination, the oral bioavailability of ranitidine is about 50—60%. The presence of food in the GI tract does not appear to affect the extent or rate of absorption. The drug distributes throughout the body fluids and tissues, and can be found in breast milk and CSF. Using inhibition of pentagastrin-induced acid secretion as an indicator, ranitidine's effects persist for 8—12 hours.

Ranitidine undergoes partial metabolism (30%) in the liver, and both the unchanged drug and its metabolites are excreted in the urine and feces. Following IV injection, roughly 70% of ranitidine is recovered in the urine unchanged. Following oral administration, roughly 30% of an administered dose is excreted unchanged in the urine. The half-life of the drug is 2—3 hours but increases to roughly 5 hours in patients with renal impairment (CrCl < 35 ml/min). Elderly patients have decreased renal function and the elimination half-life in this group is about 3—4 hours. Tubular secretion as well as glomerular filtration account for ranitidine renal elimination. The manufacturer states that in patients with compensated cirrhosis, there are minor but clinically insignificant alterations in ranitidine distribution, half-life, and clearance.

Description, Mechanism of Action, Pharmacokinetics last revised 3/13/2007 12:25:00 PM

Indications

- aspiration prophylaxis†
- duodenal ulcer
- dyspepsia
- esophagitis
- gastric ulcer
- gastritis†
- gastroesophageal reflux disease (GERD)
- Helicobacter pylori
- multiple endocrine adenoma syndrome
- NSAID-induced ulcer prophylaxis†
- pyrosis (heartburn)
- stress gastritis prophylaxis†
- systemic mastocytosis
- Zollinger-Ellison syndrome

† non-FDA-approved indication

Dosage

For the self-medication of non-ulcer dyspepsia (acid indigestion), pyrosis (heartburn), and sour stomach:

•for prophylaxis:

Oral dosage - OTC product:

Adults including the elderly, and adolescents: 75—150 mg PO immediately before eating or up to 60 minutes before consuming food and beverages that may cause heartburn. Maximum daily dosage is 150 mg. Patients should not take for more than 2 weeks without consulting a physician.

Children < 12 years of age: Do not self-medicate. Use only if advised by qualified health care prescriber.

•for treatment:

Oral dosage - OTC product:

Adults including the elderly, and adolescents: 75—150 mg PO once or twice daily. Maximum daily dosage is 150 mg. Patients should not take for more than 2 weeks without consulting a physician.

Children < 12 years of age: Do not self-medicate. Use only if advised by qualified health care prescriber.

For the treatment of gastroesophageal reflux disease (GERD):

•for short-term treatment (acute healing phase):

Oral dosage:

Adults including the elderly, and adolescents: 150 mg PO twice daily. However, many experts recommend dosages of 300 mg PO twice daily for 4—8 weeks. Symptomatic relief usually occurs within 1—2 weeks after starting therapy.

Children and infants >= 1 month: 5—10 mg/kg/day PO, administered in 2 or 3 divided doses. Continue therapy for 6—8 weeks if improvement in symptoms is noted.[2668]

•for maintenance treatment† (relapse prevention):

Oral dosage:

Adults including the elderly, and adolescents: 150 mg PO twice daily for up to 12 months. No placebo-controlled studies have lasted for periods of longer than 1 year.

Children and infants >= 1 month: Specific guidelines for dosage for maintenance treatment of GERD have not been established.[2668]

For the treatment of erosive esophagitis:

•for endoscopically diagnosed erosive esophagitis:

Oral dosage:

Adults including the elderly, and adolescents: 150 mg PO four times per day for up to 12 weeks. Symptomatic relief may begin within 24 hours of initiation of treatment.

Children and infants >= 1 month: 5—10 mg/kg/day PO, administered in 2 or 3 divided doses.

•to maintain healing in erosive esophagitis after the initial treatment phase is complete:

Oral dosage:

Adults including the elderly, and adolescents: 150 mg PO twice daily. NOTE: Single doses administered prior to bedtime (i.e., 300 mg PO qhs) have been less effective than 150 mg PO twice daily.[494] Placebo-controlled studies have been carried out for 48 weeks.

Children and infants >= 1 month: Specific guidelines have not been established.

For the treatment of peptic ulcer disease (duodenal ulcer or gastric ulcer) or gastritis†:

NOTE: If gastritis or ulceration is due to NSAID therapy, every effort should be made to discontinue the NSAID.

•for short-term treatment of active benign gastric ulcer, active duodenal ulcer or gastritis†:

Oral dosage:

Adults including the elderly, and adolescents: 150 mg PO twice daily or 300 mg PO once daily at bedtime. Most duodenal ulcers heal within 4 weeks, most gastric ulcers heal within 6 weeks. Per the manufacturer, many foreign trials have shown that 100 mg PO twice daily has been as effective as 150 mg PO twice daily for duodenal ulcer. Safety of therapy beyond 8 weeks for uncomplicated duodenal ulcer or beyond 6 weeks for benign gastric ulcer has not been assessed. If follow-up maintenance therapy is indicated, see dosage below.

Children and infants >= 1 month: 2—4 mg/kg/day PO, administered in 2 divided doses. Maximum dosage for active treatment 300 mg/day PO.

Intermittent intravenous or intramuscular dosage:
Adults including the elderly, and adolescents: 50 mg IV (intermittent infusion) or IM every 6—8 hours.
Continuous intravenous infusion dosage:
Adults including the elderly, and adolescents: 6.25 mg/hour via continuous IV infusion (i.e., total daily dosage will equal 150 mg/24 hours).

•for maintenance therapy after treatment phase is complete:

Oral dosage:
Adults including the elderly, and adolescents: 150 mg PO once daily at bedtime. No placebo-controlled studies have lasted for longer than 1 year.
Children and infants >= 1 month: 2—4 mg/kg/day PO, administered once daily at bedtime. Maximum maintenance dosage 150 mg/day PO.

For the active treatment of *Helicobacter pylori*-associated duodenal ulcer, gastric ulcer†, or dyspepsia† in combination with bismuth subsalicylate, metronidazole, and tetracycline (e.g., Helidac® or equivalent dosage of these individual drugs in combination):

NOTE: In populations where *H. pylori* infection is common (>= 10%), patients presenting with non-ulcer dyspepsia should be tested for *H. pylori;* those found to be *H. pylori* positive should be started on combination eradication therapy (also see Helidac® monograph).[9998] [9961]
NOTE: Ranitidine is not effective as a single agent for the eradication of *H. pylori*. Quadruple regimens that include an H2-blocker as an anti-secretory agent are FDA-approved, but are associated with lower compliance and efficacy rates than other recommended regimens.[2661] It is not acceptable to substitute an H2-blocker for a PPI in any current *H. pylori* treatment regimen.[2661]
Oral dosage:
Adults including the elderly, and adolescents: 150 mg PO twice daily or 300 mg PO once daily at bedtime with bismuth subsalicylate (525 mg four times daily), metronidazole (250 mg four times daily), and tetracycline (500 mg four times daily) for 14 days. Continue ranitidine at this dosage for an additional 2—4 weeks after the discontinuation of the antibiotic therapy to ensure appropriate healing of the active ulcer. This drug combination is expected to result in eradication of *H. pylori* in 80—90% of patients.

For the treatment of pathologic GI hypersecretory conditions such as Zollinger-Ellison syndrome, systemic mastocytosis, or multiple endocrine adenoma syndrome:

Oral dosage:
Adults including the elderly, and adolescents: Initially, 150 mg PO twice daily; however, larger doses are usually necessary. Maximum dose for this condition is 6 g/day PO, administered in divided doses. Continue as long as clinically indicated.
Children† and infants† >= 1 month: 5—10 mg/kg/day PO, administered in 2 or 3 divided doses. Exact dosages for hypersecretory conditions have not been established.
Intravenous or intramuscular dosage:
Adults including the elderly, and adolescents: 50 mg IV (intermittent infusion) or IM every 6—8 hours; however, larger doses may be necessary. In general, do not exceed 400 mg/day IV, administered in divided doses.
Continuous intravenous infusion dosage:
Adults including the elderly, and adolescents: For patients with Zollinger-Ellison syndrome, begin infusion at 1 mg/kg/hour. After 4 hours, if the measured gastric acid output is > 10 mEq/hr or the patient is symptomatic, adjust the dose upward in 0.5 mg/kg/hr increments, and remeasure the acid output. Dosages up to 2.5 mg/kg/hr or infusion rates up to 220 mg/hr have been used.

For acid aspiration prophylaxis† prior to anesthesia:

NOTE: Routine use of H2-blockers prior to surgery to decrease the risks of pulmonary aspiration in patients who have no apparent increased risk for pulmonary aspiration is not recommended. Consult current practice guidelines.
IV or IM dosage:
Adults including the elderly, and adolescents: 50 mg IV or IM 45—60 minutes prior to induction of anesthesia.
Children: 1 mg/kg IV or IM 45—60 minutes prior to induction of anesthesia.

For NSAID-induced ulcer prophylaxis†:

Oral dosage:
Adults: A placeb-controlled, double blind study of 263 patients with either rheumatoid arthritis or osteoarthritis, 150 mg PO twice daily reduced the incidence of duodenal ulceration but not gastric ulceration. Efficacy was determined by endoscopy.[1190]

For stress gastritis prophylaxis† in critically-ill patients:

Intermittent intravenous dosage:
Adults including the elderly, and adolescents: 50 mg IV (via intermittent infusion) or IM every 6—8 hours.
Children and infants >= 1 month: 2—4 mg/kg/day IV in divided doses every 6—8 hours. In a prospective study of 45 critically ill patients (median age: 3 years; range: 2 weeks—22 years), a dosage of at least 3 mg/kg/day IV given in divided doses was required in most children to maintain gastric pH >= 4.[1932] Dosages of up to 1.5 mg/kg IV every 6 hours have been used.[1933]
Premature and term neonates: 1.5 mg/kg IV bolus dose; then start maintenance dose of 1.5 mg/kg/day IV in divided doses every 8—12 hours. Dosages as low as 1 mg/kg/day IV, administered in divided doses every 12 hours, have been adequate for some premature neonates. Alternatively, dosages of up to 5 mg/kg/day IV, administered in divided doses every 8 hours, have been used.[2669]
Continuous intravenous infusion dosage:
Adults including the elderly, and adolescents: 6.25 mg/hour via continuous IV infusion (i.e., total daily dosage will equal 150 mg/24 hours).
Children and infants >= 1 month: 1 mg/kg IV loading dose, followed by an infusion of 0.1—0.125 mg/kg/hr (i.e, total daily dosage will be 2.4—3 mg/kg/day given over 24 hours).
Premature and term neonates†: 1.5 mg/kg IV loading dose, followed by a 0.04 mg/kg/hour IV infusion (i.e., total daily dosage will be 1 mg/kg/day given over 24 hours).

Maximum Dosage Limits:

•*Adults:* 300 mg/day PO for most indications; 600 mg/day PO for GERD. Up to 6 grams/day PO for pathologic hypersecretory conditions.
•*Elderly:* 300 mg/day PO for most indications; 600 mg/day PO for GERD. Up to 6 grams/day PO for pathologic hypersecretory conditions.
•*Adolescents:* 300 mg/day PO for most indications; 600 mg/day PO for GERD. Up to 6 grams/day PO for pathologic hypersecretory conditions.
•*Children:* 4 mg/kg/day PO for most indications, not to exceed 300 mg/day for active treatment or 150 mg/day PO for maintenance

treatment of peptic ulcer disease. Doses of 5—10 mg/kg/day PO have been used for treatment of GERD/erosive esophagitis, and pathologic hypersecretory conditions.
•*Infants >= 1 month:* 4 mg/kg/day PO for most indications. Doses of 5—10 mg/kg/day PO have been used for treatment of GERD/erosive esophagitis, and pathologic hypersecretory conditions.

