



# pharmacists planning service, inc.

101 Lucas Valley Road, Suite 210 • San Rafael, California 94903  
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February 14, 2007

Deborah Platt Majoras, Chairman  
FTC  
6th & Pennsylvania Avenue  
Washington, DC 20580

Steve Galson, M.D., MPH  
Director, CDER  
FDA, 5515 Security Lane  
Rockville, MD 20857

**RE: DIRECT-TO-CONSUMER ADVERTISING  
PRINT SIZE READABILITY**

Dear Ms. Majoras and Dr. Galson:

Pharmacists Planning Service, Inc. (PPSI) is a 501 C (3) nonprofit public health, consumer, pharmacy education organization is greatly concerned about the direct-to-consumer (DTC) print size readability and the ability for patients and consumers who read these ads to understand them. These ads basically are for prescription drugs and in many cases are promoting the prescription drugs but patients and consumers are not able to read them.

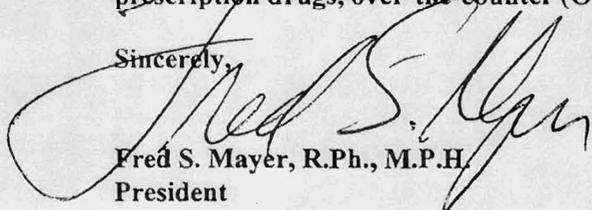
I am sending you a series of advertisements from various magazines. Please note the difficulty patients and consumers have in reading them, especially seniors, who are only 13% of the population but use 43% of all prescription drugs, over-the-counter (OTC) drugs and herbals.

In 1990 PPSI petitioned FDA on label readability guidelines and introduced legislation in California to increase the print size for patients and consumers to improve the readability on nonprescription medicine labels. California Assembly Bill 2713 was signed into law by the Governor and was enacted regarding print size on OTCs. In October, 1990 the Nonprescription Drug Manufacturers Association (NDMA) put out label readability guidelines after two years of study from a task force entitled "Draft Guidelines for Maximizing Label Readability". I am enclosing a copy of the Label Readability Guidelines by NDMA.

PPSI requests that FTC and FDA get uniformity and guidelines for readability for direct-to-consumer advertising so that patients and consumers, especially seniors, are able to read prescription drug advertisements.

Under separate cover, I would like to submit a Citizen's Petition regarding direct-to-consumer (DTC) advertising and print and label readability in the current advertising of prescription drugs, over-the-counter (OTC) drugs, herbals and alternative medicines, etc.

Sincerely,



Fred S. Mayer, R.Ph., M.P.H.  
President

Enclosures

2007P-0065

SUP 1



pharmacists planning service, inc.

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Documents Management Branch  
Food and Drug Administration  
Department of Health and Human Services  
5630 Fishers Lane, Room 1061  
Rockville, MD 20852

February 14, 2007

**Re: Direct-to-Consumer (DTC) Print Size Readability**

The undersigned submits this Petition under Section 21 CFR 10.20 and 21 CFR 10.30 and other pertinent sections of the Federal Food, Drug and Cosmetic Act or any other statutory provision which authority has been delegated of the Commissioner of Food and Drug to request the Commissioner of FDA to standardize and increase print size for direct-to-consumer advertising for readability of patients and consumers. Many of these ads are for prescription drugs, over-the-counter drugs and herbal dietary supplement drugs.

This Petition requests the FDA Commissioner to issue a Federal Regulation to increase print size of direct-to-consumer advertisements.

Some of the scientific facts which require immediate action on this Petition are as follows:

1. Prescription drugs and over-the-counter medicines along with herbals are used safely and effectively by patients and consumers.
2. Direct-to-consumer advertising has increased from less than one billion dollars in advertising four years ago to over 6.5 billion dollars today.
3. Many of the ads in newspapers and magazines have print size too small for consumers and patients to read.
4. The successful use of prescription drugs and over-the-counter medicines is self-care and is due in large part to labeling, which includes information needed for proper use of the product. The label includes: the name and identity of the product; what the product will do; net contents; active ingredients; inactive ingredients; name and location of the manufacturer, distributor or picker; directions for use; warnings; and where applicable; side effects, drug interactions, and circumstances under which a doctor's advice should be sought. If the above information is printed in direct-to-consumer advertising too small for the patient/consumer to read, this information is useless.
5. Readability describes the ease, speed and accuracy with which information on direct-to-consumer advertising can be read.
6. No single factor can of itself determine readability. Many factors interact and

the total effect of all the factors must be considered. For example, in direct-to-consumer advertising, type size, line length, and leading "spacing between lines" interact in a complex way and therefore should be selected in relation to one another.

7. The advertising designer of direct-to-consumer ads needs to be aware of the effect of the factors inherent in the production of the direct-to-consumer advertising. These include: a. the ink used; b. the substrate (material on which the copy is printed); c. the final size of the direct-to-consumer advertising; d. the final size of the type; e. the process used to create the printed direct-to-consumer advertisement.

8. The final judgment on the readability of the direct-to-consumer advertising should be made by a human being, or several, who are sensitive to the factors that go into good readability.

9. An individual or project team of several people, representative of consumers, should be designated to serve as readability evaluators.

10. Many technical factors effecting direct-to-consumer readability need to be considered: a. Layout and design; b. Typography in printing; c. Columns vs. broken lines; d. in boxes.

11. Special paragraphs need to portray most importantly drug interactions, side effects, cautions, black box warnings and special advice to patients and consumers. This information should be in the first part of the direct-to-consumer advertisement makeup.

12. Type size and spacing along with contrast, brightness and color sometimes makes it almost impossible for seniors to read and understand (see enclosed eleven ads).

**ACTION REQUESTED:**

PPSI requests the FDA to immediately increase print size on direct-to-consumer advertising for patient's and consumer's readability.

PPSI strongly believes FDA needs to act NOW.

Seniors encompass 13% of the total population in the US; however, seniors use 43% of all prescription drugs and over-the-counter medicines along with herbal supplements.

PPSI believes there is ample amount of scientific evidence and information available along with the enclosed original ads to justify this immediate action.

**Over 770,000 US citizens go to hospital emergency rooms due to adverse drug reactions, drug interactions, allergic reactions and in many cases the patient receives the wrong medication or incorrect dosage. This could be avoided if direct-to-consumer advertisements are readable and understandable especially for patients and consumers.**

**PPSI praises those ad agencies who put direct-to-consumer ads out (see ad No. 1 for Lyrica by Pfizer). Notice the important facts and how easy they are to read. All direct-to-consumer advertisements should be like this which gives the important facts in a box and bold form so patients and consumers are able to read and understand them.**

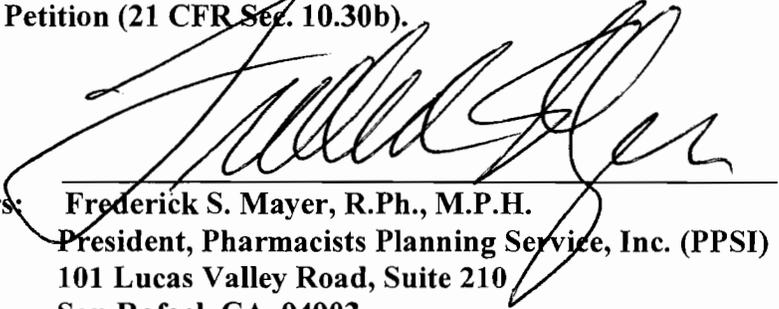
**There is no environmental impact associated with this Citizen's Petition and we wish to be excluded under 21 CFR Sec. 25.24.**

**There is no economic impact involved with this Citizen's Petition and according to a recent study there would be a thirty-three billion dollar savings on decreasing costs in hospital, emergency room and doctor's visits along with the untold lessening of unneeded deaths due to adverse drug reactions, side effects, allergies and basic information on safety issue in direct-to-consumer advertising.**

**The undersigned certified, that, to the best knowledge and belief of the undersigned this Petition includes all information and view on which the Petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the Petition (21 CFR Sec. 10.30b).**

**Signature**

**Name of Petitioners:**



**Frederick S. Mayer, R.Ph., M.P.H.  
President, Pharmacists Planning Service, Inc. (PPSI)  
101 Lucas Valley Road, Suite 210  
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**cc: Deborah Platt Majoras, Chairman, FTC  
Steve Galson, M.D., MPH, Director, CDER, FDA**



# There's relief for pain like this.

**Do you feel stabbing pain in your feet? Or uncomfortable tingling, numbness, burning or shooting sensations?**

If so, you may have nerve pain. This type of pain is different from other kinds of pain. Common pain medicines like aspirin may not work very well for this kind of pain. Ask your doctor if LYRICA® can help. Prescription LYRICA is one of several pain relief treatments for you and your doctor to consider. LYRICA was specially designed to relieve two common types of nerve pain, Diabetic Nerve Pain and Pain after Shingles. LYRICA works on the nerves that cause pain to provide the relief you need. Which is a step in the right direction.

**LYRICA is not for everyone.** Some of the most common side effects of LYRICA are dizziness and sleepiness. Others are dry mouth, swelling of hands and feet, blurry vision, weight gain, and trouble concentrating. You may have a higher chance of swelling or gaining weight if you are also taking certain diabetes medicines. And, if you drink alcohol or take medicines that make you sleepy, you may feel more sleepy when you start LYRICA. You should not drive a car or work with machines until you know how LYRICA affects you. Tell your doctor about any changes in your eyesight, muscle pain along with a fever or tired feeling, or skin sores due to diabetes. Also tell your doctor if you are planning to father a child. If you have had a drug or alcohol problem, you may be more likely to misuse LYRICA. You should talk with your doctor before you stop taking LYRICA or any other prescription medication.

*Please see important product information on adjacent page.*

**Talk to your doctor about LYRICA. To learn more visit [www.lyrica.com](http://www.lyrica.com) or call toll-free 1-888-9-LYRICA (1-888-959-7422).**

**LYRICA®**  
PRIGABALIN capsules

**Designed for Relief**

Uninsured? Need help paying for medicine? Pfizer has programs that can help, no matter your age or income. You may even qualify for free Pfizer medicines. Call 1-866-706-2400. Or visit [www.pfizerhelpfulanswers.com](http://www.pfizerhelpfulanswers.com) 

# IMPORTANT FACTS

**LYRICA**  
PRIGABALIN  
capsules

(LEER-i-kah)

## IMPORTANT SAFETY INFORMATION ABOUT LYRICA

LYRICA may make you feel dizzy or sleepy.

- Do not drive a car, work with machines, or do other dangerous things until you are sure you will be alert. Ask your doctor when it is okay to do these things.

LYRICA may cause problems with your eyesight, including blurry vision. Call your doctor if you have any changes in your eyesight.

## ABOUT LYRICA

LYRICA is a prescription medicine used to treat:

- Nerve pain from diabetes
- Nerve pain that continues after the rash from shingles heals.

This pain can be sharp or burning. It can feel like tingling, shooting, or numbness. Some people taking LYRICA had less pain by the end of the first week. LYRICA may not work for everyone.

## WHO IS LYRICA FOR?

Who can take LYRICA:

- Adults 18 years or older with nerve pain from diabetes or after shingles.

Who should NOT take LYRICA:

- Anyone who is allergic to anything in LYRICA.

LYRICA has not been studied for nerve pain in children under 18 years of age.

## BEFORE STARTING LYRICA

Tell your doctor about all your medical conditions. Tell your doctor if you:

- Have or had kidney problems or dialysis
- Have heart problems, including heart failure
- Have a bleeding problem or a low blood platelet count
- Have abused drugs or alcohol. LYRICA may cause some people to feel "high."
- Are either a man or woman planning to have children or a woman who is breast-feeding, pregnant, or might be pregnant. It is not known if LYRICA may decrease male fertility, cause birth defects, or pass into breast milk.

Tell your doctor about all your medicines. Include over-the-counter medicines, vitamins, and herbal products. Tell your doctor if you take:

- Rosiglitazone (Avandia<sup>®</sup>)<sup>\*</sup> or pioglitazone (Actos<sup>®</sup>)<sup>\*\*</sup> for diabetes
- Narcotic pain medicines such as oxycodone, tranquilizers, or medicines for anxiety such as lorazepam
- Any medicines that make you sleepy

## POSSIBLE SIDE EFFECTS OF LYRICA

LYRICA may cause serious side effects, including:

- Dizziness and sleepiness
- Eyesight problems
- Weight gain and swelling of hands and feet. Weight gain may affect control of diabetes. Weight gain and swelling can be serious for people with heart problems.
- Unexplained muscle pain, soreness, or weakness, along with a fever or tired feeling. If you have these symptoms, tell your doctor right away.
- Skin sores. In LYRICA studies, skin sores were seen in animals but not in humans. If you have diabetes, pay extra attention to your skin. Tell your doctor about any skin problems.

The most common side effects of LYRICA are:

- Dizziness
- Sleepiness
- Swelling of hands and feet
- Blurry vision
- Weight gain
- Trouble concentrating
- Dry mouth

You may have a higher chance of swelling or gaining weight if you are taking certain diabetes medicines with LYRICA. Medicines that already make you sleepy or dizzy may make you feel more sleepy or dizzy with LYRICA.

## HOW TO TAKE LYRICA

Do:

- Take LYRICA exactly as your doctor tells you. Your doctor may tell you to take it 2 or 3 times a day.
- Take LYRICA with or without food.

Don't:

- Do not drive a car or use machines if you feel sleepy while taking LYRICA.
- Do not drink alcohol or use other medicines that make you sleepy while taking LYRICA.
- Do not change the dose or stop LYRICA suddenly. You may have headaches, nausea, diarrhea, or trouble sleeping if you stop taking LYRICA suddenly.
- Do not start any new medicines without first talking to your doctor.

## NEED MORE INFORMATION?

- Ask your doctor or pharmacist. This is only a brief summary of important information.
- Go to [www.lyrica.com](http://www.lyrica.com) or call 1-888-9-LYRICA (1-888-959-7422).



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New York, NY 10017  
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**Rx only**

- <sup>\*</sup>Avandia is a registered trademark of GlaxoSmithKline.
- <sup>\*\*</sup>Actos is a registered trademark of Takeda Chemicals Industries, Ltd., and is used under license by Takeda Pharmaceuticals of America, Inc., and Eli Lilly and Co.

# Is your cholesterol out of whack?

Start getting your cholesterol right—and get a 15-day Free Trial Certificate for CRESTOR!

Did you know—high blood pressure and diabetes are among factors that make it even more important to get your bad cholesterol low? But to get your cholesterol right, your doctor may also want your good cholesterol up. And diet and exercise alone may not be enough to lower the bad cholesterol and raise the good.

**CRESTOR is a cholesterol medicine that does both.**

A 10-mg dose of CRESTOR can:

▼ <b>lower bad cholesterol</b> (LDL) by up to <b>52%</b> (vs 7% with placebo)	▲ <b>raise good cholesterol</b> (HDL) by up to <b>14%</b> (vs 3% with placebo)
your results may vary	

Is CRESTOR right for you? That's an important conversation you need to have with your doctor. If he or she prescribes CRESTOR 5 mg or 10 mg, you can get a 15-day Free Trial Certificate for CRESTOR. Simply call the toll-free number below or log on to [crestoroffer.com](http://crestoroffer.com)

**Important safety information about CRESTOR you need to know:**

CRESTOR® (rosuvastatin calcium) is prescribed along with diet for lowering high cholesterol. It has not been determined to prevent heart disease, heart attacks, or strokes. CRESTOR is not right for everyone, including women who are nursing, pregnant, or who may become pregnant, or anyone with liver problems. Your doctor will do blood tests before and during treatment with CRESTOR to monitor your liver function. Unexplained muscle pain and weakness could be a sign of a rare but serious side effect and should be reported to your doctor right away. The 40-mg dose of CRESTOR is only for patients who do not reach goal on 20 mg. Be sure to tell your doctor if you are taking any medications. Side effects occur infrequently and include muscle aches, constipation, weakness, abdominal pain, and nausea. They are usually mild and tend to go away.