Patients with hepatic impairment:

In patients with compensated cirrhosis, there are minor but clinically insignificant alterations in ranitidine half-life and clearance. It appears that no dosage adjustment is needed in patients with hepatic impairment.

Patients with renal impairment:

CrCl >= 50 ml/min: No dosage adjustment needed.
CrCl < 50 ml/min: Reduce recommended dose by 50% (or extend dosing interval). For example, the manufacturer recommends a dosage of 150 mg PO every 24 hours or 50 mg IV every 18—24 hours for adults. Depending upon the patient's condition, the PO or IV dosage may be cautiously increased to every 12 hours if required.

Intermittent Hemodialysis:

Ranitidine is removed to some degree by hemodialysis. The patient's normal dosage schedule based on CrCl should be adjusted, when possible, so that the timing of a regularly scheduled dose coincides with the end of a hemodialysis session.
†non-FDA-approved indication

Indications...Dosage last revised 3/27/2007 9:01:00 AM

Administration Guidelines

Oral Administration
•*All oral dosage forms:* May be administered without regard to meals. May administer with food, water, or milk to minimize gastric irritation.
•*EFFERdose® tablets:* Dissolve 150 mg dose in 6—8 ounces (180—240 ml) of water before administration; dissolve the 25 mg dose in no less than 5 ml of water in an appropriate measuring cup. Once the EFFERdose® tablet is completely dissolved, the solution may be administered to the patient. The solution may be administered by medicine dropper for infants. EFFERdose® tablets should not be chewed, swallowed whole, or dissolved on the tongue.
•*Syrup:* Measure dosage with calibrated oral syringe or cup prior to administration to give an accurate dosage.

Parenteral Administration
•Ranitidine injection is administered via the intramuscular or intravenous routes.
•Pharmacy bulk vial package is only available for preparing admixtures; the pre-mixed infusion bags are only for slow intravenous-infusion administration.
•Visually inspect parenteral products for particulate matter and discoloration prior to administration whenever solution and container permit.
Intramuscular injection:
•No dilution necessary.
•Inject into a large muscle mass. Aspirate prior to injection to avoid injection into a blood vessel.
Intermittent direct IV injection:
•Dilute to a maximum of 2.5 mg/ml using non-preserved NS or other compatible IV solution. For example, a 50 mg dose should be diluted to 20 ml.
•Inject at a rate no greater than 4 ml/minute (i.e., 50 mg/20 ml dose should be pushed over 5 minutes).
Intermittent IV infusion:
•Dilute to a maximum of 0.5—1 mg/ml using D5W, NS, or other compatible IV solution. The diluted solution is stable for up to 48 hours at room temperature.
•Pre-mixed ready-to-use infusion bags are available as 1 mg/ml ranitidine (i.e., 50 mg/50 ml). Premixed ready-to-use bags are for slow IV administration only.
•Infuse over 15—20 minutes (5—7 ml/minute).
Continuous 24-hour IV infusion:
•For adults, dilute 150 mg of ranitidine in 250 ml of D5W or NS or another compatible solution. The diluted solution is stable for up to 48 hours at room temperature. Infuse over 24 hours at a rate of 6.25 mg/hr or as specified by physician.
•Use a controlled-rate infusion device.
•Alternatively, the dosage may be added to a compatible TPN solution for administration over 24 hours.

Administration last revised 7/8/2005 3:14:00 PM

Contraindications/Precautions

- breast-feeding
- children
- elderly
- gastric cancer
- H2-blocker hypersensitivity
- infants
- infection
- neonatal prematurity
- neonates
- phenylketonuria
- porphyria
- pregnancy
- renal disease
- renal failure
- renal impairment
- tobacco smoking

Ranitidine is contraindicated in any patient hypersensitive to the drug or its components. Cross-sensitivity in this class of compounds has been observed, so ranitidine should be administered with caution to patients with a history of H2-blocker hypersensitivity. An

incidence of cross-reactivity among this class of agents is not currently available.
Symptomatic response to therapy with ranitidine does not preclude the presence of gastric cancer. In the patient who is self-medicating with OTC ranitidine formulations, the continuation of heartburn, acid indigestion, or dyspepsia beyond 2 weeks signals the need to consult a health-care professional for evaluation.
Symptomatic response to therapy with ranitidine does not preclude the presence of *H. pylori* infection. Ranitidine therapy does not appear to interfere with the sensitivity of gastric urease biopsy or urea breath-tests for the detection of *H. pylori* in most patients. H2-blockers, as single agents, will not eradicate *H. pylori* infection, if present.
Studies in patients with hepatic dysfunction (compensated cirrhosis) indicate that there are minor, but clinically insignificant, alterations in ranitidine half-life, distribution, clearance, and bioavailability.
Ranitidine should be used cautiously in those patients with renal disease, specifically in those with renal impairment or renal failure. Accumulation of ranitidine can occur. Ranitidine dosage should be reduced in patients with creatinine clearances of less than 50 ml/min (see Dosage). No special precautions have been advised for the elderly, but some older patients may exhibit decreased renal function. Accumulation of ranitidine can occur. Dosage adjustments may be necessary in some older individuals based on renal function. Critically ill, elderly patients have been noted in some uncontrolled studies to be more likely to exhibit central nervous system (CNS) reactions to the H2-blockers.
The safety and efficacy of ranitidine have been established in children and infants from 1 month to 16 years of age for most indications. Dosages and efficacy have not been established for hypersecretory conditions. Ranitidine has been used successfully in critically ill children and infants for the purpose of stress-ulcer or acid-reflux prophylaxis (see Dosage). There is limited information on ranitidine use in neonates. Neonatal prematurity results in decreased ranitidine elimination compared to term neonates and requires dosage adjustment (see Dosage). Self-medication (i.e., OTC) in children under the age of 12 years is not recommended.
Ranitidine is classified in FDA pregnancy category B. Animal studies have not demonstrated a risk to the fetus but there are no adequate studies in pregnant women. Ranitidine does cross the placenta, but limited epidemiological evidence has not suggested an association between the drug and congenital defects in first trimester exposure. Mean fetal: maternal ratios are approximately 0.9 after IV administration versus 0.4 for oral dosages. Risk versus benefit should be considered prior to use, and use should take place under the guidance of a qualified health care professional. Ranitidine should be used in pregnancy only when necessary, when safer drugs such as antacids have failed. Self-medication during pregnancy is not recommended. Pregnant patients should see their health care professional for a proper diagnosis and for treatment recommendations. Limited use of single dosages of ranitidine for reducing gastric acid prior to obstetric delivery, including caesarian section, have not been noted to adversely affect labor or neonatal outcomes.
Ranitidine is excreted into breast milk and should be used with caution in a woman who is breast-feeding her infant. Milk concentrations increase with time after the administration of a maternal oral dose. Mean maternal milk: plasma ratios at 2 and 6 hours after a single oral dose, ratios are 1.9 and 6.7 respectively. The effect of ranitidine or the resultant decrease in gastric acidity on the nursing infant is not known. However, the American Academy of Pediatrics has considered the use of cimetidine, a related agent that is also highly excreted into breast milk, to be compatible with breast-feeding due to a lack of reported adverse effects in nursing infants. Risk-benefit ratios should be considered, taking into account the importance of the medication to the mother.
Rare reports have suggested that ranitidine may precipitate acute porphyric attacks in patients with acute porphyria. It is recommended that ranitidine be avoided in these patients.
Certain formulations of ranitidine (i.e., Zantac® EFFERdose® tablets) contain phenylalanine and should be used cautiously in patients with phenylketonuria. Patients with phenylketonuria should be warned that these dosage forms contain 16.84 mg of phenylalanine per 150 mg of ranitidine and 2.81 mg of phenylalanine per 25 mg of ranitidine.
Tobacco smoking appears to contribute to an increased risk of developing PUD and may also impair ulcer healing or increase the risk of ulcer recurrence.

Contraindications last revised 7/17/2006 1:53:00 PM

Drug Interactions

- Alendronate
- Atazanavir
- Bismuth Subsalicylate
- Cefditoren
- Cefpodoxime
- Ceftibuten
- Cefuroxime
- Delavirdine
- Dexmethylphenidate
- Dirithromycin
- Enoxacin
- Entecavir
- Ethanol
- Gefitinib
- Iron Salts
- Isradipine
- Itraconazole
- Ketoconazole
- Lomefloxacin
- Mefloquine
- Memantine
- Metformin
- Methylphenidate
- Nicardipine
- Nifedipine
- Propantheline
- Saquinavir
- Sucralfate
- Sulfonylureas
- Theophylline, Aminophylline
- Triazolam
- Trospium
- Warfarin

NOTE: Although ranitidine has been reported to bind weakly to cytochrome P-450 *in vitro*, recommended doses of the drug do not inhibit the action of the cytochrome P-450 enzyme system. However, there have been isolated reports of drug interactions that suggest that ranitidine may affect the bioavailability of certain drugs by some mechanism as yet unidentified (e.g., a pH-dependent