## 15-Day Free Trial

Try CRESTOR  
free for your  
first 15 days

Redeem this offer in 2 easy steps:

1. Take this voucher to your doctor and ask whether CRESTOR is right for you.
2. If your doctor prescribes CRESTOR 5 mg or 10 mg, present both this voucher and your prescription to your pharmacist.

Call 1-888-569-5356 or visit [crestor.com](http://crestor.com) for answers to commonly asked questions about CRESTOR.

**Terms and Conditions:** Limit one 15-day free trial certificate per person for the duration of the offer. Valid ONLY at retail pharmacies; no mail order. Please see patient eligibility restrictions and other terms and conditions on the back of this certificate.

RxBIN #	RxPCN #	RxGRP #	Identification #
003858	A4	DSVA	1296270052

This offer is good through 5/21/07.



CR



PARADE ANSERCARD

PRINTED IN USA

Please read this summary carefully and then ask your doctor about CRESTOR. No advertisement can provide all the information needed to determine if a drug is right for you. This advertisement does not take the place of careful discussions with your doctor. Only your doctor has the training to weigh the risks and benefits of a prescription drug.

**BRIEF SUMMARY:** For full Prescribing Information, see package insert.

**INDICATIONS AND USAGE:** CRESTOR is indicated: 1. as an adjunct to diet to reduce elevated total-C, LDL-C, ApoB, nonHDL-C, and TG levels and to increase HDL-C in patients with primary hypercholesterolemia (heterozygous) and mixed dyslipidemia (Fredrickson Type IIa and IIb); 2. as an adjunct to diet for the treatment of patients with elevated serum TG levels (Fredrickson Type IV); 3. to reduce LDL-C, total-C, and ApoB in patients with homozygous familial hypercholesterolemia as an adjunct to other lipid-lowering treatments (e.g., LDL apheresis) or if such treatments are unavailable. **CONTRAINDICATIONS:** CRESTOR is contraindicated in patients with a known hypersensitivity to any component of this product. Rosuvastatin is contraindicated in patients with active liver disease or with unexplained persistent elevations of serum transaminases (see WARNINGS, Liver Enzymes). **Pregnancy and Lactation:** Atherosclerosis is a chronic process and discontinuation of lipid-lowering drugs during pregnancy should have little impact on the outcome of long-term therapy of primary hypercholesterolemia. Cholesterol and other products of cholesterol biosynthesis are essential components for fetal development (including synthesis of steroids and cell membranes). Since HMG-CoA reductase inhibitors decrease cholesterol synthesis and possibly the synthesis of other biologically active substances derived from cholesterol, they may cause fetal harm when administered to pregnant women. Therefore, HMG-CoA reductase inhibitors are contraindicated during pregnancy and in nursing mothers. ROSUVASTATIN SHOULD BE ADMINISTERED TO WOMEN OF CHILDBEARING AGE ONLY WHEN SUCH PATIENTS ARE HIGHLY UNLIKELY TO CONCEIVE AND HAVE BEEN INFORMED OF THE POTENTIAL HAZARDS. If the patient becomes pregnant while taking this drug, therapy should be discontinued immediately and the patient apprised of the potential hazard to the fetus.

**WARNINGS:** **Liver Enzymes:** HMG-CoA reductase inhibitors, like some other lipid-lowering therapies, have been associated with biochemical abnormalities of liver function. The incidence of persistent elevations (>3 times the upper limit of normal [ULN]) occurring on 2 or more consecutive occasions in serum transaminases in fixed dose studies was 0.4, 0, 0, and 0.1% in patients who received rosuvastatin 5, 10, 20, and 40 mg, respectively. In most cases, the elevations were transient and resolved or improved on continued therapy or after a brief interruption in therapy. There were two cases of jaundice, for which a relationship to rosuvastatin therapy could not be determined, which resolved after discontinuation of therapy. There were no cases of liver failure or irreversible liver disease in these trials. It is recommended that liver function tests be performed before and at 12 weeks following both the initiation of therapy and any elevation of dose, and periodically (e.g., semiannually) thereafter. Liver enzyme changes generally occur in the first 3 months of treatment with rosuvastatin. Patients who develop increased transaminase levels should be monitored until the abnormalities have resolved. Should an increase in ALT or AST of >3 times ULN persist, reduction of dose or withdrawal of rosuvastatin is recommended. Rosuvastatin should be used with caution in patients who consume substantial quantities of alcohol and/or have a history of liver disease (see CLINICAL PHARMACOLOGY, Special Populations, Hepatic Insufficiency). Active liver disease or unexplained persistent transaminase elevations are contraindications to the use of rosuvastatin (see CONTRAINDICATIONS). **Myopathy/Rhabdomyolysis:** Rare cases of rhabdomyolysis with acute renal failure secondary to myoglobinuria have been reported with rosuvastatin and with other drugs in this class. Uncomplicated myalgia has been reported in rosuvastatin-treated patients (see ADVERSE REACTIONS). Creatine kinase (CK) elevations (>10 times upper limit of normal) occurred in 0.2% to 0.4% of patients taking rosuvastatin at doses up to 40 mg in clinical studies. Treatment-related myopathy, defined as muscle aches or muscle weakness in conjunction with increases in CK values >10 times upper limit of normal, was reported in up to 0.1% of patients taking rosuvastatin doses of up to 40 mg in clinical studies. In clinical trials, the incidence of myopathy and rhabdomyolysis increased at doses of rosuvastatin above the recommended dosage range (5 to 40 mg). In postmarketing experience, effects on skeletal muscle, e.g., uncomplicated myalgia, myopathy, and rarely, rhabdomyolysis have been reported in patients treated with HMG-CoA reductase inhibitors including rosuvastatin. As with other HMG-CoA reductase inhibitors, reports of rhabdomyolysis with rosuvastatin are rare, but higher at the highest marketed dose (40 mg). Factors that may predispose patients to myopathy with HMG-CoA reductase inhibitors include advanced age ( $\geq 65$  years), hypothyroidism, and renal insufficiency. Consequently, 1. Rosuvastatin should be prescribed with caution in patients with predisposing factors for myopathy, such as, renal impairment (see DOSAGE AND ADMINISTRATION), advanced age, and inadequately treated hypothyroidism. 2. Patients should be advised to promptly report unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever. Rosuvastatin therapy should be discontinued if markedly elevated CK levels occur or myopathy is diagnosed or suspected. 3. The 40 mg dose of rosuvastatin is reserved only for those patients who have not achieved their LDL-C goal utilizing the 20 mg dose of rosuvastatin once daily (see DOSAGE AND ADMINISTRATION). 4. The risk of myopathy during treatment with rosuvastatin may be increased with concurrent administration of other lipid-lowering therapies or cyclosporine. (see CLINICAL PHARMACOLOGY, Drug Interactions, PRECAUTIONS, Drug Interactions, and DOSAGE AND ADMINISTRATION). The benefit of further alterations in lipid levels by the combined use of rosuvastatin with fibrates or niacin should be carefully weighed against the potential risks of this combination. Combination therapy with rosuvastatin and gemfibrozil should generally be avoided. (see DOSAGE AND ADMINISTRATION and PRECAUTIONS, Drug Interactions). 5. The risk of myopathy during treatment with rosuvastatin may be increased in circumstances which increase rosuvastatin drug levels (see CLINICAL PHARMACOLOGY, Special Populations, Race and Renal Insufficiency, and PRECAUTIONS, General). 6. Rosuvastatin therapy should also be temporarily withheld in any patient with an acute, serious condition suggestive of myopathy or predisposing to the development of renal failure secondary to rhabdomyolysis (e.g., sepsis, hypotension, dehydration, major surgery, trauma, severe metabolic, endocrine, and electrolyte disorders, or recent alcohol abuse).

**PRECAUTIONS:** **General:** Before instituting therapy with rosuvastatin, an attempt should be made to control hypercholesterolemia with appropriate diet and exercise, weight reduction in obese patients, and treatment of underlying medical problems (see INDICATIONS AND USAGE). Administration of rosuvastatin 20 mg to patients with severe renal impairment ( $Cl_{CR} < 30$  mL/min/1.73 m<sup>2</sup>) resulted in a 3-fold increase in plasma concentrations of rosuvastatin compared with healthy volunteers (see WARNINGS, Myopathy/Rhabdomyolysis and DOSAGE AND ADMINISTRATION). The result of a large pharmacokinetic study conducted in the US demonstrated an approximate 2-fold elevation in median exposure in Asian subjects (having either Filipino, Chinese, Japanese, Korean, Vietnamese or Asian-Indian origin) compared with a Caucasian control group. This increase should be considered when making rosuvastatin dosing decisions for Asian patients. (See WARNINGS, Myopathy/Rhabdomyolysis; CLINICAL PHARMACOLOGY, Special Populations, Race, and DOSAGE AND ADMINISTRATION). **Information for Patients:** Patients should be advised to report promptly unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever. When taking rosuvastatin with an aluminum and magnesium hydroxide combination antacid, the antacid should be taken at least 2 hours after rosuvastatin administration (see CLINICAL PHARMACOLOGY, Drug Interactions). **Laboratory Tests:** In the rosuvastatin clinical trial program, dipstick-positive proteinuria and microscopic hematuria were observed among rosuvastatin-treated patients, predominantly in patients dosed above the recommended dose range (i.e., 80 mg). However, this finding was more frequent in patients taking rosuvastatin 40 mg, when compared to lower doses of rosuvastatin or comparator statins, though it was generally transient and was not associated with worsening renal function. Although the clinical significance of this finding is unknown, a dose reduction should be considered for patients on rosuvastatin 40 mg therapy with unexplained persistent proteinuria during routine urinalysis testing. **Drug Interactions:** **Cyclosporine:** When rosuvastatin 10 mg was coadministered with cyclosporine in cardiac-transplant patients, rosuvastatin mean  $C_{max}$  and mean AUC were increased 11-fold and 7-fold, respectively,

compared with healthy volunteers. These increases are considered to be clinically significant and require special consideration in the dosing of rosuvastatin to patients taking concomitant cyclosporine (see WARNINGS, Myopathy/Rhabdomyolysis; and DOSAGE AND ADMINISTRATION). **Warfarin:** Coadministration of rosuvastatin to patients on stable warfarin therapy resulted in clinically significant rises in INR (>4, baseline 2-3). In patients taking coumatin anticoagulants and rosuvastatin concomitantly, INR should be determined before starting rosuvastatin and frequently enough during early therapy to ensure that no significant alteration of INR occurs. Once a stable INR has been documented, INR can be monitored at the intervals usually recommended for patients on coumatin anticoagulants. If the dose of rosuvastatin is changed, the same procedure should be repeated. Rosuvastatin therapy has not been associated with bleeding or with changes in INR in patients not taking anticoagulants. **Gemfibrozil:** Coadministration of a single rosuvastatin dose to healthy volunteers on gemfibrozil (600 mg twice daily) resulted in a 2.2- and 1.9-fold, respectively, increase in mean  $C_{max}$  and mean AUC of rosuvastatin (see DOSAGE AND ADMINISTRATION). **Endocrine Function:** Although clinical studies have shown that rosuvastatin alone does not reduce basal plasma cortisol concentration or impair adrenal reserve, caution should be exercised if any HMG-CoA reductase inhibitor or other agent used to lower cholesterol levels is administered concomitantly with drugs that may decrease the levels or activity of endogenous steroid hormones such as testosterone, spiroprolactone, and clobetasol. **CNS Toxicity:** CNS vascular lesions, characterized by perivascular hemorrhages, edema, and mononuclear cell infiltration of perivascular spaces, have been observed in dogs treated with several other members of this drug class. A chemically similar drug in this class produced dose-dependent optic nerve degeneration (Wallerian degeneration of retinoganglionic fibers) in dogs, at a dose that produced plasma drug levels about 30 times higher than the mean drug level in humans taking the highest recommended dose. Edema, hemorrhage, and partial necrosis in the interstitium of the choroid plexus was observed in a female dog sacrificed moribund at day 24 at 80 mg/kg/day by oral gavage (systemic exposures 100 times the human exposure at 40 mg/day based on AUC comparisons). Corneal opacity was seen in dogs treated for 52 weeks at 6 mg/kg/day by oral gavage (systemic exposures 20 times the human exposure at 40 mg/day based on AUC comparisons). Cataracts were seen in dogs treated for 12 weeks by oral gavage at 30 mg/kg/day (systemic exposures 60

times the human exposure at 40 mg/day based on AUC comparisons). Retinal dysplasia and retinal loss were seen in dogs treated for 4 weeks by oral gavage at 90 mg/kg/day (systemic exposures 100 times the human exposure at 40 mg/day based on AUC). Doses  $\leq 30$  mg/kg/day (systemic exposures  $\leq 60$  times the human exposure at 40 mg/day based on AUC comparisons) following treatment up to one year, did not reveal retinal findings. **Carcinogenesis, Mutagenesis, Impairment of Fertility:** In a 104-week carcinogenicity study in rats at dose levels of 2, 20, 60, or 80 mg/kg/day by oral gavage, the incidence of uterine stromal polyps was significantly increased in females at 80 mg/kg/day at systemic exposure 20 times the human exposure at 40 mg/day based on AUC. Increased incidence of polyps was not seen at lower doses. In a 107-week carcinogenicity study in mice given 10, 60, 200 mg/kg/day by oral gavage, an increased incidence of hepatocellular adenoma/carcinoma was observed at 200 mg/kg/day at systemic exposures 20 times human exposure at 40 mg/day based on AUC. An increased incidence of hepatocellular tumors was not seen at lower doses. Rosuvastatin was not mutagenic or clastogenic with or without metabolic activation in the Ames test with *Salmonella typhimurium* and *Escherichia coli*, the mouse lymphoma assay, and the chromosomal aberration assay in Chinese hamster lung cells. Rosuvastatin was negative in the *in vivo* micronucleus test. In rat fertility studies with oral gavage doses of 5, 15, 50 mg/kg/day, males were treated for 9 weeks prior to and throughout mating and females were treated 2 weeks prior to mating and throughout mating until gestation day 7. No adverse effect on fertility was observed at 50 mg/kg/day (systemic exposures up to 10 times human exposure at 40 mg/day based on AUC comparisons). In testicles of dogs treated with rosuvastatin at 30 mg/kg/day for one month, spermatid giant cells were seen. Spermatid giant cells were observed in monkeys after 6-month treatment at 30 mg/kg/day in addition to vacuolization of seminiferous tubular epithelium. Exposures in the dog were 20 times and in the monkey 10 times human exposure at 40 mg/day based on body surface area comparisons. Similar findings have been seen with other drugs in this class. **Pregnancy:** **Pregnancy Category X** (See CONTRAINDICATIONS). Rosuvastatin may cause fetal harm when administered to a pregnant woman. Rosuvastatin is contraindicated in women who are or may become pregnant. Safety in pregnant women has not been established. There are no adequate and well-controlled studies of rosuvastatin in pregnant women. Rosuvastatin crosses the placenta and is found in fetal tissue and amniotic fluid at 3% and 20%, respectively, of the maternal plasma concentration following a single 25 mg/kg oral gavage dose on gestation day 15 in rats. A higher fetal tissue distribution (25% maternal plasma concentration) was observed in rabbits after a single oral gavage dose of 1 mg/kg on gestation day 18. If a drug is administered to a woman with reproductive potential, the patient should be apprised of the potential hazard to a fetus. In female rats given oral gavage doses of 5, 15, 50 mg/kg/day rosuvastatin before mating and continuing through day 7 postpartum results in decreased fetal body weight (female pups) and delayed ossification at the high dose (systemic exposures 10 times human exposure at 40 mg/day based on AUC comparisons). In pregnant rats given oral gavage doses of 2, 20, 50 mg/kg/day from gestation day 7 through lactation day 21 (weaning), decreased pup survival occurred in groups given 50 mg/kg/day, systemic exposures  $\geq 12$  times human exposure at 40 mg/day based on body surface area comparisons. In pregnant rabbits given oral gavage doses of 0.3, 1, 3 mg/kg/day from gestation day 6 to lactation day 18 (weaning), exposures equivalent to human exposure at 40 mg/day based on body surface area comparisons; decreased fetal viability and maternal mortality was observed. Rosuvastatin was not teratogenic in rats at  $\leq 25$  mg/kg/day or in rabbits  $\leq 3$  mg/kg/day (systemic exposures equivalent to human exposure at 40 mg/day based on AUC or body surface area comparison, respectively). **Nursing Mothers:** It is not known whether rosuvastatin is excreted in human milk. Studies in lactating rats have demonstrated that rosuvastatin is secreted into breast milk at levels 3 times higher than that obtained in the plasma following oral gavage dosing. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from rosuvastatin, a decision should be made whether to discontinue nursing or administration of rosuvastatin taking into account the importance of the drug to the lactating woman. **Pediatric Use:** The safety and effectiveness in pediatric patients have not been established. Treatment experience with rosuvastatin in a pediatric population is limited to 8 patients with homozygous FH. None of these patients were  $\geq 12$  years of age. **Geriatric Use:** Of the 10,275 patients in clinical studies with rosuvastatin, 3,159 (31%) were 65 years and older, and 696 (6.8%) were 75 years and older. The overall frequency of adverse events and types of adverse events were similar in patients above and below 65 years of age. (See WARNINGS, Myopathy/Rhabdomyolysis.) The efficacy of rosuvastatin in the geriatric population ( $\geq 65$  years of age) was comparable to the efficacy observed in the non-elderly.



**ADVERSE REACTIONS:** Rosuvastatin is generally well tolerated. Adverse reactions have usually been mild and transient. In clinical studies of 10,275 patients, 3.7% were discontinued due to adverse experiences attributable to rosuvastatin. The most frequent adverse events thought to be related to rosuvastatin were myalgia, constipation, asthenia, abdominal pain, and nausea. **Clinical Adverse Experiences:** Adverse experiences, regardless of causality assessment, reported in  $\geq 2\%$  of patients in placebo-controlled clinical studies of rosuvastatin are shown in Table 1; discontinuations due to adverse events in these studies of up to 12 weeks duration occurred in 3% of patients on rosuvastatin and 5% on placebo.

Table 1. Adverse Events in Placebo-Controlled Studies

Adverse event	Rosuvastatin N=744	Placebo N=382
Pharyngitis	9.0	7.6
Headache	5.5	5.0
Diarrhea	3.4	2.9
Dyspepsia	3.4	3.1
Nausea	3.4	3.1
Myalgia	2.8	1.3
Asthenia	2.7	2.6
Back pain	2.6	2.4
Flu syndrome	2.3	1.8
Urinary tract infection	2.3	1.6
Rhinitis	2.2	2.1
Sinusitis	2.0	1.8

In addition, the following adverse events were reported, regardless of causality assessment, in  $\geq 1\%$  of 10,275 patients treated with rosuvastatin in clinical studies. The events in italics occurred in  $\geq 2\%$  of these patients. **Body as a Whole:** Abdominal pain, accidental injury, chest pain, infection, pain, pelvic pain, and neck pain. **Cardiovascular System:** Hypertension, angina pectoris, vasodilatation, and palpitation. **Digestive System:** Constipation, gastroenteritis, vomiting, flatulence, periodontal abscess, and gastritis. **Endocrine:** Diabetes mellitus. **Hemic and Lymphatic System:** Anemia and ecchymosis. **Metabolic and Nutritional Disorders:** Peripheral edema. **Musculoskeletal System:** Arthritis, arthralgia, and pathological fracture. **Nervous System:** Dizziness, insomnia, hypertonia, paresthesia, depression, anxiety, vertigo, and neuralgia. **Respiratory System:** Bronchitis, cough increased, dyspnea, pneumonia, and asthma. **Skin and Appendages:** Rash and pruritus. **Laboratory Abnormalities:** In the rosuvastatin clinical trial program, dipstick-positive proteinuria and microscopic hematuria were observed among rosuvastatin-treated patients, predominantly in patients dosed above the recommended dose range (i.e., 80 mg). However, this finding was more frequent in patients taking rosuvastatin 40 mg, when compared to lower doses of rosuvastatin or comparator statins, though it was generally transient and was not associated with worsening renal function. (See PRECAUTIONS, Laboratory Tests.) Other abnormal laboratory values reported were elevated creatinine phosphokinase, transaminases, hyperglycemia, glutamyl transaminase, alkaline phosphatase, bilirubin, and thyroid function abnormalities. Other adverse events reported less frequently than 1% in the rosuvastatin clinical study program, regardless of causality assessment, included arrhythmia, hepatitis, hypersensitivity reactions (i.e., face edema, thrombocytopenia, leukopenia, vesiculobullous rash, urticaria, and angioedema), kidney failure, syncope, myasthenia, myositis, pancreatitis, photosensitivity reaction, myopathy, and rhabdomyolysis. **Postmarketing Experience:** In addition to the events reported above, as with other drugs in this class, the following event has been reported during post-marketing experience with CRESTOR, regardless of causality assessment: very rare cases of jaundice.

**OVERDOSAGE:** There is no specific treatment in the event of overdose. In the event of overdose, the patient should be treated symptomatically and supportive measures instituted as required. Hemodialysis does not significantly enhance clearance of rosuvastatin.

**DOSAGE AND ADMINISTRATION:** The patient should be placed on a standard cholesterol-lowering diet before receiving CRESTOR and should continue on this diet during treatment. CRESTOR can be administered as a single dose at any time of day, with or without food. **Hypercholesterolemia (Heterozygous Familial and Nonfamilial) and Mixed Dyslipidemia (Fredrickson Type IIa and IIb):** The dose range for CRESTOR is 5 to 40 mg once daily. Therapy with CRESTOR should be individualized according to goal of therapy and response. The usual recommended starting dose of CRESTOR is 10 mg once daily. However, initiation of therapy with 5 mg once daily should be considered for patients requiring less aggressive LDL-C reductions, who have predisposing factors for myopathy, and as noted below for special populations such as patients taking cyclosporine, Asian patients, and patients with severe renal insufficiency (see CLINICAL PHARMACOLOGY, Race, and Renal Insufficiency, and Drug Interactions). For patients with marked hypercholesterolemia (LDL-C  $> 190$  mg/dL) and aggressive lipid targets, a 20-mg starting dose may be considered. After initiation and/or upon titration of CRESTOR, lipid levels should be analyzed within 2 to 4 weeks and dosage adjusted accordingly. The 40-mg dose of CRESTOR is reserved only for those patients who have not achieved their LDL-C goal utilizing the 20 mg dose of CRESTOR once daily (see WARNINGS, Myopathy/Rhabdomyolysis). When initiating statin therapy or switching from another statin therapy, the appropriate CRESTOR starting dose should first be utilized, and only then titrated according to the patient's individualized goal of therapy. **Homozygous Familial Hypercholesterolemia:** The recommended starting dose of CRESTOR is 20 mg once daily in patients with homozygous FH. The maximum recommended daily dose is 40 mg. CRESTOR should be used in these patients as an adjunct to other lipid-lowering treatments (e.g., LDL apheresis) or if such treatments are unavailable. Response to therapy should be estimated from pre-apheresis LDL-C levels. **Dosage in Asian Patients:** Initiation of CRESTOR therapy with 5 mg once daily should be considered for Asian patients. The potential for increased systemic exposures relative to Caucasians is relevant when considering escalation of dose in cases where hypercholesterolemia is not adequately controlled at doses of 5, 10, or 20 mg once daily. (See WARNINGS, Myopathy/Rhabdomyolysis; CLINICAL PHARMACOLOGY, Special Populations, Race, and PRECAUTIONS, General). **Dosage in Patients Taking Cyclosporine:** In patients taking cyclosporine, therapy should be limited to CRESTOR 5 mg once daily (see WARNINGS, Myopathy/Rhabdomyolysis, and PRECAUTIONS, Drug Interactions). **Concomitant Lipid-Lowering Therapy:** The effect of CRESTOR on LDL-C and total-C may be enhanced when used in combination with a bile acid binding resin. If CRESTOR is used in combination with gemfibrozil, the dose of CRESTOR should be limited to 10 mg once daily (see WARNINGS, Myopathy/Rhabdomyolysis, and PRECAUTIONS, Drug Interactions). **Dosage in Patients With Renal Insufficiency:** No modification of dosage is necessary for patients with mild to moderate renal insufficiency. For patients with severe renal impairment ( $Cl_{CR} < 30$  mL/min/1.73 m<sup>2</sup>) not on hemodialysis, dosing of CRESTOR should be started at 5 mg once daily and not to exceed 10 mg once daily (see PRECAUTIONS, General, and CLINICAL PHARMACOLOGY, Special Populations, Renal Insufficiency).

**NOTE:** This summary provides important information about CRESTOR. For more information, please ask your doctor or health care professional about the full Prescribing Information and discuss it with them.

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# A POWERFUL SSRI that's well tolerated

#**1**  
PRESCRIBED  
**SRI**  
BY PSYCHIATRISTS

For **DEPRESSION**  
and **ANXIETY**

**UP TO 90%** of depressed patients  
present with symptoms of anxiety<sup>2</sup>

**PROVEN EFFICACY** for Major Depressive Disorder  
and Generalized Anxiety Disorder<sup>3</sup>

**Lexapro**  
escitalopram oxalate   
**POWER TO ENJOY LIFE™**

**IMPORTANT SAFETY INFORMATION** – Depression is a serious condition that can lead to suicidal thoughts and behavior. Antidepressants increased the risk of suicidal thinking and behavior (2% to 4%) in short-term studies of 9 antidepressant drugs in children and adolescents with major depressive disorder (MDD) and other psychiatric disorders. Patients started on therapy should be observed closely for clinical worsening, suicidality, or unusual changes in behavior, especially at the beginning of therapy or at the time of dose changes. This risk may persist until significant remission occurs. Families and caregivers should be advised of the need for close observation and communication with the prescriber. **Lexapro is not approved for use in pediatric patients.**

Lexapro is contraindicated in patients taking monoamine oxidase inhibitors (MAOIs), pimozone (see DRUG INTERACTIONS – Pimozone and Celexa), or in patients with hypersensitivity to escitalopram oxalate. As with other SSRIs, caution is indicated in the coadministration of tricyclic antidepressants (TCAs) with Lexapro. As with other psychotropic drugs that interfere with serotonin reuptake, patients should be cautioned regarding the risk of bleeding associated with the concomitant use of Lexapro with NSAIDs, aspirin, or other drugs that affect coagulation. The most common adverse events with Lexapro versus placebo (approximately 5% or greater and approximately 2x placebo) were nausea, insomnia, ejaculation disorder, somnolence, increased sweating, fatigue, decreased libido, and anorgasmia.

**References:** 1. IMS National Prescription Audit. May 2005. 2. Sadock BJ, Sadock VA. *Kaplan and Sadock's Synopsis of Psychiatry: Behavioral Sciences/Clinical Psychiatry*. 9th ed. Philadelphia, Pa: Lippincott Williams & Wilkins; 2003:552. 3. LEXAPRO [package insert]. St Louis, Mo: Forest Pharmaceuticals, Inc.; 2006.

Please see brief summary of prescribing information for LEXAPRO on following page.

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 **Benicar**<sup>®</sup>  
(olmesartan medoxomil)

 **Benicar HCT**<sup>®</sup>  
(olmesartan medoxomil • hydrochlorothiazide)

160/110

150/100

140/90

130/85

**USE IN PREGNANCY**

When used in pregnancy during the second and third trimesters, drugs that act directly on the renin-angiotensin system can cause injury and even death to the developing fetus. When pregnancy is detected, BENICAR or BENICAR HCT should be discontinued as soon as possible. See **WARNINGS, Fetal/Neonatal Morbidity and Mortality** in the prescribing information.

BENICAR and BENICAR HCT are indicated for the treatment of hypertension. They may be used alone or in combination with other antihypertensive agents. BENICAR HCT is not indicated for initial therapy.

**Please see following page for important safety information.**

Please see brief summary of prescribing information for BENICAR and BENICAR HCT.

**References:** 1. Data representing May 2002-May 2006 from IMS Health, National Prescription Audit, May 2006. 2. Based on NRx volume for the first 30 months following the launch of the respective ARB from IMS Health, National Prescription Audit, December 2005.



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Although any chloride deficit is generally mild and usually does not require specific treatment except under extraordinary circumstances (as in liver disease or renal disease), chloride replacement may be required in the treatment of metabolic alkalosis.

Dilutional hyponatremia may occur in edematous patients in hot weather; appropriate therapy is water restriction, rather than administration of salt except in rare instances when the hyponatremia is life-threatening. In actual salt depletion, appropriate replacement is the therapy of choice.

Hyperuricemia may occur or frank gout may be precipitated in certain patients receiving thiazide therapy.

In diabetic patients dosage adjustments of insulin or oral hypoglycemic agents may be required. Hypoglycemia may occur with thiazide diuretics. Thus latent diabetes mellitus may become manifest during thiazide therapy.

The antihypertensive effects of the drug may be enhanced in the post-sympathectomy patient.

If progressive renal impairment becomes evident consider withholding or discontinuing diuretic therapy.

Thiazides have been shown to increase the urinary excretion of magnesium; this may result in hypomagnesemia.

Thiazides may decrease urinary calcium excretion. Thiazides may cause intermittent and slight elevation of serum calcium in the absence of known disorders of calcium metabolism. Marked hypercalcemia may be evidence of hyperparathyroidism. Thiazides should be discontinued before carrying out tests for parathyroid function.

Increases in cholesterol and triglyceride levels may be associated with thiazide diuretic therapy.

**Impaired Renal Function**

As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals treated with olmesartan medoxomil. In patients whose renal function may depend upon the activity of the renin-angiotensin-aldosterone system (e.g., patients with severe congestive heart failure), treatment with angiotensin converting enzyme inhibitors and angiotensin receptor antagonists has been associated with oliguria and/or progressive azotemia and (rarely) with acute renal failure and/or death. Similar results may be anticipated in patients treated with olmesartan medoxomil. (See **CLINICAL PHARMACOLOGY, Special Populations** in the full prescribing information.)

In studies of ACE inhibitors in patients with unilateral or bilateral renal artery stenosis, increases in serum creatinine or blood urea nitrogen (BUN) have been reported. There has been no long-term use of olmesartan medoxomil in patients with unilateral or bilateral renal artery stenosis, but similar results may be expected.

Thiazides should be used with caution in severe renal disease. In patients with renal disease, thiazides may precipitate azotemia. Cumulative effects of the drug may develop in patients with impaired renal function.

**Information for Patients**

**Pregnancy:** Female patients of childbearing age should be told about the consequences of second and third trimester exposure to drugs that act on the renin-angiotensin system and they should be told also that these consequences do not appear to have resulted from intrauterine drug exposure that has been limited to the first trimester. These patients should be asked to report pregnancies to their physicians as soon as possible.