effect on absorption or a change in volume of distribution).[5980]
Reports in the literature have suggested ranitidine increases theophylline serum concentrations [7885] [7886], but clinical studies in healthy subjects have failed to identify this effect [7887] [7888]. Furthermore, a clinical study in 12 healthy subjects demonstrated a lack of effect of ranitidine doses up to 4200 mg/day on theophylline metabolism.[7889] However, caution should be exercised when using even larger doses, such as in the treatment of Zollinger-Ellison syndrome (see dosage), since the occurrence of cimetidine-like drug interactions at these doses is unknown.
Ranitidine appears to have less of an effect on hepatic metabolism of warfarin than cimetidine. Most studies have found that in oral dosages of 300 mg/day or less or equivalent, ranitidine is not likely to have any effect on warfarin pharmacodynamics or pharmacokinetics. However, variable effects on INR's have been reported. Excessive hypoprothrombinemia has occurred when ranitidine, in dosages > 300 mg/day, was added to an established warfarin regimen in rare instances. One extensive review has concluded that adequate evidence of an interaction between ranitidine and warfarin has yet to be reported.[367]
Ketoconazole and itraconazole are weak bases. Both require an acidic environment for oral absorption and therapy with ranitidine can reduce their bioavailability.[5980] The mechanism involves decreased ionization and dissolution of the antifungals. Due to the sustained action of H2-blockers, a clinically-significant drug interaction with these azole antifungals may still occur even if administration times are adjusted. When possible, concurrent use of H2-blockers with either ketoconazole [4699] [5833] or itraconazole [4700] should be avoided.
H2-blockers appear to increase the systemic absorption of bismuth from bismuth-containing compounds like bismuth subsalicylate.[7825] The clinical significance of this finding is uncertain.
H2-blockers can affect the pharmacokinetics of some orally-administered cephalosporins. Ranitidine has been shown to reduce oral cefuroxime axetil [7796] AUC by more than 40% and reduce the AUC of oral cefpodoxime [7797] by 29%. The interactions are probably due to increased gastric pH and subsequent pH-induced changes in the oral absorption of these cephalosporins. Clinicians should watch for antibiotic failure in patients receiving cefpodoxime or cefuroxime who are concurrently receiving H2-blockers. Conversely, the oral bioavailability of ceftibuten [6665] was reported to be increased by the administration of 150 mg of ranitidine PO every 12 hours for 3 days, but this interaction is of unknown clinical relevance. Furthermore, co-administration of a single dose of an intravenous H2-blocker (famotidine) reduced the oral absorption of a single 400 mg dose of cefditoren [5253] pivoxil administered after a meal. There was a 27% and 22% decrease in mean Cmax and AUC, respectively. Although the clinical significance is not known, it is recommended that cefditoren pivoxil not be taken concomitantly with any H2-blockers.
Although some studies have suggested that H2-receptor antagonists inhibit gastric alcohol dehydrogenase and thus decrease the first pass metabolism of ethanol [5305], a small study of patients receiving treatment for duodenal ulcer with either famotidine or ranitidine did not demonstrate altered ethanol pharmacokinetics.[135] A meta-analysis evaluating the effects of H2-blockers on blood ethanol concentrations reported that only cimetidine and ranitidine, but not other H2-blockers, caused small elevations in serum ethanol levels. However, it was reported that larger studies were less likely to show an effect and that these elevations were not likely to be clinically relevant.[5305]
Propantheline bromide increases the bioavailability of ranitidine by 23% when the drugs are administered concomitantly. Propantheline bromide is believed to delay gastric emptying, increase transit time, and thereby increase the peak plasma concentration of ranitidine.[5980]
Ranitidine has been shown to affect the pharmacokinetics of some oral sulfonylureas, notably, glipizide [5281] and glyburide [6157]. In one placebo controlled study, diabetic patients stabilized on glipizide were given ranitidine 3 hours before a meal. Ranitidine significantly reduced the rise in blood glucose after a meal by a mean of 25% and also increased plasma glipizide AUC by approximately 20%. Similar effects have been reported with glyburide. The mechanism of the interaction is not clear, but asymptomatic hypoglycemia has been observed as a result of this interaction. Animal studies to date have not noted pharmacokinetic interactions between ranitidine and other sulfonylureas (e.g., tolbutamide), but caution is advised. Patients receiving sulfonylureas should be observed for evidence of altered glycemic response when ranitidine is instituted or discontinued.
Cationic medications, like ranitidine, may decrease the renal clearance of metformin [7775] secondary to competition for renal tubular transport systems. Such an interaction has been observed when cimetidine was administered with metformin. The decrease in renal excretion led to a 40% increase in metformin AUC. Although interactions with cationic drugs remain theoretical (except for cimetidine), caution is warranted when ranitidine and metformin are prescribed concurrently. Famotidine may be less likely to interact with metformin because of less tubular excretion.
Ranitidine has been shown to decrease the bioavailability of orally-administered enoxacin [7795] by up to 40%, and this interaction is thought to be due to decreased gastric acidity. Patients taking the two medications concurrently should be observed for antibiotic failures. Ranitidine appears to have variable effects on the pharmacokinetics of other quinolone antibiotics. Ranitidine does not appear to decrease the oral absorption of ciprofloxacin. The renal tubular secretion of lomefloxacin [7890] has been shown to be decreased by ranitidine, and is probably due to competition for renal tubular secretion.
Sucralfate may slightly decrease ranitidine bioavailability.[7891] Sucralfate does not appear to reduce the bioavailability of other orally-administered H2-antagonists to a clinically significant degree. Drugs that reduce gastric acidity (e.g. H2-blockers) were formerly thought to decrease the ability of sucralfate to bind to ulcerated tissues in the GI tract; however, *in vitro* animal studies have not supported an interaction between the H2-antagonists and sucralfate. The concurrent use of H2-blockers does not appear to interfere with the appropriate action of sucralfate.
Ranitidine has been reported to increase the plasma concentrations of oral triazolam when administered concurrently. Mean triazolam AUCs were 10—28% higher following the use of ranitidine versus those occurring with triazolam alone in patients under the age of 60 years. In the elderly, mean triazolam AUC values increased by 30%. Ranitidine does not alter the AUC of intravenous triazolam. It is postulated by the manufacturer of ranitidine that reduced gastric acidity may increase triazolam bioavailability, as no changes in triazolam half-life or metabolic pathways were observed.[5980]
The absorption of dirithromycin is slightly enhanced when administered immediately following antacids or H2-blockers.[5642] The clinical significance of this interaction is unclear.
The bioavailability of oral iron salts is influenced by gastric pH, and concomitant administration of H2-blockers may decrease iron absorption. Limited data suggest cimetidine decreases gastric, non-heme iron absorption. However, the clinical significance of this interaction is unclear since it is not a well recognized complication of cimetidine therapy.[7892] Iron salts provide non-heme iron which requires an acidic intragastric pH to be reduced to ferrous and to be absorbed. At higher pH values iron is more readily ionized to its ferric state, which is more poorly absorbed. Since H2-blockers have long-lasting effects, adjusting administration times may not alleviate the possible interaction. Although significant data are lacking, It is likely that other H2-blockers, including ranitidine, can also reduce the oral absorption of iron supplements.
Cimetidine can increase nifedipine [5803] area-under-the-curve by inhibiting hepatic metabolism of nifedipine. Ranitidine has been shown to have a similar, but lesser effect on nifedipine pharmacokinetics. Clinicians should be alert for exaggerated nifedipine effects

if ranitidine is added to the regimen. Although data are lacking, similar precautions may apply to the addition of ranitidine to isradipine [5865] or nicardipine [5620]. Ranitidine does not appear to interact with amlodipine or felodipine.
Drugs that cause a significant sustained elevation in gastric pH (e.g., H2-blockers, gastric acid-pump inhibitors) may reduce plasma concentrations of gefitinib and thus potentially may reduce gefitinib efficacy. Concurrent administration of high doses of ranitidine with sodium bicarbonate to maintain the gastric pH > 5 reduced the mean gefitinib AUC by 44%.[5012]
Memantine is excreted in part by renal tubular secretion.[5905] Cationic drugs that are eliminated by renal tubular secretion (e.g., ranitidine [5980]) may decrease memantine elimination by competing for common renal tubular transport systems. Careful patient monitoring and dose adjustment of memantine and/or ranitidine is recommended. Of the H2-antagonists, cimetidine is most likely to interact with memantine in this manner; famotidine and nizatidine may be less likely to interact with memantine because of less tubular excretion.
Coadministration of delavirdine with antacids results in decreased absorption of delavirdine. When given in combination with an antacid (Maalox TC®), the Cmax of delavirdine was decreased by 52% and the delavirdine AUC was decreased by 44%. Administration of delavirdine and antacids should be separated by at least 1 hour. H2-blockers and proton pump inhibitors (PPIs), which increase gastric pH, may also reduce the absorption of delavirdine. However, since these agents affect gastric pH for an extended period, separation of doses may not eliminate the interaction. Chronic use of H2-blockers and proton pump inhibitors (PPIs) with delavirdine is not recommended.[5206]
Atazanavir solubility decreases as gastric pH increases. The coadministration of atazanavir (400 mg once daily) with famotidine (40 mg twice daily) resulted in substantially decreased atazanavir plasma concentrations. Significant reductions in atazanavir serum concentrations may lead to therapeutic failure and the development of HIV resistance. However, H2-blockers (famotidine, nizatidine, ranitidine, and cimetidine) can be used during treatment with atazanavir under specific administration restrictions. In treatment-naive patients 2 regimens may be used: 1) atazanavir 400 mg once daily with food given at least 2 hours before and at least 10 hours after the H2-blocker or 2) atazanavir 300 mg boosted with ritonavir 100 mg given once daily with food without the need for separation from the H2-blocker. Treatment-experienced patients should receive atazanavir 300 mg boosted with ritonavir 100 mg given once daily with food at least 2 hours before and at least 10 hours after the H2-blocker.[4865]
Both trospium and ranitidine are eliminated by active renal tubular secretion [5980] [5974]; coadministration has the potential to increase serum concentrations of trospium or ranitidine due to competition for the drug elimination pathway. Careful patient monitoring and dosage adjustment of trospium and/or ranitidine is recommended.
Although the clinical significance has not been determined, the bioavailability of oral alendronate is doubled by concomitant administration of intravenous ranitidine.[5375] Investigations have not been undertaken to determine if other H2-antagonists have a similar effect on bioavailability.[5375] Patients should be closely monitored when antiulcer medications, such as proton pump inhibitors (PPIs), gastric mucosal agents, and H2-blockers, or other medications for GI disorders, are coadministered as they may affect the bioavailability of alendronate, leading to a higher likelihood of developing GI adverse effects while taking alendronate.
Ranitidine does not have a significant *in vivo* drug interaction with voriconazole. An open-label, placebo-controlled, three-way crossover study [6478] evaluated the effects of cimetidine and ranitidine on the pharmacokinetics of voriconazole. Twenty healthy male subjects received voriconazole alone, voriconazole plus cimetidine, and voriconazole plus ranitidine; treatment periods were separated by at least 7 days. The AUC of voriconazole was increased 22% by cimetidine and 4% by ranitidine; neither cimetidine nor ranitidine altered the half-life of voriconazole. According to manufacturer recommendations, these interactions are not clinically significant and dose adjustment of voriconazole is not required with these agents.[4882]
Both entecavir and ranitidine are secreted by active tubular secretion.[8007] [5980] In theory, coadministration of entecavir with ranitidine may increase the serum concentrations of either drug due to competition for the drug elimination pathway. The manufacturer of entecavir recommends monitoring for adverse effects when these drugs are coadministered.
The effects of gastrointestinal pH alterations on the absorption of methylphenidate extended release capsules (Ritalin® LA) and dexmethylphenidate extended-release tablets (Focalin™ XR) have not been studied. Although the SODAS® system (drug delivery system utilized in Ritalin® LA and Focalin™ XR) is thought to be minimally affected by changes in pH [8068], per the manufacturer, the modified release characteristics of both extended-release formulations are pH-dependent. It is possible that the administration of H2-blockers or other acid suppressants could alter the release of dexmethylphenidate or methylphenidate.[8067] [8069] Patients receiving these extended-release products (Focalin™ XR or Ritalin® LA) with acid suppressants should be monitored for adverse effects and therapeutic efficacy.
The coadministration of saquinavir and ranitidine increases saquinavir plasma concentrations.[5730] However, the increase is not thought to be clinically relevant.[5730] No dose adjustment of saquinavir is recommended. Nevertheless, until more is known about the concomitant use of ranitidine with saquinavir, clinicians should monitor their patients closely for elevated plasma saquinavir concentrations and signs of saquinavir toxicity.
Antacids, H2-blockers, and proton pump inhibitors (PPIs) may increase plasma concentrations of mefloquine. In a small study involving 6 healthy subjects and 6 peptic ulcer patients, cimetidine increased the Cmax and AUC of mefloquine. In the study, the pharmacokinetics of mefloquine were determined after receiving a single oral mefloquine 500 mg dose alone and after 3-days of cimetidine 400 mg PO bid. In both healthy subjects and peptic ulcer patients, mefloquine Cmax was increased 42.4% and 20.5%, respectively, and AUC was increased by 37.5% in both groups. Elimination half-life, total clearance, and volume of distribution were not significantly affected. An increase in adverse reactions was not noted. Patients on chronic mefloquine therapy might be at increased risk of adverse reactions, especially in patients with a neurological or psychiatric history.[9417]

Interactions last revised 4/4/2007 3:39:00 PM

Adverse Reactions

- abdominal pain
- agitation
- agranulocytosis
- alopecia
- anaphylactoid reactions
- angioedema
- headache
- hemolytic anemia
- hepatitis
- impotence (erectile dysfunction)
- infection
- insomnia

- aplastic anemia
- arthralgia
- AV block
- blurred vision
- bradycardia
- bronchospasm
- confusion
- constipation
- delirium
- depression
- diarrhea
- dizziness
- elevated hepatic enzymes
- eosinophilia
- erythema multiforme
- gynecomastia
- hallucinations
- jaundice
- leukopenia
- libido decrease
- maculopapular rash
- myalgia
- nausea/vomiting
- neutropenia
- pancreatitis
- pancytopenia
- paranoia
- premature ventricular contractions (PVCs)
- sinus tachycardia
- Stevens-Johnson syndrome
- thrombocytopenia
- toxic epidermal necrolysis
- vasculitis

Similar to other H2 antagonists, adverse reactions during ranitidine therapy are infrequent. Adverse reactions during ranitidine therapy occur rarely and are usually mild and transient. In 1997, one safety review from the manufacturer noted that data available from more than 26,000 patients in controlled clinical trials in over a decade of use indicated that ranitidine was associated with adverse events in roughly 20% of patients treated, but the incidence was not significantly different from the number reported with placebo (i.e., 27%).