**Symptomatic Hypotension:** A patient receiving BENICAR HCT® should be cautioned that light-headedness can occur, especially during the first days of therapy, and that it should be reported to the prescribing physician. The patients should be told that if syncope occurs, BENICAR HCT® should be discontinued until the physician has been consulted.

All patients should be cautioned that inadequate fluid intake, excessive perspiration, diarrhea or vomiting can lead to an excessive fall in blood pressure, with the same consequences of light-headedness and possible syncope.

**Drug Interactions**

**Olfmesartan medoxomil**  
No significant drug interactions were reported in studies in which olmesartan medoxomil was administered with hydrochlorothiazide, digoxin or warfarin in healthy volunteers. The bioavailability of olmesartan was not significantly altered by the co-administration of antacids [Al(OH)<sub>3</sub>/Mg(OH)<sub>2</sub>]. Olmesartan medoxomil is not metabolized by the cytochrome P450 system and has no effects on P450 enzymes; thus, interactions with drugs that inhibit, induce or are metabolized by those enzymes are not expected.

**Hydrochlorothiazide**

When administered concurrently the following drugs may interact with thiazide diuretics:

**Alcohol, Barbiturates, Or Narcotics** – potentiation of orthostatic hypotension may occur.

**Antidiabetic Drugs (oral agents and insulin)** – dosage adjustment of the anti-diabetic drug may be required.

**Other Antihypertensive Drugs** – additive effect or potentiation.

**Cholestyramine and Colestipol Resins** – absorption of hydrochlorothiazide is impaired in the presence of anionic exchange resins. Single doses of either cholestyramine or colestipol resins bind the hydrochlorothiazide and reduce its absorption from the gastrointestinal tract by up to 85 and 43 percent, respectively.

**Corticosteroids, ACTH** – intensified electrolyte depletion, particularly hypokalemia.

**Pressor Amines (e.g., Norepinephrine)** – possible decreased response to pressor amines but not sufficient to preclude their use.

**Skeletal Muscle Relaxants, Non depolarizing (e.g., Tubocurarine)** – possible increased responsiveness to the muscle relaxant.

**Lithium** – should not generally be given with diuretics. Diuretic agents reduce the renal clearance of lithium and add a high risk of lithium toxicity. Refer to the package insert for lithium preparations before use of such preparation with olmesartan medoxomil-hydrochlorothiazide.

**Non-steroidal Anti-inflammatory Drugs** – in some patients the administration of a non-steroidal anti-inflammatory agent can reduce the diuretic, natriuretic and anti-hypertensive effects of loop, potassium-sparing and thiazide diuretics. Therefore, when olmesartan medoxomil-hydrochlorothiazide tablets and non-steroidal anti-inflammatory agents are used concomitantly, the patients should be observed closely to determine if the desired effect of the diuretic is obtained.

**Carcinogenesis, Mutagenesis, Impairment of Fertility**

**Olfmesartan medoxomil-hydrochlorothiazide**  
No carcinogenicity studies with olmesartan medoxomil-hydrochlorothiazide have been conducted.

Olmesartan medoxomil-hydrochlorothiazide in a ratio of 20:12.5 was negative in the *Salmonella-Escherichia coli* mammalian chromosome reversion mutation test up to the maximum recommended plate concentration for the standard assays. Olmesartan medoxomil and hydrochlorothiazide were tested individually and in combination ratios of 40:12.5, 20:12.5 and 10:12.5, for clastogenic activity in the *in vitro* Chinese hamster lung (CHL) chromosomal aberration assay. A positive response was seen for each component and combination ratio. However, no synergism in clastogenic activity was detected between olmesartan medoxomil and hydrochlorothiazide in any combination ratio. Olmesartan medoxomil-hydrochlorothiazide in a ratio of 20:12.5, administered orally, tested negative in the *in vivo* mouse bone marrow erythrocyte micronucleus assay at administered doses of up to 3144 mg/kg.

No studies of impairment of fertility with olmesartan medoxomil-hydrochlorothiazide have been conducted.

**Olfmesartan medoxomil**

Olmesartan medoxomil was not carcinogenic when administered by dietary administration to rats for up to 2 years. The highest dose tested (2000 mg/kg/day) was, on a mg/m<sup>2</sup> basis, about 480 times the maximum recommended human dose (MRHD) of 40 mg/day. Two carcinogenicity studies conducted in mice, a 6-month gavage study in the p53 knockout mouse and a 6-month dietary

administration study in the Hras2 transgenic mouse, at doses of up to 1000 mg/kg/day (about 120 times the MRHD), revealed no evidence of a carcinogenic effect of olmesartan medoxomil.

Both olmesartan medoxomil and olmesartan tested negative in the *in vitro* Syrian hamster embryo cell transformation assay and showed no evidence of genetic toxicity in the Ames (bacterial mutagenicity) test. However, both were shown to induce chromosomal aberrations in cultured cells *in vitro* (Chinese hamster lung) and both tested positive for thymidine kinase mutations in the *in vitro* mouse lymphoma assay. Olmesartan medoxomil tested negative *in vivo* for mutations in the *Muta* Mouse intestine and kidney, and for clastogenicity in mouse bone marrow (micronucleus test) at oral doses of up to 2000 mg/kg (olmesartan not tested). Fertility of rats was unaffected by administration of olmesartan medoxomil at dose levels as high as 1000 mg/kg/day (240 times the MRHD) in a study in which dosing was begun 2 (female) or 9 (male) weeks prior to mating.

**Hydrochlorothiazide**

Two-year feeding studies in mice and rats conducted under the auspices of the National Toxicology Program (NTP) uncovered no evidence of a carcinogenic potential of hydrochlorothiazide in female mice (at doses of up to approximately 600 mg/kg/day) or in male and female rats (at doses of up to approximately 100 mg/kg/day). The NTP, however, found equivocal evidence for hepatocarcinogenicity in male mice.

Hydrochlorothiazide was not genotoxic *in vitro* in the Ames mutagenicity assay of *Salmonella typhimurium* strains TA 98, TA 100, TA 1535, TA 1537 and TA 1538, or in the Chinese Hamster Ovary (CHO) test for chromosomal aberrations. It was also not genotoxic *in vivo* in assays using mouse germinal cell chromosomes, Chinese hamster bone marrow chromosomes, or the *Drosophila* sex-linked recessive lethal trait gene. Positive test results were obtained in the *in vitro* CHO Sister Chromatid Exchange (clastogenicity) assay, the Mouse Lymphoma Cell (mutagenicity) assay and the *Aspergillus nidulans* non-disjunction assay.

Hydrochlorothiazide had no adverse effects on the fertility of mice and rats of either sex in studies wherein these species were exposed, via their diet, to doses of up to 100 and 4 mg/kg, respectively, prior to mating and throughout gestation.

**Pregnancy**

Pregnancy Categories C (first trimester) and D (second and third trimesters) (See **WARNINGS: Fetal/Neonatal Morbidity and Mortality**.)

**Nursing Mothers**

It is not known whether olmesartan is excreted in human milk, but olmesartan is secreted at low concentration 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 nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Thiazides appear in human milk. Because of the potential for adverse effects on the nursing infant, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

**Pediatric Use**

Safety and effectiveness in pediatric patients have not been established.

**Geriatric Use**

Clinical studies of BENICAR HCT® did not include sufficient numbers of subjects aged 65 and over 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 an elderly patient 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 diseases or other drug therapy.

Olmesartan and hydrochlorothiazide are substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function.

**ADVERSE REACTIONS**

**Olfmesartan medoxomil-hydrochlorothiazide**

Olmesartan medoxomil-hydrochlorothiazide has been evaluated for safety in 1243 hypertensive patients. Treatment with olmesartan medoxomil-hydrochlorothiazide was well tolerated, with an incidence of adverse events similar to placebo. Events generally were mild, transient and had no relationship to the dose of olmesartan medoxomil-hydrochlorothiazide.

In the clinical trials, the overall frequency of adverse events was not dose-related. Analysis of gender, age and race groups demonstrated no differences between olmesartan medoxomil-hydrochlorothiazide and placebo-treated patients. The rate of withdrawals due to adverse events in all trials of hypertensive patients was 2.0% (25/1243) of patients treated with olmesartan medoxomil-hydrochlorothiazide and 2.0% (7/342) of patients treated with placebo.

In a placebo-controlled clinical trial, the following adverse events reported with olmesartan medoxomil-hydrochlorothiazide occurred in >2% of patients, and more often on the olmesartan medoxomil-hydrochlorothiazide combination than on placebo, regardless of drug relationship:

	Olfmesartan/ HCT (N=247) (%)	Placebo (N=42) (%)	Olfmesartan (N=125) (%)	HCT (N=88) (%)
<b>Gastrointestinal</b>				
Nausea	3	0	2	1
<b>Metabolic</b>				
Hyperuricemia	4	2	0	2
<b>Nervous System</b>				
Dizziness	9	2	1	8
<b>Respiratory</b>				
Upper Respiratory Tract Infection	7	0	6	7

The following adverse events were also reported at a rate of >2%, but were as, or more, common in the placebo group: headache and urinary tract infection.

Other adverse events that have been reported with an incidence of greater than 1.0%, whether or not attributed to treatment, the more than 1200 hypertensive patients treated with olmesartan medoxomil-hydrochlorothiazide in controlled or open-label trials are listed below.

**Body as a Whole:** chest pain, back pain, peripheral edema  
**Central and Peripheral Nervous System:** vertigo  
**Gastrointestinal:** abdominal pain, dyspepsia, gastroenteritis, diarrhea  
**Liver and Biliary System:** SGOT increased, GGT increased, SGPT increased  
**Metabolic and Nutritional:** hyperlipemia, creatine phosphokinase increased, hyperglycemia  
**Musculoskeletal:** arthritis, arthralgia, myalgia  
**Respiratory System:** coughing  
**Skin and Appendages Disorders:** rash  
**Urinary System:** hematuria

Facial edema was reported in 2/1243 patients receiving olmesartan medoxomil-hydrochlorothiazide. Angioedema has been reported with angiotensin II receptor antagonists.

**Olfmesartan medoxomil**

Other adverse events that have been reported with an incidence of greater than 0.5%, whether or not attributed to treatment, in more than 3100 hypertensive patients treated with olmesartan medoxomil monotherapy in controlled or open-label trials are tachycardia and hypercholesterolemia.

**Hydrochlorothiazide**

Other adverse experiences that have been reported with hydrochlorothiazide, without regard to causality, are listed below:

**Body as a Whole: weakness**

**Digestive:** pancreatitis, jaundice (intrahepatic cholestatic jaundice), sialadenitis, cramping, gastric irritation

**Hematologic:** aplastic anemia, agranulocytosis, leukopenia, hemolytic anemia, thrombocytopenia

**Hypersensitivity:** purpura, photosensitivity, urticaria, necrotizing angitis (vasculitis and cutaneous vasculitis), fever, respiratory distress including pneumonitis and pulmonary edema, anaphylactic reactions

**Metabolic:** hyperglycemia, glycosuria, hyperuricemia

**Musculoskeletal:** muscle spasm

**Nervous System/Psychiatric:** restlessness

**Renal:** renal failure, renal dysfunction, interstitial nephritis

**Skin:** erythema multiforme including Stevens-Johnson syndrome, exfoliative dermatitis including toxic epidermal necrolysis

**Special Senses:** transient blurred vision, xanthopsia

**Laboratory Test Findings**

In controlled clinical trials, clinically important changes in standard laboratory parameters were rarely associated with administration of olmesartan medoxomil-hydrochlorothiazide.

**Creatinine, Blood Urea Nitrogen:** Increases in blood urea nitrogen (BUN) and serum creatinine of >50% were observed in 1.3% of patients. No patients were discontinued from clinical trials of olmesartan medoxomil-hydrochlorothiazide due to increased BUN or creatinine.

**Hemoglobin and Hematocrit:** A greater than 20% decrease in hemoglobin and hematocrit was observed in 0.0% and 0.4% (one patient), respectively, of olmesartan medoxomil-hydrochlorothiazide patients, compared with 0.0% and 0.0%, respectively, in placebo-treated patients. No patients were discontinued due to anemia.

**Post-Marketing Experience:** The following adverse reactions have been reported in post-marketing experience:

**Body as a Whole:** Asthenia, angioedema

**Gastrointestinal:** Vomiting

**Musculoskeletal:** Rhabdomyolysis

**Urinary System:** Acute renal failure, increased blood creatinine levels

**Skin and Appendages:** Alopecia, pruritus, urticaria

**OVERDOSAGE**

**Olfmesartan medoxomil**

Limited data are available related to overdosage in humans. The most likely manifestations of overdosage may be hypotension and tachycardia; bradycardia could be encountered if parasympathetic (vagal) stimulation occurs. If symptomatic hypotension should occur, supportive treatment should be initiated. The dialyzability of olmesartan is unknown.

No lethality was observed in acute toxicity studies in mice and rats given single oral doses up to 2000 mg/kg olmesartan medoxomil. The minimum lethal oral dose of olmesartan medoxomil in dogs was greater than 1500 mg/kg.

**Hydrochlorothiazide**

The most common signs and symptoms of overdose observed in humans are those caused by electrolyte depletion (hypokalemia, hypochloremia, hyponatremia) and dehydration resulting from excessive diuresis. If digitalis has also been administered, hypokalemia may accentuate cardiac arrhythmias. The degree to which hydrochlorothiazide is removed by hemodialysis has not been established. The oral LD<sub>50</sub> of hydrochlorothiazide is greater than 10 g/kg in both mice and rats.

**DOSEAGE AND ADMINISTRATION**

The usual recommended starting dose of BENICAR® (olmesartan medoxomil) is 20 mg once daily when used as monotherapy in patients who are not volume-contracted. For patients requiring further reduction in blood pressure after 2 weeks of therapy, the dose may be increased to 40 mg. Doses above 40 mg do not appear to have greater effect. Twice-daily dosing offers no advantage over the same total dose given once daily.

No initial dosage adjustment is recommended for elderly patients, for patients with moderate to marked renal impairment (creatinine clearance <40 mL/min) or with moderate to marked hepatic dysfunction (see **CLINICAL PHARMACOLOGY, Special Populations** in the full prescribing information). For patients with possible depletion of intravascular volume (e.g., patients treated with diuretics, particularly those with impaired renal function), BENICAR® should be initiated under close medical supervision and consideration should be given to use of a lower starting dose (see **WARNINGS, Hypotension in Volume- or Salt-Depleted Patients**).

Hydrochlorothiazide is effective in doses between 12.5 mg and 50 mg once daily. The side effects (see **WARNINGS**) of BENICAR® are generally rare and independent of dose; those of hydrochlorothiazide are most typically dose-dependent (primarily hypokalemia). Some dose-independent phenomena (e.g., pancreatitis) do occur with hydrochlorothiazide. Therapy with any combination of olmesartan medoxomil and hydrochlorothiazide will be associated with both sets of dose-independent side effects.

To minimize dose-independent side effects, it is usually appropriate to begin combination therapy only after a patient has failed to achieve the desired effect with monotherapy.

**Replacement Therapy**

BENICAR HCT® (olmesartan medoxomil-hydrochlorothiazide) may be substituted for its titrated components.

**Dose Titration by Clinical Effect**

BENICAR HCT® is available in strengths of 20 mg/12.5 mg, 40 mg/12.5 mg and 40 mg/25 mg. A patient whose blood pressure is inadequately controlled by BENICAR® or hydrochlorothiazide alone may be switched to once daily BENICAR HCT® (olmesartan medoxomil-hydrochlorothiazide).

Dosing should be individualized. Depending on the blood pressure response, the dose may be titrated at intervals of 2-4 weeks.

If blood pressure is not controlled by BENICAR® alone, hydrochlorothiazide may be added starting with a dose of 12.5 mg and later titrated to 25 mg once daily.

If a patient is taking hydrochlorothiazide, BENICAR® may be added starting with a dose of 20 mg once daily and titrated to 40 mg, for inadequate blood pressure control. If large doses of hydrochlorothiazide have been used as monotherapy and volume depletion or hyponatremia is present, caution should be used when adding BENICAR® or switching to BENICAR HCT® as marked decreases in blood pressure may occur (see **WARNINGS, Hypotension in Volume- or Salt-Depleted Patients**). Consideration should be given to reducing the dose of hydrochlorothiazide to 12.5 mg before adding BENICAR®.

The antihypertensive effect of BENICAR HCT® is related to the dose of both components over the range of 10 mg/12.5 mg to 40 mg/25 mg (see **CLINICAL PHARMACOLOGY, Clinical Trials** in the full prescribing information). The dose of BENICAR HCT® is one tablet once daily. More than one tablet daily is not recommended.

BENICAR HCT® may be administered with other antihypertensive agents.

**Patients with Renal Impairment**

The usual regimens of therapy with BENICAR HCT® may be followed provided the patient's creatinine clearance is >30 mL/min. In patients with more severe renal impairment, loop diuretics are preferred to thiazides, so BENICAR HCT® is not recommended.

**Patients with Hepatic Impairment**

No dosage adjustment is necessary with hepatic impairment (see **CLINICAL PHARMACOLOGY, Special Populations** in the full prescribing information).

Manufactured for Sankyo Pharma Inc., Parsippany, NJ 07054

**Rx Only**

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# MASTER THE FINE ART OF SLEEP

PRESCRIBE LUNESTA  
FIRST-LINE—FOR A FULL  
7 TO 8 HOURS OF SLEEP

LUNESTA has been studied in large, well-controlled clinical trials in all of the following patient types:

- Patients With Insomnia Comorbid With Major Depressive Disorder
- Patients With Insomnia Comorbid With Generalized Anxiety Disorder
- Patients With Insomnia Comorbid With Rheumatoid Arthritis
- Patients With Insomnia Comorbid With Menopause

The failure of insomnia to remit after 7 to 10 days of treatment should be medically evaluated.

LUNESTA is indicated for the treatment of insomnia in controlled outpatient and sleep laboratory studies. LUNESTA is indicated for nocturnal decrease in sleep latency and improved sleep maintenance. LUNESTA is not indicated for the treatment of depression, generalized anxiety disorder, rheumatoid arthritis, or menopause.

### Important Safety Information

LUNESTA, like other hypnotics, has CNS depressant effects. Because of the rapid onset of action, LUNESTA should only be ingested immediately prior to going to bed, or after the patient has gone to bed and has experienced difficulty falling asleep. Patients should not take LUNESTA unless they are prepared to not do things that require alertness. As with other hypnotics, patients receiving LUNESTA should be cautioned against engaging in hazardous occupations requiring complete mental alertness or motor coordination, and operating machinery, or driving a motor vehicle, or other activities that may be impaired by impairment of the performance of such activities that may occur the day following ingestion of LUNESTA. In clinical trials, the most common adverse events associated with LUNESTA were drowsiness and headache, which were mild to moderate in severity.

LUNESTA has been classified as a Schedule IV controlled substance. Sedative hypnotics have potential for abuse, which may increase with duration of use. The abuse potential of LUNESTA is less than that of Schedule I, II, or III controlled substances. However, the abuse potential of LUNESTA is greater than that of Schedule IV controlled substances. Sedative hypnotics have also been associated with the development of tolerance and dependence. Withdrawal symptoms may be observed if a patient discontinues use of LUNESTA abruptly. Patients should be advised to avoid alcohol consumption while taking LUNESTA. Patients should be advised to avoid grapefruit juice consumption while taking LUNESTA. Patients should be advised to avoid driving a motor vehicle or operating machinery while taking LUNESTA.

LUNESTA, like other hypnotics, may interact with CNS depressants that cause respiratory depression, hypotension, circulatory depression, and other effects that may be additive. CNS depression. LUNESTA should not be taken with alcohol. The drug should not be taken with other CNS depressants. LUNESTA is contraindicated in patients with acute angle-closure glaucoma.

In patients treated with a sedative hypnotic, performance after repeated exposure may be impaired, but this impairment is usually reversible. Patients should be advised to avoid driving a motor vehicle or operating machinery while taking LUNESTA.

Please see brief summary of complete prescribing information.

Any night is your night.

Leave the rest to...

**Lunesta**  
(eszopiclone)  
1, 2 AND 3 MG TABLETS

**BRIEF SUMMARY**

**INDICATIONS AND USAGE**

LUNESTA is indicated for the treatment of insomnia. In controlled outpatient and sleep laboratory studies, LUNESTA administered at bedtime decreased sleep latency and improved sleep maintenance.

**CONTRAINDICATIONS**

None known.

**WARNINGS**

Because sleep disturbances may be the presenting manifestation of a physical and/or psychiatric disorder, symptomatic treatment of insomnia should be initiated only after a careful evaluation of the patient. The failure of insomnia to remit after 7 to 10 days of treatment may indicate the presence of a primary psychiatric and/or medical illness that should be evaluated. Worsening of insomnia or the emergence of new thinking or behavior abnormalities may be the consequence of an unrecognized psychiatric or physical disorder. Such findings have emerged during the course of treatment with sedative/hypnotics, including LUNESTA. Because some of the important adverse effects of LUNESTA appear to be dose-related, it is important to use the lowest possible effective dose, especially in the elderly (see **DOSE AND ADMINISTRATION in the Full Prescribing Information**).

A variety of abnormal thinking and behavior changes have been reported to occur in association with the use of sedative/hypnotics. Some of these changes may be characterized by decreased inhibition (e.g., aggressiveness and extroversion that seem out of character), similar to effects produced by alcohol and other CNS depressants. Other reported behavioral changes have included bizarre behavior, agitation, hallucinations, and depersonalization. Amnesia and other neuropsychiatric symptoms may occur unpredictably, in primarily depressed patients, worsening of depression, including suicidal thinking, has been reported in association with the use of sedative/hypnotics.

It can rarely be determined with certainty whether a particular instance of the abnormal behaviors listed above are drug-induced, spontaneous in origin, or a result of an underlying psychiatric or physical disorder. Nonetheless, the emergence of any new behavioral sign or symptom of concern requires careful and immediate evaluation.

Following rapid dose decrease or abrupt discontinuation of the use of sedative/hypnotics, there have been reports of signs and symptoms similar to those associated with withdrawal from other CNS-depressant drugs (see **DRUG ABUSE AND DEPENDENCE**).

LUNESTA, like other hypnotics, has CNS-depressant effects. Because of the rapid onset of action, LUNESTA should only be ingested immediately prior to going to bed or after the patient has gone to bed and has experienced difficulty falling asleep. Patients receiving LUNESTA should be cautioned against engaging in hazardous occupations requiring complete mental alertness or motor coordination (e.g., operating machinery or driving a motor vehicle) after ingesting the drug, and be cautioned about potential impairment of the performance of such activities on the day following ingestion of LUNESTA. LUNESTA, like other hypnotics, may produce additive CNS-depressant effects when coadministered with other psychotropic medications, anticonvulsants, antihistamines, ethanol, and other drugs that themselves produce CNS depression. LUNESTA should not be taken with alcohol. Dose adjustment may be necessary when LUNESTA is administered with other CNS-depressant agents, because of the potentially additive effects.

**PRECAUTIONS**

**General**

**Timing Of Drug Administration:** LUNESTA should be taken immediately before bedtime. Taking a sedative/hypnotic while still up and about may result in short-term memory impairment, hallucinations, impaired coordination, dizziness, and lightheadedness.

**Use In The Elderly And/or Debilitated Patients:** Impaired motor and/or cognitive performance after repeated exposure or unusual sensitivity to sedative/hypnotic drugs is a concern in the treatment of elderly and/or debilitated patients. The recommended starting dose of LUNESTA for these patients is 1 mg (see **DOSE AND ADMINISTRATION in the Full Prescribing Information**).

**Use In Patients With Concomitant Illness:** Clinical experience with eszopiclone in patients with concomitant illness is limited. Eszopiclone should be used with caution in patients with diseases or conditions that could affect metabolism or hemodynamic responses.

A study in healthy volunteers did not reveal respiratory-depressant effects at doses 2.5-fold higher (7 mg) than the recommended dose of eszopiclone. Caution is advised, however, if LUNESTA is prescribed to patients with compromised respiratory function.

The dose of LUNESTA should be reduced to 1 mg in patients with severe hepatic impairment, because systemic exposure is doubled in such subjects. No dose adjustment appears necessary for subjects with mild or moderate hepatic impairment. No dose adjustment appears necessary in subjects with any degree of renal impairment, since less than 10% of eszopiclone is excreted unchanged in the urine.

The dose of LUNESTA should be reduced in patients who are administered potent inhibitors of CYP3A4, such as ketoconazole, while taking LUNESTA. Downward dose adjustment is also recommended when LUNESTA is administered with agents having known CNS-depressant effects.

**Use In Patients With Depression:** Sedative/hypnotic drugs should be administered with caution to patients exhibiting signs and symptoms of depression. Suicidal tendencies may be present in such patients, and protective measures may be required. Intentional overdose is more common in this group of patients; therefore, the least amount of drug that is feasible should be prescribed for the patient at any one time.

**Information For Patients:** Patient information is printed in the complete prescribing information.

**Laboratory Tests:** There are no specific laboratory tests recommended.

**Drug Interactions**

**CNS-Active Drugs**

**Ethanol:** An additive effect on psychomotor performance was seen with coadministration of eszopiclone and ethanol 0.70 g/kg for up to 4 hours after ethanol administration.

**Paroxetine:** Coadministration of single doses of eszopiclone 3 mg and paroxetine 20 mg daily for 7 days produced no pharmacokinetic or pharmacodynamic interaction.

**Lorazepam:** Coadministration of single doses of eszopiclone 3 mg and lorazepam 2 mg did not have clinically relevant effects on the pharmacodynamics or pharmacokinetics of either drug.

**Diazepam:** Coadministration of eszopiclone 3 mg and diazepam 10 mg produced a decrease in DSSST scores. The interaction was pharmacodynamic; there was no alteration in the pharmacokinetics of either drug.

**Drugs That Inhibit CYP3A4 (Ketoconazole):** CYP3A4 is a major metabolic pathway for elimination of eszopiclone. The AUC of eszopiclone was increased 2.2-fold by coadministration of ketoconazole, a potent inhibitor of CYP3A4, 400 mg daily for 5 days.  $C_{1-2}$  and  $t_{1/2}$  were increased 1.4-fold and 1.3-fold, respectively. Other strong inhibitors of CYP3A4 (e.g., itraconazole, clarithromycin, nefazodone, troleanandomycin, ritonavir, neflavinir) would be expected to behave similarly.

**Drugs That Induce CYP3A4 (Rifampicin):** Racemic zopiclone exposure was decreased 80% by concomitant use of rifampicin, a potent inducer of CYP3A4. A similar effect would be expected with eszopiclone.

**Drugs Highly Bound To Plasma Protein:** Eszopiclone is not highly bound to plasma proteins (52-59% bound); therefore, the disposition of eszopiclone is not expected to be sensitive to alterations in protein binding. Administration of eszopiclone 3 mg to a patient taking another drug that is highly protein-bound would not be expected to cause an alteration in the free concentration of either drug.

**Drugs With A Narrow Therapeutic Index**

**Digoxin:** A single dose of eszopiclone 3 mg did not affect the pharmacokinetics of digoxin measured at steady state following dosing of 0.5 mg twice daily for one day and 0.25 mg daily for the next 6 days.

**Warfarin:** Eszopiclone 3 mg administered daily for 5 days did not affect the pharmacokinetics of (R)- or (S)-warfarin, nor were there any changes in the pharmacodynamic profile (prothrombin time) following a single 25-mg oral dose of warfarin.

**Carcinogenesis, Mutagenesis, Impairment of Fertility**

**Carcinogenesis:** In a carcinogenicity study in Sprague-Dawley rats in which eszopiclone was given by oral gavage, no increases in tumors were seen; plasma levels (AUC) of eszopiclone at the highest dose used in this study (16 mg/kg/day) are estimated to be 80 (females) and 20 (males) times those in humans receiving the maximum recommended human dose (MRHD). However, in a carcinogenicity study in

Sprague-Dawley rats in which racemic zopiclone was given in the diet, and in which plasma levels of eszopiclone were reached that were greater than those reached in the above study of eszopiclone, an increase in mammary gland adenocarcinomas in females and an increase in thyroid gland follicular cell adenomas and carcinomas in males were seen at the highest dose of 100 mg/kg/day. Plasma levels of eszopiclone at this dose are estimated to be 150 (females) and 70 (males) times those in humans receiving the MRHD. The mechanism for the increase in mammary adenocarcinomas is unknown. The increase in thyroid tumors is thought to be due to increased levels of TSH secondary to increased metabolism of circulating thyroid hormones, a mechanism that is not considered to be relevant to humans.

In a carcinogenicity study in B6C3F1 mice in which racemic zopiclone was given in the diet, an increase in pulmonary carcinomas and carcinomas plus adenomas in females and an increase in skin fibromas and sarcomas in males were seen at the highest dose of 100 mg/kg/day. Plasma levels of eszopiclone at this dose are estimated to be 8 (females) and 20 (males) times those in humans receiving the MRHD. The skin tumors were due to skin lesions induced by aggressive behavior, a mechanism that is not relevant to humans. A carcinogenicity study was also performed in which CD-1 mice were given eszopiclone at doses up to 100 mg/kg/day by oral gavage; although this study did not reach a maximum tolerated dose, and was thus inadequate for overall assessment of carcinogenic potential, no increases in either pulmonary or skin tumors were seen at doses producing plasma levels of eszopiclone estimated to be 90 times those in humans receiving the MRHD—i.e., 12 times the exposure in the racemate study.

Eszopiclone did not increase tumors in a p53 transgenic mouse bioassay at oral doses up to 300 mg/kg/day.

**Mutagenesis:** Eszopiclone was positive in the mouse lymphoma chromosomal aberration assay and produced an equivocal response in the Chinese hamster ovary cell chromosomal aberration assay. It was not mutagenic or clastogenic in the bacterial Ames gene mutation assay, in an unscheduled DNA synthesis assay, or in an *in vivo* mouse bone marrow micronucleus assay.

**(S)-N-desmethyl zopiclone,** a metabolite of eszopiclone, was positive in the Chinese hamster ovary cell and human lymphocyte chromosomal aberration assays. It was negative in the bacterial Ames mutation assay, in an *in vitro*  $\mu$ -postlabeling DNA adduct assay, and in an *in vivo* mouse bone marrow chromosomal aberration and micronucleus assay.

**Impairment Of Fertility:** Eszopiclone was given by oral gavage to male rats at doses up to 45 mg/kg/day from 4 weeks pre-mating through mating and to female rats at doses up to 180 mg/kg/day from 2 weeks pre-mating through day 7 of pregnancy. An additional study was performed in which only females were treated, up to 180 mg/kg/day. Eszopiclone decreased fertility, probably because of effects in both males and females, with no females becoming pregnant when both males and females were treated with the highest dose; the no-effect dose in both sexes was 5 mg/kg (16 times the MRHD on a mg/m<sup>2</sup> basis). Other effects included increased preimplantation loss (no-effect dose 25 mg/kg), abnormal estrus cycles (no-effect dose 25 mg/kg), and decreases in sperm number and motility and increases in morphologically abnormal sperm (no-effect dose 5 mg/kg).