GI adverse reactions have been reported in patients receiving ranitidine. These reactions include diarrhea or constipation, nausea/vomiting and abdominal pain. Although rare, hepatitis, jaundice, and elevated hepatic enzymes have been reported with ranitidine. Pancreatitis, a rare but serious reaction, has also been reported.

Although data exist associating ranitidine with various types of blood dyscrasias, the overall incidence of these reactions is low. Neutropenia and thrombocytopenia are the most commonly encountered blood count changes. Other factors including underlying diseases or additional drugs may have contributed to these hematologic alterations. If the dyscrasia is ranitidine-mediated, recovery is usually rapid after ranitidine discontinuation. Rare cases of agranulocytosis, leukopenia, pancytopenia or aplastic anemia have all been reported.[603] Exceedingly rare cases of immune hemolytic anemia have also been reported.

The relationship of ranitidine to reported CNS adverse reactions is unclear in many cases. Headache, which is sometimes severe, is the only CNS reaction that seems to be causally associated with ranitidine administration. Reversible mental status changes, including agitation, confusion, delirium, hallucinations, hostility, paranoia, depression, and disorientation, have been reported following ranitidine therapy. Most of these reactions have been reported in critically-ill elderly patients. Other CNS adverse reactions include blurred vision, dizziness, insomnia, malaise, and vertigo. A review of central nervous system reactions to H2-blockers revealed that the incidence rate varies widely depending on the specific report, and that no single H2-antagonist is more likely to induce CNS reactions than another.[34] The CNS reactions appear to be primarily idiosyncratic and not dose-related.[34] The incidence of CNS-related events for all H2-blockers is estimated at 0.2% for outpatients and up to 1.9% of hospitalized inpatients.

Gynecomastia and sexual dysfunction, including libido decrease and impotence (erectile dysfunction), have been seen during ranitidine therapy in male patients, but the incidence is rare and similar to the incidence of these events in the normal male population. It should be noted that cimetidine, another H2-blocker, more commonly produces these effects due to cimetidine's antiandrogenic activity, and the use of ranitidine, when substituted for cimetidine in such patients, often results in resolution of cimetidine-induced endocrine dysfunction.

Dermatologic and hypersensitivity-mediated reactions are rarely reported and include maculopapular rash, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, alopecia, and vasculitis. Hypersensitivity, including anaphylactoid reactions, angioedema, bronchospasm, fever, or eosinophilia have been reported, but are rare. Rare musculoskeletal events include arthralgia and myalgia, but causality has not been established.

As with other H2-blockers, rare and idiosyncratic reports of sinus tachycardia, sinus bradycardia, atrioventricular (AV block), and premature ventricular contractions (PVCs) have occurred during ranitidine therapy.

Small increases in serum creatinine may occur during ranitidine therapy, but the increase does not reflect a decrease in renal function. Ranitidine can compete with creatinine for proximal tubular secretion. This uncommon drug-induced alteration in plasma creatinine concentration may be of clinical significance only when GFR is estimated or calculated by using serum creatinine.

Acid suppressive therapy has been linked to an increased susceptibility to respiratory infection by raising gastric pH. Gastric pH serves as a barrier against pathogenic colonization of the gastrointestinal tract. An increase in gastric pH allows for bacterial and viral invasion which, in theory, can precipitate respiratory infections. A large epidemiological study suggested an increased risk of developing pneumonia in current users of H2-blockers compared to patients who had stopped H2-blocker treatment, with an observed adjusted relative risk of 1.63 (95% CI, 1.07—2.48). A causal relationship between use of ranitidine and pneumonia has not been established.[5980] [9503]

Atrophic gastritis, a precursor for gastric cancer, has been associated with prolonged acid suppression with high dose H2-blockers in patients who are *H. pylori* positive. A 'test and treat' approach for baseline *H. pylori* infections is recommended for patients with reflux esophagitis on long term acid suppression therapy. Treatment of baseline infection decreases inflammation and may reverse corpus gastritis.[9961]

Adverse Reactions last revised 2/28/2007 12:20:00 PM

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Omeprazole; Sodium Bicarbonate
Zegerid®
Classification:
- Gastrointestinal Agents
  - Antiulcer Agents
    - Antacids
- Gastrointestinal Agents
  - Antiulcer Agents
    - Proton pump inhibitors (PPIs)

Description, Mechanism of Action, Pharmacokinetics

Description: Omeprazole; sodium bicarbonate is an immediate-release product combining a proton pump inhibitor (PPI) and sodium bicarbonate buffer. It is available under the brand name Zegerid® as a powder for oral suspension or a capsule. Zegerid® oral suspension is the only PPI product FDA-approved for stress ulcer prophylaxis in critically ill patients.[8851] It is also used for gastroesophageal reflux disease (GERD), erosive esophagitis, and gastric or duodenal ulcers. Omeprazole; sodium bicarbonate is very potent and has a long duration of action, allowing for once-daily dosing. Like other PPIs, omeprazole is unstable in the acidic environment of the stomach and conventional oral formulations are available as delayed-release products with enteric coatings. Because the absorption of most oral PPIs is delayed by the enteric coating, the antisecretory effect is also delayed. Combining uncoated omeprazole powder with sodium bicarbonate allows for rapid delivery to the site of drug absorption, while decreasing gastric acid degradation following administration. The oral suspension formulation is expected to especially be beneficial for patients who have swallowing difficulties, are critically ill, are mechanically ventilated, and/or have gastric tubes. In critically ill patients, omeprazole; sodium bicarbonate, compared to cimetidine IV, reduced the incidence of clinically significant bleeding (3.9% vs. 5.5%) and overt bleeding (19.1% vs. 32%), and had a lower incidence of inadequate pH control (18% vs. 58%).[8855] Before the availability of the combination product, a 'simplified omeprazole suspension' (SOS) could have been extemporaneously formulated from delayed-release omeprazole capsules and sodium bicarbonate, although comparative studies showed absorption of omeprazole from SOS was less efficient than from intact delayed-release omeprazole capsules (comparative bioavailability of 81.2% after a single dose, falling to 58.4% after 5 days of once-daily dosing).[8856] Compared to delayed-release omeprazole capsules, omeprazole; sodium bicarbonate has an earlier detectable antisecretory effect that last at least as long as delayed-release formulations.[8863] The more rapid onset may be due, in part, to the immediate neutralizing capacity of sodium bicarbonate. Because of the sodium bicarbonate content, patients receive a sodium load equivalent to 300 mg of sodium in the capsules and 460 mg in the suspension; an alternative PPI may be a more appropriate treatment option for patients on a sodium-restricted diet. Santarus, Inc. received FDA approval for Zegerid® 20 mg immediate-release omeprazole powder for oral suspension in June 2004, for 40 mg immediate-release powder for oral suspension in December 2004, and for 20 and 40 mg immediate-release capsules in February 2006.

Mechanism of Action: Omeprazole belongs to the class of GI antisecretory agents, the substituted benzimidazoles, that suppress gastric acid secretion by inhibiting the H+/K+ ATPase enzyme system of parietal cells. Omeprazole is a lipophilic weak base (pKa 4) [8864] and is transformed into an active acidic sulfonamide form when exposed to acidic conditions.[8852] Following activation, omeprazole binds selectively and irreversibly to the H+/K+ ATPase pump on the secretory surface of the parietal cell membrane. Subsequently, the secretion of hydrogen ions into the gastric lumen is inhibited. Omeprazole is characterized as a gastric acid or proton pump inhibitor (PPI) because it blocks the final step of gastric acid production. This effect is dose-dependent and leads to the inhibition of both basal and stimulus-induced acid secretion. As with all PPIs, omeprazole is acid-labile and is rapidly degraded by gastric acid. Conventional PPIs are enteric-coated to avoid degradation, while Zegerid® suspension and capsules (omeprazole; sodium bicarbonate) contain non-enteric coated omeprazole powder. By administering omeprazole with sodium bicarbonate, omeprazole is protected against acid degradation until it can be absorbed.[8851] Furthermore, the concomitant administration of omeprazole with sodium bicarbonate may also provide a temporary stimulus to gastrin release which may stimulate the parietal cell mass and promote omeprazole entry into and inhibition of the H+/K+ ATPase pumps. Sodium bicarbonate may be responsible for the rapid rise in intragastric pH seen after administration, while prolonged antisecretory effects are due to omeprazole absorption.[8863] Treatment with omeprazole; sodium bicarbonate (Zegerid®) is highly effective at reducing the production of gastric acid, measured by the percent decrease from baseline in 24 hour integrated gastric acidity. Following administration of a repeated once daily dose of 40 mg and 20 mg omeprazole; sodium bicarbonate in healthy subjects, the 24 hour integrated gastric acidity (mmol*hr/L) is 84% and 82%, respectively.[8851] During a 14 day trial, the majority of critically ill patients have documented gastric pH values >= 4 while receiving 40 mg Zegerid® oral suspension administered once daily via gastric tube.[8851] [8855] Approximately 99% and 92% of patients have gastric pH values >= 4 measured at 1—2.5 and 6 hours after the first dose, respectively.[8851] [8855] The antisecretory effects last longer than would be expected from the very short plasma half-life, apparently due to irreversible binding