**Pregnancy Category C:** Eszopiclone administered by oral gavage to pregnant rats and rabbits during the period of organogenesis showed no evidence of teratogenicity up to the highest doses tested (250 and 16 mg/kg/day in rats and rabbits, respectively; these doses are 800 and 100 times, respectively, the maximum recommended human dose [MRHD] on a mg/m<sup>2</sup> basis). In the rat, slight reductions in fetal weight and evidence of developmental delay were seen at maternally toxic doses of 125 and 150 mg/kg/day, but not at 62.5 mg/kg/day (200 times the MRHD on a mg/m<sup>2</sup> basis). Eszopiclone was also administered by oral gavage to pregnant rats throughout the pregnancy and lactation periods at doses of up to 180 mg/kg/day. Increased post-implantation loss, decreased postnatal pup weights and survival, and increased pup stunted response were seen at all doses; the lowest dose tested, 60 mg/kg/day, is 200 times the MRHD on a mg/m<sup>2</sup> basis. These doses did not produce significant maternal toxicity. Eszopiclone had no effects on other behavioral measures or reproductive function in the offspring.

There are no adequate and well-controlled studies of eszopiclone in pregnant women. Eszopiclone should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

**Labor And Delivery:** LUNESTA has no established use in labor and delivery.

**Nursing Mothers:** It is not known whether LUNESTA is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when LUNESTA is administered to a nursing woman.

**Pediatric Use:** Safety and effectiveness of eszopiclone in children below the age of 18 have not been established.

**Geriatric Use:** A total of 287 subjects in double-blind, parallel-group, placebo-controlled clinical trials who received eszopiclone were 65 to 96 years of age. The overall pattern of adverse events for elderly subjects (median age = 71 years) in 2-week studies with nighttime dosing of 2 mg eszopiclone was not different from that seen in younger adults. LUNESTA 2 mg exhibited significant reduction in sleep latency and improvement in sleep maintenance in the elderly population.

**ADVERSE REACTIONS**

The premarketing development program for LUNESTA included eszopiclone exposures in patients and/or normal subjects from two different groups of studies: approximately 400 normal subjects in clinical pharmacology/pharmacokinetic studies, and approximately 1550 patients in placebo-controlled clinical effectiveness studies, corresponding to approximately 263 patient-exposure years. The conditions and duration of treatment with LUNESTA varied greatly and included (in overlapping categories) open-label and double-blind phases of studies, inpatients and outpatients, and short-term and longer-term exposure. Adverse reactions were assessed by collecting adverse events, results of physical examinations, vital signs, weights, laboratory analyses, and ECGs.

Adverse events during exposure were obtained primarily by general inquiry and recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of events into a smaller number of standardized event categories. In the tabulations that follow, COSTART terminology has been used to classify reported adverse events.

The stated frequencies of adverse events represent the proportion of individuals who experienced, at least once, a treatment-emergent adverse event of the type listed. An event was considered treatment-emergent if it occurred for the first time or worsened while the patient was receiving therapy following baseline evaluation.

**Adverse Findings Observed In Placebo-Controlled Trials**

**Adverse Events Resulting In Discontinuation Of Treatment:** In placebo-controlled, parallel-group clinical trials in the elderly, 3.8% of 208 patients who received placebo, 2.3% of 215 patients who received 2 mg LUNESTA, and 1.4% of 72 patients who received 1 mg LUNESTA discontinued treatment due to an adverse event. In the 6-week parallel-group study in adults, no patients in the 3 mg arm discontinued because of an adverse event. In the long-term 6-month study in adult insomnia patients, 7.2% of 195 patients who received placebo and 12.8% of 593 patients who received 3 mg LUNESTA discontinued due to an adverse event. No event that resulted in discontinuation occurred at a rate of greater than 2%.

**Adverse Events Observed At An Incidence of  $\geq 2\%$  In Controlled Trials.** The following lists the incidence (% placebo, 2 mg, 3 mg, respectively) of treatment-emergent adverse events from a Phase 3 placebo-controlled study of LUNESTA at doses of 2 or 3 mg in non-elderly adults. Treatment duration in this trial was 44 days. Data are limited to adverse events that occurred in 2% or more of patients treated with LUNESTA 2 mg (n=104) or 3 mg (n=105) in which the incidence in patients treated with LUNESTA was greater than the incidence in placebo-treated patients (n=99).<sup>1</sup>

**Body as a whole:** headache (13%, 21%, 17%), viral infection (1%, 3%, 3%). **Digestive system:** dry mouth (3%, 5%, 7%), dyspepsia (4%, 4%, 5%), nausea (4%, 5%, 4%), vomiting (1%, 3%, 0%). **Nervous system:** anxiety (0%, 3%, 1%), confusion (0%, 0%, 3%), depression (0%, 4%, 1%), dizziness (4%, 5%, 7%), hallucinations (0%, 1%, 3%), libido decreased (0%, 0%, 3%), nervousness (3%, 5%, 0%), somnolence (3%, 10%, 8%). **Respiratory system:** infection (3%, 5%, 10%). **Skin and appendages:** rash (1%, 3%, 4%). **Special senses:** unpleasant taste (3%, 17%, 34%). **Urogenital system:** dysmenorrhea\* (0%, 3%, 0%), gynecostasia\*\* (0%, 3%, 0%).

\*Gender-specific adverse event in females  
 \*\*Gender-specific adverse event in males

Events for which the LUNESTA incidence was equal to or less than placebo are not listed, but included the following: abnormal dreams, accidental injury, back pain, diarrhea, flu syndrome, myalgia, pain, pharyngitis, and rhinitis.

Adverse events that suggest a dose-response relationship in adults include viral infection, dry mouth, dizziness, hallucinations, infection, rash, and unpleasant taste, with this relationship clearest for unpleasant taste.

The following lists the incidence (% placebo, 2 mg, 3 mg, respectively) of treatment-emergent adverse events from combined Phase 3 placebo-controlled studies of LUNESTA at doses of 1 or 2 mg in elderly adults (ages 65-86). Treatment duration in these trials was 14 days. Data are limited to events that occurred in 2% or more of patients treated with LUNESTA 1 mg (n=72) or 2 mg (n=215) in which the incidence in patients treated with LUNESTA was greater than the incidence in placebo-treated patients.<sup>1</sup>

**Body as a whole:** accidental injury (1%, 0%, 3%), headache (14%, 15%, 13%), pain (2%, 4%, 5%). **Digestive system:** diarrhea (2%, 4%, 2%), dry mouth (2%, 3%, 7%), dyspepsia (2%, 6%, 2%). **Nervous system:** abnormal dreams (0%, 3%, 1%), dizziness (2%, 1%, 6%), nervousness (1%, 0%, 2%), neuralgia (0%, 3%, 0%). **Skin and appendages:** pruritus (1%, 4%, 1%). **Special senses:** unpleasant taste (0%, 8%, 12%). **Urogenital system:** urinary tract infection (0%, 3%, 0%).

Events for which the LUNESTA incidence was equal to or less than placebo are not listed, but included the following: abdominal pain, asthenia, nausea, rash, and somnolence.

Adverse events that suggest a dose-response relationship in elderly adults include pain, dry mouth, and unpleasant taste, with this relationship again clearest for unpleasant taste. These figures cannot be used to predict the incidence of adverse events in the course of usual medical practice because patient characteristics and other factors may differ from those that prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators.

The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contributions of drug and non-drug factors to the adverse event incidence rate in the population studied.

**Other Events Observed During The Premarketing Evaluation Of LUNESTA.** Following is a list of modified COSTART terms that reflect treatment-emergent adverse events as defined in the introduction to the **ADVERSE REACTIONS** section and reported by approximately 1550 subjects treated with LUNESTA at doses in the range of 1 to 3.5 mg/day during Phase 2 and 3 clinical trials throughout the United States and Canada. All reported events are included except those already listed here or listed elsewhere in labeling, minor events common in the general population, and events unlikely to be drug-related. Although the events reported occurred during treatment with LUNESTA, they were not necessarily caused by it.

Events are listed in order of decreasing frequency according to the following definitions: **frequent** adverse events are those that occurred on one or more occasions in at least 1/100 patients; **infrequent** adverse events are those that occurred in fewer than 1/100 patients but in at least 1/1,000 patients; **rare** adverse events are those that occurred in fewer than 1/1,000 patients. Gender-specific events are categorized based on their incidence for the appropriate gender.

**Frequent:** chest pain, migraine, peripheral edema.

**Infrequent:** acne, agitation, allergic reaction, alopecia, amenorrhea, anemia, anorexia, apathy, arthritis, asthma, ataxia, breast engorgement, breast enlargement, breast neoplasm, breast pain, bronchitis, burstis, cellulitis, cholelithiasis, conjunctivitis, contact dermatitis, cystitis, dry eyes, dry skin, dyspnea, dysuria, eczema, ear pain, emotional lability, epistaxis, face edema, female lactation, fever, halitosis, heat stroke, hematuria, hernia, hiccup, hostility, hypercholesterolemia, hypertension, hypotension, hyposthesia, incoordination, increased appetite, insomnia, joint disorder (mainly swelling, stiffness, and pain), kidney calculus, kidney pain, laryngitis, leg cramps, lymphadenopathy, malaise, mastitis, melena, meningeal irritation, menorrhagia, metrorrhagia, mouth ulceration, myasthenia, neck rigidity, nervousness, nystagmus, otitis externa, otitis media, paresthesia, photosensitivity, reflexes decreased, skin discoloration, sweating, thinking abnormal (mainly difficulty concentrating), thirst, stomatitis, twitching, ulceration, stomatitis, urinary frequency, urinary incontinence, uterine hemorrhage, vaginal hemorrhage, vaginitis, vertigo, vestibular disorder, weight gain, weight loss.

**Rare:** abnormal gait, arthralgia, colitis, dehydration, dysphagia, erythema multiforme, euphoria, furunculosis, gastritis, gout, hepatitis, herpes zoster, herpes simplex, hirsutism, hyperacusis, hyperesthesia, hyperlipemia, hypokalemia, hypokinesia, iritis, liver damage, maculopapular rash, mydriasis, myopathy, neuritis, neuropathy, oliguria, photophobia, ptosis, pyelonephritis, rectal hemorrhage, stomach ulcer, stomatitis, stupor, thrombophlebitis, tongue edema, tremor, urethritis, vesiculobullous rash.

**DRUG ABUSE AND DEPENDENCE**

**Controlled Substance Class:** LUNESTA is a Schedule IV controlled substance under the Controlled Substances Act. Other substances under the same classification are benzodiazepines and the nonbenzodiazepine hypnotic, zolpidem. While eszopiclone is a hypnotic agent with a chemical structure unrelated to benzodiazepines, it shares some of the pharmacologic properties of the benzodiazepines.

**Abuse, Dependence, and Tolerance**

**Abuse and Dependence:** In a study of abuse liability conducted in individuals with known histories of benzodiazepine abuse, eszopiclone at doses of 6 and 12 mg produced euphoric effects similar to those of diazepam 20 mg. In this study, at doses 2-fold or greater than the maximum recommended doses, a dose-related increase in reports of amnesia and hallucinations was observed for both LUNESTA and diazepam.

The clinical trial experience with LUNESTA revealed no evidence of a serious withdrawal syndrome. Nevertheless, the following adverse events included in DSM-IV criteria for uncomplicated sedative/hypnotic withdrawal were reported during clinical trials following placebo substitution occurring within 48 hours following the last LUNESTA treatment: anxiety, abnormal dreams, nausea, and upset stomach. These reported adverse events occurred at an incidence of 2% or less. Use of benzodiazepines and similar agents may lead to physical and psychological dependence. The risk of abuse and dependence increases with the dose and duration of treatment and concomitant use of other psychoactive drugs. The risk is also greater for patients who have a history of alcohol or drug abuse or history of psychiatric disorders. These patients should be under careful surveillance when receiving LUNESTA or any other hypnotic.

**Tolerance:** Some loss of efficacy to the hypnotic effect of benzodiazepines and benzodiazepine-like agents may develop after repeated use of these drugs for a few weeks. No development of tolerance to any parameter of sleep measurement was observed over six months. Tolerance to the efficacy of LUNESTA 3 mg was assessed by 4-week objective and 6-week subjective measurements of time to sleep onset and sleep maintenance for LUNESTA in a placebo-controlled 44-day study, and by subjective assessments of time to sleep onset and WASO in a placebo-controlled study for 6 months.

**OVERDOSAGE**

There is limited premarketing clinical experience with the effects of an overdose of LUNESTA. In clinical trials with eszopiclone, one case of overdose with up to 36 mg of eszopiclone was reported in which the subject fully recovered. Individuals have fully recovered from racemic zopiclone overdoses up to 340 mg (56 times the maximum recommended dose of eszopiclone).

**Signs And Symptoms:** Signs and symptoms of overdose effects of CNS depressants can be expected to present as exaggerations of the pharmacological effects noted in preclinical testing. Impairment of consciousness ranging from somnolence to coma has been described. Rare individual instances of fatal outcomes following overdose with racemic zopiclone have been reported in European postmarketing reports, most often associated with overdose with other CNS-depressant agents.

**Recommended Treatment:** General symptomatic and supportive measures should be used along with immediate gastric lavage where appropriate. Intravenous fluids should be administered as needed. Flumazenil may be useful. As in all cases of drug overdose, respiration, pulse, blood pressure, and other appropriate signs should be monitored and general supportive measures employed. Hypotension and CNS depression should be monitored and treated by appropriate medical intervention. The value of dialysis in the treatment of overdose has not been determined.

**Poison Control Center:** As with the management of all overdoses, the possibility of multiple drug ingestion should be considered. The physician may wish to consider contacting a poison control center for up-to-date information on the management of hypnotic drug product overdose.

Rx only.

**SEPRACOR**

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12/06

**First and Only Immediate-Release oral PPI**

**NIGHTTIME OR DAYTIME  
ACID CONTROL**

**First and Only Immediate-Release oral PPI**

**Zegerid<sup>®</sup>**

omeprazole/sodium bicarbonate

**Rapid release. Continued control.**

**Indications and Dosing for ZEGERID**

Zegerid (omeprazole/sodium bicarbonate) is indicated for the treatment of gastroesophageal reflux disease (GERD) in long-term treatment of patients with erosive esophagitis, and for the treatment of patients with erosive esophagitis who are intolerant to or who have failed treatment with H<sub>2</sub> antagonists. Zegerid is also indicated for the treatment of patients with erosive esophagitis who are intolerant to or who have failed treatment with H<sub>2</sub> antagonists. Zegerid is also indicated for the treatment of patients with erosive esophagitis who are intolerant to or who have failed treatment with H<sub>2</sub> antagonists.

**Important Safety Information about ZEGERID**

Patients taking Zegerid should be advised to avoid alcohol consumption and to avoid taking grapefruit juice while taking Zegerid. Patients should be advised to avoid taking Zegerid with other proton pump inhibitors. Patients should be advised to avoid taking Zegerid with other medications that may interact with Zegerid. Patients should be advised to avoid taking Zegerid with other medications that may interact with Zegerid.

Zegerid is a proton pump inhibitor (PPI) that works by blocking the production of stomach acid. Zegerid is used to treat heartburn, acid reflux, and other symptoms of gastroesophageal reflux disease (GERD). Zegerid is also used to treat erosive esophagitis, a condition in which the lining of the esophagus is damaged by stomach acid.

Zegerid is available in two strengths: 30 mg and 60 mg. Zegerid should be taken once daily, with or without food. Zegerid should be taken with water. Zegerid should not be taken with other proton pump inhibitors.

Please see brief summary of full Prescribing Information on the following page.

**SANTARIS**

www.zegerid.com

[www.zegerid.com](http://www.zegerid.com)

# Zegerid®

omeprazole/sodium bicarbonate

## Brief Summary of Prescribing Information

### INDICATIONS AND USAGE

#### Duodenal Ulcer

ZEGERID is indicated for short-term treatment of active duodenal ulcer. Most patients heal within four weeks. Some patients may require an additional four weeks of therapy.

#### Gastric Ulcer

ZEGERID is indicated for short-term treatment (4-8 weeks) of active benign gastric ulcer. (See CLINICAL PHARMACOLOGY, Clinical Studies, Gastric Ulcer.)

#### Treatment of Gastroesophageal Reflux Disease (GERD)

##### Symptomatic GERD

ZEGERID is indicated for the treatment of heartburn and other symptoms associated with GERD.

##### Erosive Esophagitis

ZEGERID is indicated for the short-term treatment (4-8 weeks) of erosive esophagitis which has been diagnosed by endoscopy. (See CLINICAL PHARMACOLOGY, Clinical Studies.)

The efficacy of ZEGERID used for longer than 8 weeks in these patients has not been established. In the rare instance of a patient not responding to 8 weeks of treatment, it may be helpful to give up to an additional 4 weeks of treatment. If there is recurrence of erosive esophagitis or GERD symptoms (eg, heartburn), additional 4-8 week courses of omeprazole may be considered.

##### Maintenance of Healing Erosive Esophagitis

ZEGERID is indicated to maintain healing of erosive esophagitis. Controlled studies do not extend beyond 12 months.

**Reduction of Risk of Upper Gastrointestinal Bleeding in Critically Ill Patients**  
ZEGERID Powder for Oral Suspension 40 mg/1680 mg is indicated for the reduction of risk of upper GI bleeding in critically ill patients.

### CONTRAINDICATIONS

ZEGERID is contraindicated in patients with known hypersensitivity to any components of the formulation.

### PRECAUTIONS

#### General

Symptomatic response to therapy with omeprazole does not preclude the presence of gastric malignancy.

Atrophic gastritis has been noted occasionally in gastric corpus biopsies from patients treated long-term with omeprazole.

Each ZEGERID Capsule contains 1100 mg (113 mEq) of sodium bicarbonate (equivalent to 300 mg of Na<sup>+</sup>). Each packet of ZEGERID Powder for Oral Suspension contains 1680 mg (20 mEq) of sodium bicarbonate (equivalent to 460 mg of Na<sup>+</sup>). The sodium content of ZEGERID products should be taken into consideration when administering to patients on a sodium restricted diet. Sodium bicarbonate is contraindicated in patients with metabolic alkalosis and hypocalcemia. Sodium bicarbonate should be used with caution in patients with Bartter's syndrome, hypokalemia, respiratory alkalosis, and problems with acid-base balance. Long-term administration of bicarbonate with calcium or milk can cause milk-alkali syndrome.

#### Information for Patients

ZEGERID should be taken on an empty stomach at least one hour prior to a meal. ZEGERID is available either as 40 mg or 20 mg capsules with 1100 mg sodium bicarbonate. ZEGERID is also available either as 40 mg or 20 mg single-dose packets of powder for oral suspension with 1680 mg sodium bicarbonate.

#### Directions for Use

Capsules: Swallow intact capsule with water. DO NOT USE OTHER LIQUIDS. DO NOT OPEN CAPSULE AND SPRINKLE CONTENTS INTO FOOD.

Powder for Oral Suspension: Empty packet contents into a small cup containing 1-2 tablespoons of water. DO NOT USE OTHER LIQUIDS OR FOODS. Stir well and drink immediately. Refill cup with water and drink.

#### Drug Interactions

Omeprazole can prolong the elimination of diazepam, warfarin and phenytoin, drugs that are metabolized by oxidation in the liver. There have been reports of increased INR and prothrombin time in patients receiving omeprazole, proton pump inhibitors, including omeprazole, and warfarin concomitantly. Increases in INR and prothrombin time may lead to abnormal bleeding and even death. Patients treated with proton pump inhibitors and warfarin may need to be monitored for increases in INR and prothrombin time. Although in normal subjects no interaction with theophylline or propranolol was found, there have been clinical reports of interaction with other drugs metabolized via the cytochrome P-450 system (eg, cyclosporine, diazepam, benzodiazepines). Patients should be monitored to determine if it is necessary to adjust the dosage of these drugs when taken concomitantly with ZEGERID. Because of its profound and long-lasting inhibition of gastric acid secretion, it is theoretically possible that omeprazole may interfere with absorption of drugs whose gastric pH is an important determinant of their bioavailability (eg, ketoconazole, ampicillin esters, and iron salts). In the clinical efficacy trials, antacids were used concomitantly with the administration of omeprazole. Concomitant administration of omeprazole and atazanavir has been reported to reduce the plasma levels of atazanavir. Concomitant administration of omeprazole and tacrolimus may increase the serum levels of tacrolimus.

Co-administration of omeprazole and clarithromycin have resulted in increases of plasma levels of omeprazole, clarithromycin, and 14-hydroxy-clarithromycin (see also CLINICAL PHARMACOLOGY, Pharmacokinetics).

#### Carcinogenesis, Mutagenesis, Impairment of Fertility

In two 24-month carcinogenicity studies in rats, omeprazole doses of 1.7, 3.4, 13.8, 44.0 and 140.8 mg/kg/day (approximately 0.5 to 28.5 times the human dose of 40 mg/day, based on body surface area) produced gastric ECL cell carcinomas in a dose-related manner in both male and female rats; the incidence of this effect was markedly higher in female rats, which had higher blood levels of omeprazole. Gastric carcinomas seldom occur in the untreated rat. In addition, ECL cell hyperplasia was present in all treated groups of both sexes. In one of these studies, female rats were treated with 13.8 mg omeprazole/kg/day (approximately 2.8 times the human dose of 40 mg/day, based on body surface area) plus a proinflammatory agent, indomethacin, which is a known promoter of gastric ECL cell hyperplasia. An increased incidence of treatment-related ECL cell hyperplasia was observed at the end of one year (94% treated vs 10% controls). By the second year the difference between treated and control rats was much smaller (46% vs 26%) but still showed more hyperplasia in the treated group. Gastric adenocarcinomas were seen in one rat (2%). No similar tumor was seen in male or female rats treated for two years. For this strain of rat, no similar tumor has been noted historically, but a finding involving only one tumor is difficult to interpret. In a 52-week toxicity study in Sprague-Dawley rats, brain astrocytomas were found in a great number of males that received omeprazole at dose levels of 0.4, 2, and 16 mg/kg/day (about 0.1 to 3.3 times the human dose of 40 mg/day, based on body surface area). No astrocytomas were observed in female rats. In a 2-year carcinogenicity study in Sprague-Dawley rats, no astrocytomas were found in males and females at the high dose of 140.8 mg/kg/day (about 28.5 times the human dose of 40 mg/day, based on body surface area). A 78-week mouse carcinogenicity study of omeprazole did not show increased tumor occurrence, but the study was not conclusive. A 26-week p53 (+/-) transgenic mouse carcinogenicity study was not positive. Omeprazole was positive for clastogenic effects in an *in vitro* human lymphocyte chromosomal aberration assay, in one of two *in vitro* mouse micronucleus tests, and in an *in vivo* bone marrow cell chromosomal aberration assay. Omeprazole was negative in an *in vitro* test for *in vitro* mouse lymphoma cell forward mutation assay and in an *in vivo* rat liver DNA damage assay. Omeprazole at oral doses up to 138 mg/kg/day (about 28 times the human dose of 40 mg/day, based on body surface area) was found to have no effect on the fertility and general reproductive performance in rats.

#### Pregnancy

##### Pregnancy Category C

There are no adequate and well-controlled studies on the use of omeprazole in pregnant women. The vast majority of reported experience with omeprazole during human pregnancy is first trimester exposure and the duration of use is rarely specified, e.g., intermittent vs. chronic. An expert review of published data on experience with omeprazole use during pregnancy by TERIS—the Teratology Information System—concluded that therapeutic doses during pregnancy are unlikely to pose a substantial teratogenic risk (the quantity and quality of data were assessed as fair).

Three epidemiological studies compared the frequency of congenital abnormalities among infants born to women who used omeprazole during pregnancy to the frequency of abnormalities among infants of women exposed to H<sub>2</sub>-receptor antagonists or other controls. A population-based prospective cohort epidemiological study from the Swedish Medical Birth Registry, covering approximately 95% of pregnancies, reported on 955 infants (824 exposed during the first trimester with 39 of these exposed beyond first trimester and 131 exposed after the first trimester) whose mothers used omeprazole during pregnancy. In utero exposure to omeprazole was not associated with increased risk of any malformation (odds ratio 0.82, 95% CI 0.50-1.34), low birth weight or low Apgar score. The number of infants born with

ventricular septal defects and the number of stillborn infants was slightly higher in the omeprazole exposed infants than the expected number in the normal population. The author concluded that both effects may be random.

A retrospective cohort study reported on 688 pregnant women exposed to either H<sub>2</sub>-blockers or omeprazole in the first trimester (134 exposed to omeprazole). The overall malformation rate was 4.4% (95% CI 3.6-5.3) and the malformation rate for first trimester exposure to omeprazole was 3.6% (95% CI 1.5-8.1). The relative risk of malformations associated with first trimester exposure to omeprazole compared with nonexposed women was 0.9 (95% CI 0.3-2.2). The study could effectively rule out a relative risk greater than 2.5 for all malformations. Rates of preterm delivery or growth retardation did not differ between the groups.

A controlled prospective observational study followed 113 women exposed to omeprazole during pregnancy (89% first trimester exposure). The reported rates of major congenital malformations was 4% for the omeprazole group, 2% for controls exposed to nonteratogens, and 2.8% in disease-paired controls (background incidence of major malformations 1-5%). Rates of spontaneous and elective abortions, preterm deliveries, gestational age at delivery, and mean birth weight did not differ between the groups. The sample size in this study has 80% power to detect a 5-fold increase in the rate of major malformation.

Several studies have reported no apparent adverse short term effects on the infant when single dose oral or intravenous omeprazole was administered to over 200 pregnant women as premedication for cesarean section under general anesthesia. Teratology studies conducted in pregnant rats at doses up to 138 mg/kg/day (about 28 times the human dose of 40 mg/day, based on body surface area) and in pregnant rabbits at doses up to 69 mg/kg/day (about 28 times the human dose of 40 mg/day, based on body surface area) did not disclose any evidence for a teratogenic potential of omeprazole.

In rabbits, omeprazole in a dose range of 6.9 to 69 mg/kg/day (about 2.8 to 28 times the human dose of 40 mg/day, based on body surface area) produced dose-related increases in embryonic lethality, fetal resorptions and pregnancy disruptions. In rats, dose-related embryofetal toxicity and postnatal developmental toxicity were observed in offspring resulting from parents treated with omeprazole at 13.8 to 138.0 mg/kg/day (about 2.8 to 28 times the human dose of 40 mg/day, based on body surface area).

Chronic use of sodium bicarbonate may lead to systemic alkalosis and increased sodium intake can produce edema and weight increase. There are no adequate and well-controlled studies in pregnant women. Because animal studies and studies in humans cannot rule out the possibility of harm, omeprazole should be used during pregnancy only if the potential benefit to pregnant women justifies the potential risk to the fetus.

#### Nursing Mothers

Omeprazole concentrations have been measured in breast milk of a woman following oral administration of 20 mg. The peak concentration of omeprazole in breast milk was less than 7% of the peak serum concentration. The concentration will correspond to 0.004 mg of omeprazole in 200 mL of milk. Because omeprazole is excreted in human milk, because of the potential for serious adverse reactions in nursing infants from omeprazole, and because of the potential for teratogenicity shown for omeprazole in rat carcinogenicity studies, a decision should be taken to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. In addition, sodium bicarbonate should be used with caution in nursing mothers.

#### Pediatric Use

Clinical studies have been conducted evaluating delayed-release omeprazole in pediatric patients. There are no adequate and well-controlled studies in pediatric patients with ZEGERID.

#### Geriatric Use

Omeprazole was administered to over 2000 elderly individuals (> 65 years of age) in clinical trials in the U.S. and Europe. There were no differences in safety and effectiveness between the elderly and younger subjects. Other reported clinical experience has not identified differences in response between the elderly and younger subjects, but greater sensitivity of some older individuals cannot be ruled out.

Pharmacokinetic studies with buffered omeprazole have shown the elimination rate was somewhat decreased in the elderly and bioavailability was increased. The plasma clearance of omeprazole was 250 mL/min (about half that of young subjects). The plasma half-life averaged one hour, about the same as that in nonelderly, healthy subjects taking ZEGERID. However, no dosage adjustment is necessary in the elderly. (See CLINICAL PHARMACOLOGY.)

### ADVERSE REACTIONS

Omeprazole was generally well tolerated during domestic and international clinical trials in 3096 patients. In the U.S. clinical trial population of 465 patients, the adverse experiences summarized in Table 11 were reported to occur in 1% or more of patients on therapy with omeprazole. Numbers in parentheses indicate percentages of the adverse experiences considered by investigators as possibly, probably or definitely related to the drug.

Table 11: Adverse Experiences Occurring in 1% or More of Patients on Omeprazole Therapy

	Omeprazole (n = 465)	Placebo (n = 64)	Ranitidine (n = 195)
Headache	6.9 (2.4)	6.3	7.7 (2.6)
Diarrhea	3.0 (1.9)	3.1 (1.6)	2.1 (0.5)
Abdominal Pain	2.4 (0.4)	3.1	2.1
Nausea	2.2 (0.9)	3.1	4.1 (0.5)
URI	1.9	1.6	2.6
Dizziness	1.5 (0.6)	0.0	2.6 (1.0)
Vomiting	1.5 (0.4)	4.7	1.5 (0.5)
Rash	1.5 (1.1)	0.0	0.0
Constipation	1.1 (0.9)	0.0	0.0
Cough	1.1	0.0	1.5
Asthenia	1.1 (0.2)	1.6 (1.6)	1.5 (1.0)
Back Pain	1.1	0.0	0.5

Table 12 summarizes the adverse reactions that occurred in 1% or more of omeprazole-treated patients from international double-blind, and open-label clinical trials in which 2,631 patients and subjects received omeprazole.

Table 12: Incidence of Adverse Experiences ≥ 1% Causal Relationship Not Assessed

	Omeprazole (n = 2631)	Placebo (n = 120)
Body as a Whole, site unspecified		
Abdominal pain	5.2	3.3
Asthenia	1.3	0.8
Digestive System		
Constipation	1.5	0.8
Diarrhea	3.7	2.5
Flatulence	2.7	5.8
Nausea	4.0	6.7
Vomiting	3.2	10.0
Acid regurgitation	1.9	3.3
Nervous System/Psychiatric		
Headache	2.9	2.5

A controlled clinical trial conducted in 359 critically ill patients, comparing ZEGERID 40 mg/1680 mg suspension once daily to I.V. cimetidine 1200 mg/day for up to 14 days. The incidence and total number of AEs experienced by ≥ 3% of patients in either group are presented in Table 13 by body system and preferred term.