to the parietal H+/K+ ATPase enzyme.
Serum gastrin concentrations increase during the initial 1—2 weeks of therapy, and median increases in gastrin are greater than the increases produced by H2-receptor antagonists. Gastrin levels return to baseline within 1—2 weeks following discontinuation of therapy. Animal data suggest that prolonged elevations of serum gastrin may be associated with tumors (see Contraindications).
Pharmacokinetics: Omeprazole; sodium bicarbonate is administered orally and should be taken on an empty stomach. Absorption is rapid, with mean peak plasma concentrations of omeprazole (Tmax) occurring at about 30 minutes after a single dose or repeated administration. After a two-dose 40 mg loading regimen, the AUC approximately doubles after the second 40 mg dose. A greater than linear mean increase in AUC (3-fold increase) is observed when doubling the dose from 20 mg to 40 mg. When omeprazole; sodium bicarbonate is administered 1 hour after a meal, the Cmax and AUC are reduced by approximately 62% and 26%, respectively, compared to administration on an empty stomach. Omeprazole is approximately 95% bound to plasma proteins. The absolute bioavailability is 30—40% at doses of 20—40 mg, due in large part to first-pass metabolism. Extensive hepatic metabolism occurs, and the metabolites have minimal antisecretory activity. The onset of action of omeprazole; sodium bicarbonate is about 1 hour, and the duration of action is > 72 hours. In healthy subjects, the mean plasma half-life is 1 hour. Approximately 77% of a dose is eliminated in the urine as metabolites, and the remainder of the dose is excreted in the feces. It is not known if omeprazole; sodium bicarbonate crosses the placenta, but it is excreted into breast milk. Gastrointestinal secretory activity returns to normal 3—5 days after therapy is discontinued.
•***Special Populations:*** In elderly subjects, the elimination rate of omeprazole is somewhat decreased and the bioavailability is increased; however, no dosage adjustment is needed. In renal impairment (CrCl 10—62 ml/min/1.73m2), the bioavailability of omeprazole is slightly increased. Because omeprazole is primarily excreted in the urine, elimination slows in proportion to decreased CrCl. In patients with chronic hepatic disease, the bioavailability of buffered omeprazole solution increases to approximately 100%, reflecting decreased first-pass effect. Additionally, the half-life increases to nearly 3 hours in chronic hepatic impairment as compared to the mean half-life of 1 hour in normal subjects. Plasma clearance averages 70 ml/min, compared to a value of 500—600 ml/min in normal subjects. Consider dosage adjustment for hepatically impaired patients. Asian patients exhibit a four-fold increase in AUC of omeprazole compared to Caucasians (see Contraindications). The pharmacokinetics of omeprazole; sodium bicarbonate have not been studied in pediatric patients.

Description, Mechanism of Action, Pharmacokinetics last revised 4/12/2006 9:55:00 AM

Indications

- duodenal ulcer
- esophagitis
- gastric ulcer
- gastroesophageal reflux disease (GERD)
- stress gastritis

Dosage

NOTE: The Zegerid® brand of omeprazole; sodium bicarbonate contains 1680 mg (20 mEq) sodium bicarbonate in each packet of oral suspension and 1100 mg (13 mEq) in each capsule. Because of this, two 20 mg dosage units of Zegerid® should not be substituted for one 40 mg dosage unit.[8851]
For the short-term treatment of active duodenal ulcer:
Oral dosage (powder for suspension or capsules):
Adults, including the elderly: 20 mg PO once daily for up to four weeks. Some patients may require an additional four weeks of therapy.
Adolescents and children: Safe and effective use has not been established.

For the short-term treatment of active benign gastric ulcer:
Oral dosage (powder for suspension or capsules):
Adults, including the elderly: 40 mg PO once a day for 4—8 weeks. For endoscopically diagnosed gastric ulcer size larger than 1 cm, 40 mg once daily was significantly more effective than 20 mg once daily at 8 weeks. For ulcer size <= 1 cm, no difference in healing rates between 40 mg and 20 mg daily doses were observed.
Adolescents and children: Safe and effective use has not been established.

For the treatment and maintenance of gastroesophageal reflux disease (GERD) or erosive esophagitis:
•for the short-term treatment of symptomatic GERD or erosive esophagitis:
Oral dosage (powder for suspension or capsules):
Adults, including the elderly: 20 mg PO once daily for up to 4 weeks for patients with no esophageal lesions. In patients with symptomatic GERD and erosive esophagitis, the dosage is 20 mg PO once daily for 4—8 weeks. If the patient does not respond by 8 weeks, an additional 4 weeks of therapy may be needed. For recurrences of erosive esophagitis or GERD symptoms, additional 4—8 week courses of therapy may be considered. To prevent relapse, which occurs commonly, chronic therapy with omeprazole; sodium bicarbonate may be necessary; the maintenance dosage is 20 mg PO once daily.
Adolescents and children: Safe and effective use has not been established.
•for the maintenance of healing of erosive esophagitis:
Oral dosage (powder for suspension or capsules):
Adults, including the elderly: 20 mg PO once daily. Controlled studies do not extend beyond 12 months. For Asian patients, the manufacturer of Zegerid® states that dosage reduction should be considered; however, no specific dosage guidelines are available (see Contraindications).
Adolescents and children: Safe and effective use has not been established.
•for nocturnal acid breakthrough†:
Oral dosage (powder for suspension):
Adults: 40 mg once daily at bedtime or 20—40 mg PO twice daily (breakfast and bedtime). After repeated once daily dosing of omeprazole; sodium bicarbonate 40 mg suspension or pantoprazole 40 mg delayed-release tablets, significantly fewer patients

experienced nocturnal acid breakthrough (NAB) with omeprazole taken at bedtime than after pantoprazole taken before dinner (53% vs. 78%, respectively). Additionally, the percentage of patients with NAB after twice daily dosing of omeprazole 20 mg, omeprazole 40 mg, and pantoprazole 40 mg were 46.7%, 11.8%, and 70.6 %, respectively.[8865]
Adolescents and children: Safe and effective use has not been established.

For stress gastritis prophylaxis in critically ill patients:

Oral dosage (powder for suspension):
Adults, including the elderly: Initially, 40 mg PO, followed by 40 mg PO in 6—8 hours on day 1, then 40 mg PO once daily for up to 14 days. Use beyond 14 days has not been evaluated in critically ill patients. An evaluation comparing omeprazole; sodium bicarbonate oral suspension and IV cimetidine infusion for the prevention of upper GI bleeding found favorable results in the omeprazole-treated group.[8855] The 14 day study showed that omeprazole; sodium bicarbonate suspension administered via gastric tube, compared to IV cimetidine 50 mg/hr (after 300 mg IV loading dose), reduced the incidence of clinically significant bleeding (3.9% vs. 5.5%, respectively) and overt bleeding (19.1% vs. 32%, respectively). Additionally, inadequate pH control, defined as two consecutive gastric pH determinations of < 4, were reported in 18% of omeprazole-treated patients compared to 58% of IV cimetidine-treated patients ($p < 0.001$).[8855]
Adolescents and children: Safe and effective use has not been established.

Maximum Dosage Limits:
•*Adults:* Zegerid® capsules 80 mg/day PO (omeprazole 80 mg; 2200 mg sodium bicarbonate) or Zegerid® packets for oral suspension 80 mg/day PO (omeprazole 80 mg; 3360 mg sodium bicarbonate).
•*Elderly:* Zegerid® capsules 80 mg/day PO (omeprazole 80 mg; 2200 mg sodium bicarbonate) or Zegerid® packets for oral suspension 80 mg/day PO (omeprazole 80 mg; 3360 mg sodium bicarbonate).
•*Adolescents:* Safe and effective use has not been established.
•*Children:* Safe and effective use has not been established.

Patients with hepatic impairment:
Consider dosage reduction in patients with hepatic impairment (see Contraindications).

Patients with renal impairment:
Specific guidelines for dosage adjustments in renal impairment are not available; it appears that no dosage adjustments are needed.

Intermittent hemodialysis:
Since omeprazole is highly protein bound, it is not likely to be significantly removed by hemodialysis. No dosage adjustments are needed.
†non-FDA-approved indications

Indications...Dosage last revised 3/30/2006 9:36:00 AM

Administration Guidelines

NOTE: The sodium content per Zegerid® (omeprazole; sodium bicarbonate) dose is 460 mg for the oral suspension and 300 mg for the capsules.

Oral Administration
•Administer on an empty stomach at least 1 hour prior to a meal.
•*Immediate-release capsules:* Swallow intact capsule with water. Do not administer with any other liquid besides water. Do not open capsules and sprinkle the contents into food. The 20 mg and 40 mg capsules each contain 1100 mg sodium bicarbonate per capsule; two capsules of 20 mg are not equivalent to, and should not be substituted for, one 40 mg capsule.[8851]
•*Immediate-release oral suspension:* Prepare the suspension by emptying packet contents into a small cup containing 1—2 tablespoons (15—30 ml) of water; do not use other liquids or foods. Stir the mixture well and administer immediately. Refill the cup with water and drink. The 20 mg and 40 mg suspension packets each contain 1680 mg sodium bicarbonate; two packets of 20 mg are not equivalent to, and should not be substituted for, one 40 mg packet.[8851]
•*Patients with a gastric tube:* Use the oral suspension. For patients receiving continuous gastric tube feeding, suspend the enteral feeding approximately 3 hours before and 1 hour after administration. For administration via nasogastric (NG) or orogastric (OG) tube, constitute the oral suspension with approximately 20 ml of water only, do not use other liquids or foods. Stir the mixture well and administer immediately, using an appropriately-sized syringe to instill the suspension into the tube, then flush the tube with an additional 20 ml of plain water.

Administration last revised 3/29/2006 9:19:00 AM

Contraindications/Precautions

- *hypocalcemia*
- *metabolic alkalosis*
- *proton pump inhibitors (PPIs) hypersensitivity*
- Asian patients
- Bartter's syndrome
- breast-feeding
- cardiac disease
- children
- corticosteroid therapy
- Cushing's syndrome
- gastric cancer
- heart failure
- hyperaldosteronism
- hypernatremia
- hypertension
- hypokalemia
- peripheral edema
- pregnancy
- pulmonary edema
- renal disease
- renal failure
- renal impairment
- respiratory alkalosis
- sodium restriction

- hepatic disease
- vitamin B12 deficiency

• *Absolute contraindications are in italics.*

NOTE: This monograph discusses the contraindications/precautions of omeprazole; sodium bicarbonate combination products. Clinicians may wish to consult the individual monographs for more information about each agent.
Omeprazole; sodium bicarbonate is contraindicated in patients with known hypersensitivity to omeprazole; sodium bicarbonate or other substituted benzimidazoles such as esomeprazole or lansoprazole (i.e., known *proton pump inhibitors (PPIs) hypersensitivity)*. Although rare, occasionally such reactions can be serious (e.g., result in anaphylaxis or angioedema). There has been evidence of PPI cross-sensitivity in some sensitive individuals in literature reports.
The Zegerid® brand of omeprazole; sodium bicarbonate contains 1680 mg (20 mEq) of sodium bicarbonate in each packet of oral suspension and 1100 mg (13 mEq) in each capsule. Because of the sodium bicarbonate content found in these formulations, the combination product is contraindicated in patients with *metabolic alkalosis* and *hypocalcemia*. Products containing sodium bicarbonate should be used cautiously in patients with Bartter's syndrome, hypokalemia, and respiratory alkalosis. Other causes of metabolic alkalosis include Cushing's syndrome and primary hyperaldosteronism; sodium bicarbonate should be used cautiously in patients with these conditions. Furthermore, milk-alkali syndrome may occur with the long-term coadministration of calcium or milk with bicarbonate. Sodium bicarbonate therapy should be used with caution in patients receiving corticotropin or corticosteroid therapy.[8851]
The Zegerid® brand of omeprazole; sodium bicarbonate contains 460 mg of sodium in each packet of oral suspension and 300 mg of sodium in each capsule. This additional sodium load should be taken into consideration when sodium restriction is required. Due to the sodium content, sodium bicarbonate products should be used with caution in patients with cardiac disease, heart failure, hypernatremia, renal impairment, renal disease, renal failure, peripheral edema, pulmonary edema, or other conditions in which sodium retention could be detrimental. Patients with hypertension should cautiously be prescribed sodium bicarbonate products; hypertension has been reported with the use of omeprazole; sodium bicarbonate in critically ill patients during clinical evaluation (see Adverse Reactions).

Omeprazole; sodium bicarbonate should be administered with caution to patients with hepatic disease since clearance of the drug can be prolonged. Dosage reduction should be considered in patients with hepatic impairment (e.g., cirrhotic liver disease), especially those receiving long-term therapy. In patients with chronic hepatic disease, the bioavailability of buffered omeprazole solution increases to approximately 100%, reflecting decreased first-pass effect. Additionally, the half-life increases to nearly 3 hours in chronic hepatic impairment as compared to the mean half-life of 1 hour in normal subjects. Plasma clearance averages 70 mL/min, compared to a value of 500—600 ml/min in normal subjects. In addition, omeprazole has been associated with hepatitis and, in rare instances, hepatic failure.
Asian patients exhibit a four-fold increase in AUC of omeprazole compared to Caucasian patients. The manufacturer of Zegerid® states that dosage reduction should be considered when administering omeprazole; sodium bicarbonate to Asian patients, particularly when maintenance treatment for healing of erosive esophagitis is indicated.[8851] No specific dosage guidelines are available at this time.
Symptomatic response to therapy with omeprazole; sodium bicarbonate does not preclude the presence of gastric cancer or other malignancy. Omeprazole; sodium bicarbonate decreases intragastric acidity. Subsequently, the number of bacteria in gastric secretions and, correspondingly, the amount of carcinogenic N-nitroso compounds produced by these bacteria increase. The overall risk of carcinoid tumors during therapy with proton pump inhibitors (PPI) is low based on cumulative safety experience; monitoring of serum gastrin levels during PPI therapy is generally not necessary.[2859] One trial studied 25 patients with H2-receptor antagonist-resistant gastroesophageal reflux disease (GERD) who were treated and then followed on long-term (>= 4 years) omeprazole therapy; neoplasia or dysplasia were not seen in biopsies.[617]
Daily treatment with a gastric acid-suppressing medication such as omeprazole over a long period of time (e.g., longer than 3 years) may lead to malabsorption of cyanocobalamin and vitamin B12 deficiency caused by hypo- or achlorhydria. Rare reports of cyanocobalamin deficiency occurring with acid-suppression therapy have been reported in the literature (see Adverse Reactions). This possibility should be considered if clinical symptoms consistent with cyanocobalamin deficiency are observed.[162] [6226]
Safe and effective use of omeprazole; sodium bicarbonate has not been established in children. There are no adequate and well-controlled studies in patients < 18 years with omeprazole; sodium bicarbonate (Zegerid®) capsules or suspension.
Omeprazole; sodium bicarbonate is classified as FDA pregnancy risk category C. There are no adequate and well-controlled studies on the use of omeprazole; sodium bicarbonate in pregnancy. Available data, including several reports and retrospective studies, indicate the likelihood of low risk of fetal harm associated with omeprazole use during pregnancy.[8931] [8851] Although no untoward effects have been observed in humans, chronic use of sodium bicarbonate may lead to systemic alkalosis, and increased sodium intake can produce edema and weight increase. Caution is advised in regular use of omeprazole; sodium bicarbonate during pregnancy. As with any drug therapy, avoidance during pregnancy, and especially in the first trimester, is the safest recommendation.
It is prudent to avoid breast-feeding during use of omeprazole; sodium bicarbonate.[8931] Omeprazole is excreted into human breast milk and there is a potential for adverse reactions in the nursing infant, including suppression of gastric acid secretion. Sodium bicarbonate has no specific precautions for use in breast-feeding women. It may be advisable to discontinue breast-feeding or to discontinue the drug, taking into account the importance of the drug to the mother.

Contraindications last revised 8/14/2006 10:04:00 AM

Drug Interactions

- Acetaminophen
- Alendronate
- Ammonium Chloride
- Ampicillin
- Fluvastatin
- Fluvoxamine
- food
- Fosphenytoin

Antimuscarinics
- Atazanavir
- Atovaquone; Proguanil
- Bisacodyl
- Bortezomib
- Budesonide
- Calcium Carbonate
- Carbamazepine
- Carisoprodol
- Cefpodoxime
- Ceftibuten
- Cilostazol
- Citalopram
- Clarithromycin
- Clomipramine
- Clozapine
- Cyanocobalamin, Vitamin B12
- Cyclosporine
- Dasatinib
- Delavirdine
- Dexmethylphenidate
- Diazepam
- Digoxin
- Disulfiram
- Doxercalciferol
- Efavirenz
- Escitalopram
- Gefitinib

H2-blockers
- Indinavir
- Indomethacin
- Iron Salts
- Itraconazole
- Ketoconazole
- Mefloquine
- Methotrexate
- Methylphenidate
- Misoprostol
- Naproxen
- Nelfinavir
- Octreotide
- Phenytoin
- Polysaccharide-Iron Complex
- Sertraline
- St. John's Wort, Hypericum perforatum
- Sucralfate
- Tacrolimus

Tetracyclines
- Tirofiban
- Tolmetin
- Trovafloxacin, Alatrofloxacin
- Valdecoxib
- Voriconazole
- Warfarin

NOTE: This monograph discusses the use of omeprazole; sodium bicarbonate combination products. Clinicians may wish to consult the individual monographs for more information about each agent.
NOTE: In the hepatic oxidative system, omeprazole is metabolized primarily by CYP2C19 and secondarily by CYP3A4.[6305] Omeprazole inhibits CYP2C19 [6305], which could lead to increased plasma concentrations of CYP2C19 substrates. Omeprazole does not appear to inhibit CYP3A4 activity (evaluated via erythromycin breath test).[4594]
Food or drugs with a high sodium content (e.g., tomato juice) could increase the risk of complications of sodium excess when given with omeprazole; sodium bicarbonate. The Zegerid® brand of omeprazole; sodium bicarbonate contains 460 mg sodium in each packet of powder for oral suspension and 300 mg sodium in each capsule. This should be taken into consideration for patients on a sodium-restricted diet.[8851]
Omeprazole (CYP2C19 inhibitor) [6305] can prolong the elimination of warfarin, particularly R-warfarin which is a CYP2C19 substrate [4718]. Although R-warfarin is less potent than S-warfarin in anticoagulant activity, the combined use of omeprazole and warfarin has been associated with reports of increased INR and prothrombin time (PT).[6305] In addition, post-marketing reports of the combination of esomeprazole and warfarin have indicated elevations in PT. It is prudent to monitor the INR more closely if omeprazole; sodium bicarbonate is coadministered with warfarin.
Sorafenib is a competitive inhibitor of CYP2C19. Administration of sorafenib (400 mg twice daily for 28 days) did not alter the exposure of concomitantly administered omeprazole.[8637]
In one study, multiple dose administration of omeprazole increased the Cmax, AUC, and elimination half-life of carbamazepine when given as an extended-release formulation in healthy male volunteers. Based on these results, it would be prudent to monitor carbamazepine serum concentrations if omeprazole; sodium bicarbonate is added to or removed from the drug regimen.[4593]
Reduce the omeprazole; sodium bicarbonate dose by one-half when initiating voriconazole therapy in patients who are currently receiving omeprazole at doses of 40 mg/day or greater.[4882] Concentrations of omeprazole may increase by up to 2-fold due to CYP2C19 and CYP3A4 inhibition by voriconazole.[4882] Omeprazole is also a CYP2C19 inhibitor, which theoretically could increase voriconazole concentrations by roughly 15%; however, no dosage adjustment of voriconazole is recommended.[4882]
Omeprazole; sodium bicarbonate increases the pH of the stomach.[6305] The increase in intragastric pH can interfere with the absorption of ampicillin administered in ester form.[6305]
Omeprazole; sodium bicarbonate increases the pH of the stomach.[6305] The increase in intragastric pH can interfere with the absorption of iron salts (e.g., polysaccharide-iron complex).[6305] The bioavailability of polysaccharide-iron complex and other oral iron salts is influenced by gastric pH, and the concomitant administration of a proton pump inhibitor, with or without an antacid, can decrease iron absorption.[6924] The non-heme ferric form of iron needs an acidic intragastric pH to be reduced to ferrous and to be absorbed. Iron salts and polysaccharide-iron complex provide non-heme iron.
Omeprazole; sodium bicarbonate increases the pH of the stomach.[6305] The increase in intragastric pH can interfere with the absorption of itraconazole [4700] or ketoconazole [4699].
Omeprazole; sodium bicarbonate increases the pH of the stomach.[6305] Changes in intragastric pH can potentially alter the bioavailability of other drugs with pH-dependent absorption. It has also been shown that omeprazole can impair absorption of cyanocobalamin, vitamin B12. In a study of 10 healthy male volunteers, omeprazole, in doses of 20 mg/day and 40 mg/day, caused a significant decrease in the oral absorption of vitamin B12.[162] It is thought that omeprazole interferes with secretion of gastric acid and pepsin which are necessary for the release of B12 from its protein binding sites in food.[162]
Omeprazole has been reported to delay methotrexate elimination half-life. Methotrexate undergoes active tubular secretion in the kidney and omeprazole may interfere with renal ATPase leading to methotrexate toxicity. Therefore, for safety reasons, if omeprazole; sodium bicarbonate therapy is necessary in a patient who is about to receive methotrexate, the combination should be discontinued four to five days before methotrexate administration.[6200][8852]
Cilostazol is metabolized by the CYP2C19 hepatic isoenzyme and appears to have pharmacokinetic interactions with many

medications that are potent inhibitors of CYP2C19. When given concurrently with omeprazole, cilostazol AUC is increased by 26%; and the AUC of the active metabolite 3,4-dehydro-cilostazol is increased by 69%.[5167] When significant CYP2C19 inhibitors are administered concomitantly with cilostazol, the cilostazol dosage should be reduced by 50%.[5167]
Sucralfate has been shown to delay absorption and reduce the bioavailability of lansoprazole by about 17%.[5142] Lansoprazole should be taken no less than 30 minutes before sucralfate if these drugs are to be used concomitantly.[5142] It has not been established if a similar interaction occurs with omeprazole; sodium bicarbonate.
The oral absorption of digoxin can be decreased if given concomitantly with sodium bicarbonate. On the other hand, gastric acid pump-inhibitors may increase digoxin bioavailability. The clinical significance of the interactions of digoxin with omeprazole; sodium bicarbonate are not known. Omeprazole increases the AUC of digoxin by about 10%.[6108] When rabeprazole is coadministered with digoxin, the AUC and Cmax for digoxin increases approximately 19% and 29%, respectively.[5515] Patients with digoxin serum concentrations at the upper end of the therapeutic range may need to be monitored for potential increases in serum digoxin concentrations when omeprazole; sodium bicarbonate is coadministered.
When clarithromycin (500 mg every 8 hours) was given in combination with omeprazole (40 mg daily) the plasma concentrations of both clarithromycin and its active 14-OH metabolite were increased.[6305] For clarithromycin, the mean Cmax was 10% greater, the mean Cmin was 27% greater, and the mean 8-hour AUC was 15% greater with concurrent therapy with omeprazole as compared to clarithromycin alone. For 14-OH clarithromycin, the Cmax was 45% greater, the mean Cmin was 57% greater, and the mean 8-hour AUC was 45% greater with omeprazole. Clarithromycin concentrations in the gastric tissue and mucus were also increased with concomitant administration of omeprazole. The steady state plasma concentrations of omeprazole were increased (Cmax, AUC, and half-life increases of 30%, 89%, and 34%, respectively) with concomitant administration of clarithromycin.[8851] The mean 24-hour gastric pH value was 5.2 when omeprazole was administered alone and 5.7 when coadministered with clarithromycin.[4964]
Early reports noted an increase in the excretion of tetracyclines during coadministration with sodium bicarbonate [7074], and that the oral absorption of tetracyclines is reduced by sodium bicarbonate via increased gastric pH [7075]. However, conflicting data have been reported, and further study is needed. Two recent studies show no effect of oral sodium bicarbonate administration on tetracycline oral bioavailability.[7076] [7077] In one of these trials, coadministration with sodium bicarbonate was reported to have no effect on tetracycline urinary excretion, Cmax, or AUC.[7077] Until more information is available, avoid simultaneous administration of sodium bicarbonate and tetracyclines. When concurrent therapy is needed, stagger administration times by several hours to minimize the potential for interaction and monitor for antimicrobial efficacy.
Omeprazole has been reported to decrease the oral bioavailability of indinavir. Indinavir plasma concentrations fell to below 95% of normal in roughly half of the patients receiving omeprazole concurrently in one study.[3181] An increase in indinavir dosage resolved the interaction. It is unclear if other gastric acid-pump inhibitors would interact with indinavir in this manner.
A 40 mg dose of omeprazole given 2 hours prior to trovafloxacin (300 mg PO) resulted in a 17% reduction in trovafloxacin AUC and 17% reduction in trovafloxacin Cmax.[6306] [6819] The clinical significance of this potential interaction with trovafloxacin, alatrofloxacin is not known.
Drugs that cause a significant sustained elevation in gastric pH, like with omeprazole; sodium bicarbonate, may reduce plasma concentrations of gefitinib, potentially reducing gefitinib efficacy.[5012]
The American College of Gastroenterology states that the effectiveness of proton pump inhibitors (PPIs) may be decreased if given with other antisecretory agents (e.g., antimuscarinics, octreotide, H2-blockers, or misoprostol).[1569] Proton pump inhibitors (PPIs) inhibit only actively secreting H+-pumps.
Omeprazole inhibits the CYP2C19 metabolic pathway for diazepam [6305]; however, the effect on diazepam pharmacodynamics is not known. Omeprazole can increase the plasma concentrations and the elimination half-life of diazepam.[6307] [6308] It is recommended that patients receiving omeprazole; sodium bicarbonate and diazepam concomitantly should be monitored for enhanced diazepam response.[8851]
A blinded, cross-over trial of renal transplant patients has reported that omeprazole does not significantly alter cyclosporine blood concentrations; however, this trial was limited to ten patients, and the results varied per assay technique (HPLS vs. RIA analysis).[6309] A possible interaction with omeprazole and cyclosporine has been described in two case report, although, the results are conflicting (increase or decrease in cyclosporine blood concentrations).[6310] [6311] Additional data are needed to evaluate the potential for drug interactions during concurrent omeprazole and cyclosporine therapy. Patients should be monitored to determine if it is necessary to adjust the dosage of cyclosporine when taken concomitantly with omeprazole; sodium bicarbonate.[8851]
Omeprazole can exhibit a dose-dependent inhibition of hepatic cytochrome P-450 enzymes, specifically CYP2C19.[6305] Omeprazole can interfere with the clearance of drugs metabolized via this pathway, resulting in increased plasma concentrations. Examples of drugs metabolized by the CYP2C19 pathway include: carisoprodol [4718], citalopram [4718], clomipramine [4718], diazepam [4718], escitalopram [4718], other proton pump inhibitors (PPIs) [4718], phenytoin or fosphenytoin [5265], mephenytoin [4718], proguanil (atovaquone; proguanil) [4718], sertraline [4718], voriconazole [4718], and R-warfarin [4718]. This list is not inclusive of all CYP2C19 substrates. Clinical data does not exist for each of the drugs listed above, but an interaction is possible based on the known pathways of elimination. Patients should be monitored carefully for signs of increased drug effect if omeprazole; sodium bicarbonate is used with these drugs.
Coadministration with valdecoxib (40 mg twice daily) increased the AUC of omeprazole (40 mg once daily) by 46%. Valdecoxib steady state plasma concentrations were not effected significantly with concurrent therapy with multiple doses of omeprazole.[6314] Patients receiving omeprazole; sodium bicarbonate concomitantly with valdecoxib should be monitored for omeprazole toxicity. Manifestations of toxicity may include confusion, drowsiness, blurred vision, tachycardia, nausea/vomiting, flushing, headache, and dry mouth.[8851]
Concomitant administration of omeprazole; sodium bicarbonate with fluvastatin can alter fluvastatin pharmacokinetic parameters, decreasing clearance by 18—23% and increasing AUC by 24—33%.[5045]
Fluvoxamine is a major inhibitor of the cytochrome P450 enzyme (CYP) 2C19.[4718] Several proton pump inhibitors (PPIs), including omeprazole, are primary substrates of the CYP2C19 enzyme. Reduced metabolism and resulting elevated plasma concentrations of these PPIs may occur if combined with fluvoxamine. A single-dose pharmacokinetic study has shown that the mean AUC of omeprazole 40 mg was increased 2- to 6-fold when given after fluvoxamine 50 mg/day for 6 days.[6481] Monitor patients for PPI toxicity, such as headache or GI distress if these drugs are combined.
Proton pump inhibitors (PPIs), which increase gastric pH, may reduce the absorption of delavirdine. However, since these agents affect gastric pH for an extended period, separation of doses may not eliminate the interaction. Chronic use of proton pump inhibitors (PPIs) with delavirdine is not recommended.[5206]
A randomized, open-label, multiple-dose drug interaction study of atazanavir (300 mg) with ritonavir (100 mg) coadministered with omeprazole 40 mg, found a reduction in atazanavir AUC and Cmin of 76% and 78%, respectively. Based on these study results, atazanavir, with or without ritonavir, should not be coadministered with omeprazole due to the reduction in atazanavir exposure

concentrations. It is not known whether the over-the-counter dose of omeprazole (20 mg once daily) would produce similar results; therefore, coadministration is not recommended. Increasing the atazanavir and ritonavir doses to 400 and 100 mg, respectively, with omeprazole did not result in atazanavir exposures comparable to those observed with a regimen of atazanavir 300 mg with ritonavir 100 mg without omeprazole. Due to similar mechanisms, other proton pump inhibitors (PPIs) (e.g., esomeprazole, pantoprazole, rabeprazole, and lansoprazole) should not be used with atazanavir. When such substantial reductions in atazanavir serum concentrations are seen, therapeutic failure and resistance development may be expected.[4865]
Coadministration of nelfinavir (1250 mg twice daily) with omeprazole (40 mg once daily) for 4 days resulted in decreased exposure to nelfinavir (decreased AUC, Cmax, and Cmin by 36%, 37%, and 39%, respectively). The manufacturer of nelfinavir warns against using the drug with any of the proton pump inhibitors (PPIs) due to the potential for subtherapeutic antiretroviral activity and the subsequent possibility for the development of resistant mutations of HIV.[5572]
The effects of gastrointestinal pH alterations on the absorption of methylphenidate extended-release capsules (Ritalin® LA) and dexmethylphenidate extended-release tablets (Focalin™ XR) have not been studied. Although the SODAS® system (drug delivery system utilized in Ritalin® LA and Focalin™ XR) is thought to be minimally affected by changes in pH [8068], per the manufacturer, the modified release characteristics of both extended-release formulations are pH-dependent. It is possible that the administration of proton pump inhibitors (PPIs) or other acid suppressants could alter the release of dexmethylphenidate or methylphenidate.[8067] [8069] Patients receiving these extended-release products (Focalin™ XR or Ritalin® LA) with acid suppressants should be monitored for adverse effects and therapeutic efficacy.
Doxercalciferol is converted in the liver to 1,25-dihydroxyergocalciferol, the major active metabolite, and 1-alpha, 24-dihydroxyvitamin D2, a minor metabolite. Although not specifically studied, cytochrome P450 enzyme inhibitors including omeprazole may inhibit the 25-hydroxylation of doxercalciferol, thereby decreasing the formation of the active metabolite and thus, decreasing efficacy. Patients should be monitored for a decrease in efficacy if omeprazole; sodium bicarbonate is coadministered with doxercalciferol.[6904] [7566]
The addition of omeprazole to clozapine therapy resulted in a roughly 40% reduction in clozapine plasma concentrations in at least 2 patients. The mechanism is not known and clinical significance is not established. Clinicians should monitor for loss of efficacy of clozapine if omeprazole; sodium bicarbonate is added to an established clozapine regimen.[8092]
Because cefpodoxime proxetil requires a low gastric pH for dissolution, drugs which increase gastric pH (e.g., antacids; didanosine, ddI; H2-blockers, lansoprazole, omeprazole) can decrease the bioavailability of cefpodoxime. Concomitant administration high doses of antacids or H2-blockers reduce peak plasma concentrations by 24% to 42% and the extent of absorption by 27% to 32%, respectively. The rate of absorption is not affected.[5304]
The oral absorption of indomethacin can be decreased if given concomitantly with sodium bicarbonate. Staggering the administration times of omeprazole; sodium bicarbonate with this agent may minimize the effect of sodium bicarbonate on the oral bioavailability of indomethacin.
By increasing intragastric pH, omeprazole; sodium bicarbonate can affect the dissolution of oral bisacodyl tablets; administration should be separated by 1 hour.[4701]
Antacids, such as sodium bicarbonate, can delay the oral absorption of acetaminophen. This interaction is not likely to be clinically significant as the extent of acetaminophen absorption is not appreciably affected.[6086]
Ammonium chloride is an acid-forming salt.[6675] Coadministration of omeprazole; sodium bicarbonate may potentially lead to systemic alkalinization and should be avoided.
Prolonged use of omeprazole; sodium bicarbonate along with calcium carbonate may result in milk-alkali syndrome.[8243]
Concomitant administration of omeprazole and tacrolimus may increase the serum concentrations of tacrolimus.[5342] [6035]
In one patient, the combined use of disulfiram and omeprazole caused disorientation, confusion, and nightmares. These reactions occurred on two separate challenges when omeprazole was added to disulfiram therapy. Caution is advised when using disulfiram and omeprazole together. It is not known if similar proton pump inhibitors interact with disulfiram in a similar manner.[7673]
Bortezomib may inhibit CYP2C19 activity at therapeutic concentrations and increase exposure to drugs that are substrates for this enzyme.[5113] However, no drug interaction data are available and potential metabolic interactions remain theoretical. Drugs that are primary or significant substrates for CYP2C19 [4718] include the proton pump inhibitors (PPIs) lansoprazole [5142], omeprazole [6305], esomeprazole [6265], pantoprazole [6226], and rabeprazole [5515]. The clinical significance of these potential interactions has not been determined.
The effect of increased gastric pH on the bioavailability of ceftibuten was evaluated in 18 healthy adult volunteers. Each volunteer was administered one 400-mg ceftibuten capsule. A single dose of liquid antacid did not affect the Cmax or AUC of ceftibuten; however, 150 mg of ranitidine every 12 hours for 3 days increased the ceftibuten Cmax by 23% and ceftibuten AUC by 16%. The clinical relevance of these increases is not known.[6665] Although no specific studies were performed, other H2-blockers, proton pump inhibitors (PPIs), and didanosine, ddI (contains buffering agents) may possibly affect the kinetics of ceftibuten.
The enteric-coated, delayed-release naproxen tablets (EC Naprosyn®) are designed to dissolve at a pH of 6 or greater. Concomitant use of this particular naproxen product with antacids, sucralfate, H2-blockers, or proton pump inhibitors (PPIs) is not recommended due to the gastric pH alteration.[6112] Increased gastric pH will affect the dissolution site and thus, absorption characteristics of the enteric-coated, delayed-release naproxen tablets. Periodic antacid use should not be problematic as long as the antacid and enteric-coated naproxen administration are separated by at least 2 hours.
In vitro studies have shown that efavirenz inhibits CYP2C9 and CYP2C19 in the range of observed efavirenz plasma concentrations.[5172] Although drug interaction studies have not been conducted, efavirenz may inhibit the metabolism of substrates for CYP2C9 or CYP2C19 such as omeprazole [4718].
Data from the PRISM study [1740] [6891], indicate that patients who received levothyroxine or omeprazole concomitantly with tirofiban had a higher rate of tirofiban clearance than patients who did not receive levothyroxine or omeprazole. The clinical significance of this is unknown.
The bioavailability of tolmetin is reduced by 16% when given with food or milk.[6992] Also, the bioavailability of tolmetin is decreased by sodium bicarbonate.[6992] Do not use a sodium bicarbonate-containing antacid concurrently with tolmetin. To reduce GI irritation, an antacid containing magnesium or aluminum hydroxide may be given with tolmetin, if needed.
Although the clinical significance has not been determined, the bioavailability of oral alendronate is doubled by concomitant administration of intravenous ranitidine.[5375] Investigations have not been undertaken to determine if other H2-antagonists have a similar effect on bioavailability.[5375] Patients should be closely monitored when antiulcer medications, such as proton pump inhibitors (PPIs), gastric mucosal agents, and H2-blockers, or other medications for GI disorders, are coadministered as they may affect the bioavailability of alendronate, leading to a higher likelihood of developing GI adverse effects while taking alendronate.
Enteric-coated budesonide granules dissolve at a pH > 5.5.[6865] Concomitant use of budesonide oral capsules and antacids, milk, or other drugs that increase gastric pH levels can cause the coating of the granules to dissolve prematurely, possibly affecting

release properties and absorption of the drug in the duodenum. When 1 gram/day PO of cimetidine is administered with an uncoated formulation of oral budesonide, a slight increase in absorption as well as peak plasma concentrations occurs, resulting in significant cortisol suppression.[6865] In general, it may be prudent to avoid drugs such as H2-blockers [5269] or antacids in combination with enteric-coated budesonide. Omeprazole slightly inhibits CYP3A4, but has not been shown to affect the absorption or pharmacokinetics of oral budesonide; data on other proton pump inhibitors (PPIs) are not available, be alert for theoretical interactions based on changes in gastric pH that may occur as a result of acid suppression by the PPI.
Antacids, H2-blockers, and proton pump inhibitors (PPIs) may increase plasma concentrations of mefloquine. In a small study involving 6 healthy subjects and 6 peptic ulcer patients, cimetidine increased the Cmax and AUC of mefloquine. In the study, the pharmacokinetics of mefloquine were determined after receiving a single oral mefloquine 500 mg dose alone and after 3-days of cimetidine 400 mg PO bid. In both healthy subjects and peptic ulcer patients, mefloquine Cmax was increased 42.4% and 20.5%, respectively, and AUC was increased by 37.5% in both groups. Elimination half-life, total clearance, and volume of distribution were not significantly affected. An increase in adverse reactions was not noted. Patients on chronic mefloquine therapy might be at increased risk of adverse reactions, especially in patients with a neurological or psychiatric history.[9417]
Coadministration of St. John's Wort, Hypericum perforatum (300 mg three times daily) for 14 days with a one time dose of omeprazole 20 mg on day 15 resulted in decreased omeprazole plasma concentrations in healthy subjects. The AUC of omeprazole was reduced by approximately 40% in both poor and extensive metabolizers of CYP2C19. The clinical significance of this interaction is not clear; however, due to variations in the amounts of active ingredient in herbal products, the magnitude of this interaction and the resultant clinical effect may vary.[10038] Proton pump inhibitors (PPIs) are primary substrates of the CYP2C19 enzyme, therefore patients taking St. John's Wort concomitantly with a PPI should be monitored for PPI efficacy.
Data indicate that the solubility of dasatinib is pH dependent. Long-term suppression of gastric acid secretion by H2-blockers or proton pump inhibitors (PPIs) is likely to decrease the exposure to dasatinib. The concomitant use these agents is not recommended. The use of antacids should be considered in place of H2-blockers or PPIs in patients receiving dasatinib therapy.[9211]

Interactions last revised 4/23/2007 2:13:00 PM

Adverse Reactions

- abdominal pain
- agranulocytosis
- alopecia
- anaphylactoid reactions
- anemia
- angioedema
- asthenia
- atrial fibrillation
- candidiasis
- constipation
- diarrhea
- dizziness
- elevated hepatic enzymes
- erythema multiforme
- exfoliative dermatitis
- fever
- headache
- hemolytic anemia
- hepatic encephalopathy
- hepatic failure
- hepatic necrosis
- hepatitis
- hyperbilirubinemia
- hypertension
- hypokalemia
- hypophosphatemia
- jaundice
- leukocytosis
- leukopenia
- metabolic alkalosis
- nausea/vomiting
- neutropenia
- pancreatitis
- pancytopenia
- pernicious anemia
- petechiae
- photosensitivity
- pruritus
- purpura
- rash (unspecified)
- seizures
- Stevens-Johnson syndrome
- supraventricular tachycardia (SVT)
- tetany
- thrombocytopenia
- toxic epidermal necrolysis
- urticaria
- vitamin B₁₂ deficiency
- xerosis

NOTE: This monograph discusses the adverse reactions with omeprazole; sodium bicarbonate combination products. Clinicians may wish to consult the individual monographs for more information about each agent.
Adverse reactions reported during omeprazole therapy are infrequent, and are primarily related to the GI tract. The incidence of GI adverse effects is comparable to ranitidine. Out of 465 patients receiving omeprazole in domestic clinical trials, the most common reported side effect is headache occurring in 2.4% of patients (2.6%, ranitidine). The most commonly reported GI disturbances are diarrhea (3% omeprazole vs. 2.1% ranitidine), abdominal pain (2.4% omeprazole vs. 2.1% ranitidine), nausea/vomiting (1.5%/2.2% omeprazole vs. 1.5%/4.1% ranitidine), and constipation (1.1% omeprazole vs. 0% ranitidine). Dizziness, asthenia, and rash were also reported (1.5%, 1.1%, and 1.5%, respectively) compared to placebo (0%). Similar adverse events were reported in international clinical evaluations of 2,631 patients receiving omeprazole.[8851]
In a clinical trial conducted in 359 critically ill patients comparing omeprazole; sodium bicarbonate oral suspension (40 mg once daily) with IV cimetidine (1200 mg/day), adverse events were similarly reported in each group.[8851] [8855] Events reported more frequently with omeprazole; sodium bicarbonate compared to cimetidine were fever (20.2% vs. 16%), thrombocytopenia (10.1% vs. 6.1%), hypertension (7.9% vs. 3.3%), hypophosphatemia (6.2% vs. 3.9%), atrial fibrillation (6.2% vs. 3.9%), oral candidiasis (3.9% vs. 0.6%), and supraventricular tachycardia (SVT) (3.4% vs. 1.1%). In this study, the omeprazole; sodium bicarbonate group

had a higher baseline prevalence of acute renal failure, coagulopathy disorders, and sepsis.[8855]
In rare instances, hematologic abnormalities have been reported during omeprazole therapy and warrant medical attention. Pancytopenia, agranulocytosis (some fatal), thrombocytopenia, leukopenia, neutropenia, anemia, leukocytosis, and hemolytic anemia have been reported. In a study of healthy volunteers, it was shown that omeprazole caused a significant reduction in cyanocobalamin absorption (vitamin B12 deficiency).[162] Since neurologic manifestations of pernicious anemia can appear in the absence of hematologic changes, patients receiving omeprazole should be monitored for signs of pernicious anemia.
Hypersensitivity reactions have been reported with omeprazole, including rash (unspecified) (1.5% vs. 0% in clinical trials; 1.1% drug-related), angioedema, pruritus, urticaria, and anaphylactoid reactions, have been reported rarely in patients receiving omeprazole. Rare cases of severe generalized skin reactions including toxic epidermal necrolysis (some fatal), Stevens-Johnson syndrome, exfoliative dermatitis, and erythema multiforme (some severe) have occurred. Other skin manifestations have included: purpura and/or petechiae (some with rechallenge), skin inflammation, alopecia, xerosis (dry skin), photosensitivity, and hyperhidrosis.[8851]
Mild and rarely substantially elevated hepatic enzymes (ALT, AST, GGT, alkaline phosphatase), hyperbilirubinemia, and/or jaundice have occurred in patients receiving omeprazole. In rare instances, overt liver disease has developed, including hepatocellular, cholestatic, or mixed hepatitis, hepatic necrosis (some fatal), hepatic failure (some fatal), and hepatic encephalopathy.
Rare cases of acute and sometimes fatal pancreatitis have been identified in published case reports. One case of an elderly patient presenting with dyspnea and epigastric pain had initiated therapy with omeprazole 20 mg two months prior. Laboratory values for lipase and amylase were elevated consistent with acute pancreatitis. After discontinuation of omeprazole, the laboratory profile and symptoms improved shortly thereafter. The patient was rechallenged a week later and gastric pain and elevated laboratory values for lipase and amylase recurred.[8866] Similar increases in laboratory values have been observed in animal studies when rats were administered human doses of omeprazole.[8867]
The Zegerid® brand of omeprazole; sodium bicarbonate contains 1680 mg (20 mEq) sodium bicarbonate in each packet of powder for oral suspension and 1100 mg (13 mEq) sodium bicarbonate in each capsule. Adverse reactions that may be caused by significant ingestion of sodium bicarbonate include metabolic alkalosis, hypokalemia, seizures, and tetany.[8868]
Atrophic gastritis, a precursor for gastric cancer, has been noted occasionally in gastric corpus biopsies from patients treated long-term with pantoprazole, particularly in patients who were *H. pylori* positive.[6226] Other proton pump inhibitors (PPI) have also been implicated. One study compared the long-term effects of omeprazole (20—40 mg once daily) versus funduscopy in the treatment of gastroesophageal reflux. Among *H. pylori* positive patients treated with omeprazole, 30% developed atrophic gastritis ($P < 0.001$). In contrast, only 4% of omeprazole-treated patients who were not infected with *H. pylori* developed atrophic gastritis. No patients in the funduscopy group developed atrophic gastritis during the study period regardless of *H. pylori* infection status.[9496] Some studies have corroborated these results, while other studies have found no evidence of accelerated progression to atrophic gastritis in this population. Until more data are available, it may be prudent to test and treat baseline *H. pylori* infections before starting empiric omeprazole; sodium bicarbonate maintenance therapy to avoid the possible increased risk of atrophic gastritis development.[9497]

Adverse Reactions last revised 9/13/2006 9:24:00 AM

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