Table 13: Number (%) of Critically Ill Patients with Frequently Occurring (≥ 3%) Adverse Events by Body System and Preferred Term

	ZEGERID (N=178)	Cimetidine (N=181)
Med/DRA		
Body System	All AEs	All AEs
Preferred Term	n (%)	n (%)
BLOOD AND LYMPHATIC SYSTEM DISORDERS		
Anemia NOS	14 (7.9)	14 (7.7)
Anemia NOS Aggravated	4 (2.2)	3 (1.7)
Thrombocytopenia	18 (10.1)	11 (6.1)
CARDIAC DISORDERS		
Atrial Fibrillation	11 (6.2)	7 (3.9)
Bradycardia NOS	7 (3.9)	5 (2.8)
Supraventricular Tachycardia	6 (3.4)	2 (1.1)
Tachycardia NOS	6 (3.4)	6 (3.3)
Ventricular Tachycardia	8 (4.5)	6 (3.3)
GASTROINTESTINAL DISORDERS*		
Constipation	8 (4.5)	8 (4.4)
Diarrhoea NOS	7 (3.9)	15 (8.3)

Gastric Hypomotility 3 (1.7) 6 (3.3)

### GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS

Hyperpyrexia 8 (4.5) 3 (1.7)  
Oedema NOS 5 (2.8) 11 (6.1)  
Pyrexia 36 (20.2) 29 (16.0)

### INFECTIONS AND INFESTATIONS

Candidial Infection NOS 3 (1.7) 7 (3.9)  
Oral Candidiasis 7 (3.9) 0 (0.6)  
Sepsis NOS 9 (5.1) 9 (5.0)  
Urinary Tract Infection NOS 4 (2.2) 6 (3.3)

### INVESTIGATIONS

Liver Function Tests NOS Abnormal 3 (1.7) 6 (3.3)

### METABOLISM AND NUTRITION DISORDERS

Fluid Overload 9 (5.1) 14 (7.7)  
Hypocalcaemia NOS 19 (10.7) 21 (11.6)  
Cardiovascular 4 (2.2) 6 (3.3)  
Hypertension 3 (1.7) 9 (5.0)  
Hypocalcaemia 11 (6.2) 10 (5.5)  
Hypoglycaemia NOS 6 (3.4) 8 (4.4)  
Hypokalaemia 22 (12.4) 24 (13.3)  
Hypomagnesaemia 18 (10.1) 18 (9.9)  
Hypotension 7 (3.9) 5 (2.8)  
Hypophosphataemia 11 (6.2) 7 (3.9)

### PSYCHIATRIC DISORDERS

Agitation 6 (3.4) 16 (8.8)

### RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS

Acute Respiratory Distress Syndrome 6 (3.4) 7 (3.9)  
Nosocomial Pneumonia 20 (11.2) 17 (9.4)  
Pneumothorax NOS 1 (0.6) 8 (4.4)  
Respiratory Failure 3 (1.7) 6 (3.3)

### SKIN AND SUBCUTANEOUS TISSUE DISORDERS

Decubitus Ulcer 6 (3.4) 5 (2.8)  
Rash NOS 10 (5.6) 11 (6.1)

### VASCULAR DISORDERS

Hypertension NOS 14 (7.9) 6 (3.3)  
Hypotension NOS 17 (9.6) 12 (6.6)

\*Clinically significant UGI bleeding was considered an SAE but it is not included in this table.

Additional adverse experiences occurring in < 1% of patients or subjects in domestic and/or international trials conducted with omeprazole, or occurring since the drug was marketed, are shown below within each body system. In many instances, the relationship to omeprazole was unclear.

#### Body As a Whole

Allergic reactions, including, rarely, anaphylaxis (see also Skin below), fever, pain, fatigue, malaise, abdominal swelling.

#### Cardiovascular

Chest pain or angina, tachycardia, bradycardia, palpitation, elevated blood pressure, and peripheral edema.

#### Gastrointestinal

Pancreatitis (some fatal), anorexia, irritable colon, flatulence, fecal discoloration, esophageal candidiasis, mucosal atrophy of the tongue, dry mouth, stomatitis. During treatment with omeprazole, gastric fundic gland polyps have been noted rarely. These polyps are benign and appear to be reversible when treatment is discontinued. Gastrointestinal carcinomas have been reported in patients with Zollinger-Ellison syndrome on long-term treatment with omeprazole. This finding is believed to be a manifestation of the underlying condition, which is known to be associated with such tumors.

#### Hepatic

Mild and, rarely, marked elevations of liver function tests [ALT (SGPT), AST (SGOT), γ-glutamyl transpeptidase, alkaline phosphatase, and bilirubin (jaundice)]. In rare instances, overt liver disease has occurred, including hepatocellular, cholelithic, or mixed hepatitis, liver necrosis (some fatal), hepatic failure (some fatal), and hepatic encephalopathy.

#### Metabolic/Nutritional

Hypotension, hypoglycemia, and weight gain.

#### Musculoskeletal

Muscle cramps, myalgia, muscle weakness, joint pain, and leg pain.

#### Nervous System/Psychiatric

Psychic disturbances including depression, agitation, aggression, hallucinations, confusion, insomnia, nervousness, tremors, apathy, somnolence, anxiety, dream abnormalities, vertigo, paresthesia, and hemifacial dysesthesia.

#### Respiratory

Epiatitis, pharyngeal pain.

#### Skin

Rash and rarely, cases of severe generalized skin reactions including toxic epidermal necrolysis (TEN; some fatal), Stevens-Johnson syndrome, and erythema multiforme (some severe); purpura and/or petechiae (some with rechallenge); skin inflammation, urticaria, angioedema, pruritus, photosensitivity, alopecia, dry skin, and hyperhidrosis.

#### Special Senses

Tinnitus, taste perversion.

#### Ocular

Blurred vision, ocular irritation, dry eye syndrome, optic atrophy, anterior ischemic optic neuropathy, optic neuritis and double vision.

#### Urogenital

Interstitial nephritis (some with positive rechallenge), urinary tract infection, microscopic pyuria, urinary frequency, elevated serum creatinine, proteinuria, hematuria, glycosuria, testicular pain, and gynecomastia.

#### Hematologic

Rare instances of pancytopenia, agranulocytosis (some fatal), thrombocytopenia, neutropenia, leukopenia, anemia, leucocytosis, and hemolytic anemia have been reported.

The incidence of clinical adverse experiences in patients greater than 65 years of age was similar to that in patients 65 years of age or less.

Additional adverse reactions that could be caused by sodium bicarbonate, include metabolic alkalosis, seizures, and tetany.

### OVERDOSAGE

Reports have been received of overdose with omeprazole in humans. Doses ranged up to 2400 mg (120 times the usual recommended clinical dose). Manifestations were variable, but included confusion, drowsiness, blurred vision, tachycardia, nausea, vomiting, diaphoresis, flushing, headache, dry mouth, and other adverse reactions similar to those seen in normal clinical experience. (See ADVERSE REACTIONS.) Symptoms were transient, and no serious clinical outcome has been reported when omeprazole was taken alone. No specific antidote for omeprazole overdose is known. Omeprazole is extensively protein bound and is, therefore, not readily dialyzable. In the event of overdose, treatment should be symptomatic and supportive. As with the management of any overdose, the possibility of multiple drug ingestion should be considered. For current information on treatment of any drug overdose, a certified Regional Poison Control Center should be contacted. Telephone numbers are listed in the Physicians' Desk Reference (PDR) or local telephone book.

Single oral doses of omeprazole at 1350, 1339, and 1200 mg/kg were lethal to mice, rats, and dogs, respectively. Animals given these doses showed sedation, ptosis, tremors, convulsions, and decreased activity, body temperature, and respiratory rate and increased depth of respiration. In addition, a sodium bicarbonate overdose may cause hypocalcemia, hypokalemia, hypematemesis, and seizures.

Revised: February 2006  
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# THE POWER TO

## A UNIQUE SMOKING CESSATION THERAPY

- Dual action—agonist and antagonist effects at  $\alpha_4\beta_2$  nicotinic acetylcholine receptors

CHANTIX<sup>®</sup> (varenicline) is indicated as an aid to smoking cessation treatment in adults.

Subgroup efficacy of CHANTIX<sup>®</sup> in combination with other smoking cessation drug therapies have not been studied.

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**References:** 1. CHANTIX [package insert]. New York, NY: Pfizer Inc; May 2006. 2. Center for Drug Evaluation and Research. Approval of varenicline, application number NDA 21-928, statistical review(s). Food and Drug Administration Web site. Available at: [http://www.fda.gov/cder/rdmt/nda/2006/021928s1000/Chantix\\_StatR.pdf](http://www.fda.gov/cder/rdmt/nda/2006/021928s1000/Chantix_StatR.pdf). Accessed August 25, 2006. 3. Gonzales D, Rennard SI, Nides M, et al, for the Varenicline Phase 3 Study Group. Varenicline, an  $\alpha_4\beta_2$  nicotinic acetylcholine receptor partial agonist, vs sustained-release bupropion and placebo for smoking cessation: a randomized controlled trial. *JAMA*. 2006;296:47-55. 4. Jorenby DE, Hays JT, Rigotti NA, et al, for the Varenicline Phase 3 Study Group. Efficacy of varenicline, an  $\alpha_4\beta_2$  nicotinic acetylcholine receptor partial agonist, vs placebo or sustained-release bupropion for smoking cessation: a randomized controlled trial. *JAMA*. 2006;296:56-63.

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Please see brief summary of Prescribing Information on adjacent page.

virus software, are included in the price, Nelson warns. These costs often are missing from vendor quotes because the vendor does not directly provide them. "These add-ons are needed to make the system work, and they can cost \$1,000 per workstation," she says.

What about the overall cost of the EHR? Nelson recommends asking vendors for bids rather than giving them a budget to

«No product universally fits every practice. Doing your due diligence is key.»

—Donald L. Spicer, MD

shoot for. If vendors know their competitors are also making bids, they'll be more likely to offer their best price.

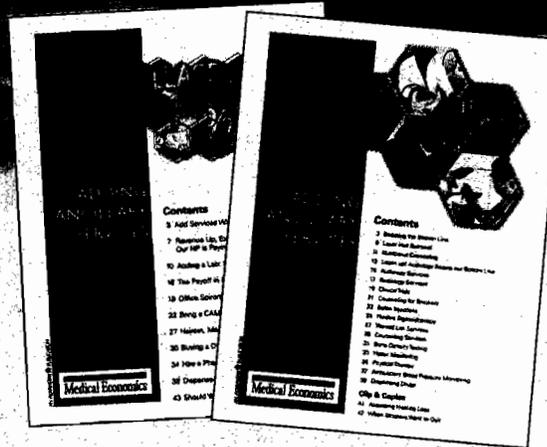
In fact, urologist Donald Spicer believes that his practice's two finalists worked hard to offer their best price because they knew they had to beat out a well-qualified competitor.

Three years later, Spicer is thrilled with the practice's EHR. Four of the five physicians are now making full use of the EHR's point of care documentation system, eliminating most of the group's dictation costs. Staff costs for maintaining records have also been reduced, as have storage costs. Most important, practice records are instantly available, making it possible to efficiently serve same-day patient appointments and respond to telephone requests.

Spicer gives much of the credit to the RFP process. "No product universally fits every practice," he says. "Doing your due diligence is key," he says.

That's sound advice, in Daigrepoint's book. "It can be tempting to skip the RFP process because you don't have time. But if you make a bad choice and pick the wrong EHR, think of how much time—and money—you'll spend getting out of your bad decision." ■

# Boosting the bottom line



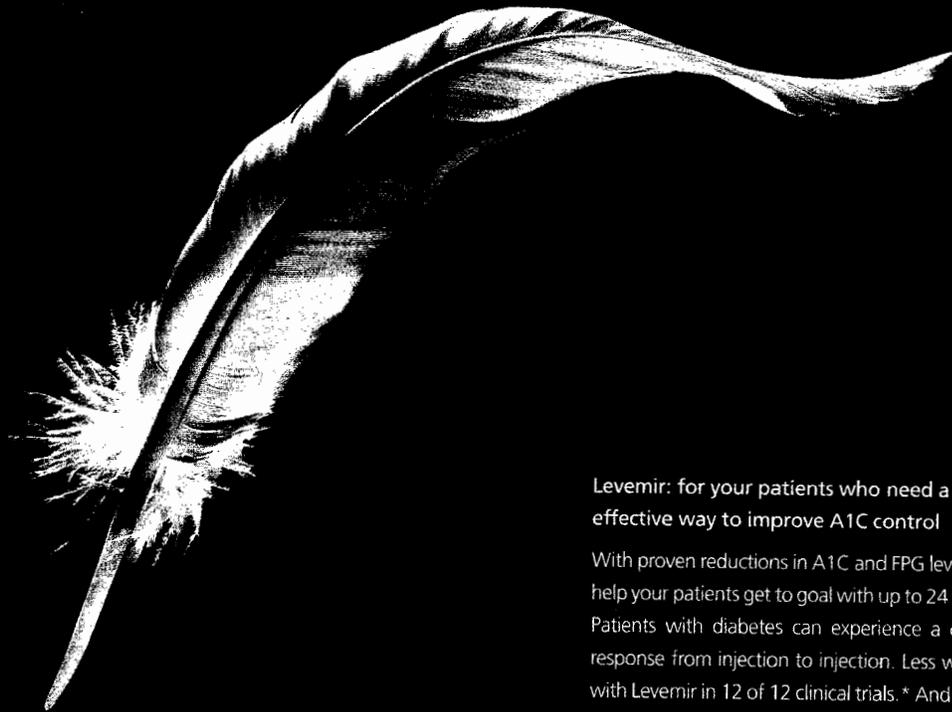
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# Discover Levemir<sup>®</sup>: a long-acting basal insulin with a light touch



Levemir: for your patients who need a safe and effective way to improve A1C control

With proven reductions in A1C and FPG levels over time, Levemir can help your patients get to goal with up to 24 hours of glycemic control. Patients with diabetes can experience a consistent blood glucose response from injection to injection. Less weight gain was observed with Levemir in 12 of 12 clinical trials.\* And Levemir is available in the Levemir<sup>®</sup> FlexPen<sup>®</sup>. FlexPen<sup>®</sup> is the world's #1 selling prefilled insulin pen.<sup>†</sup> So start your patients with diabetes on Levemir, and help them experience the light side of basal insulin.

Levemir is indicated for once- or twice-daily subcutaneous administration for the treatment of adult and pediatric patients with type 1 diabetes mellitus or adult patients with type 2 diabetes mellitus who require basal (long-acting) insulin for the control of hyperglycemia.

**Important safety information**  
Levemir should not be diluted or mixed with any other insulin preparations.

Levemir is contraindicated in patients hypersensitive to insulin detemir or one of its excipients.

Hypoglycemia is the most common adverse effect of all insulin therapies, including Levemir. As with other insulins, the timing of hypoglycemic events may differ among various insulin preparations. Glucose monitoring is recommended for all patients with diabetes. Any change of insulin dose should be made cautiously

and only under medical supervision. Concomitant oral antidiabetes treatment may require adjustment.

Levemir is not to be used in insulin infusion pumps. Inadequate dosing or discontinuation of treatment may lead to hyperglycemia and, in patients with type 1 diabetes, diabetic ketoacidosis. Insulin may cause sodium retention and edema, particularly if previously poor metabolic control is improved by intensified insulin therapy. Dose and timing of administration may need to be adjusted to reduce the risk of hypoglycemia in patients being switched to Levemir from other intermediate or long-acting insulin preparations. The dose of Levemir may need to be adjusted in patients with renal or hepatic impairment.

Other adverse events commonly associated with insulin therapy may include injection site reactions (on average, 3% to 4% of patients

in clinical trials) such as lipodystrophy, redness, pain, itching, hives, swelling, and inflammation.

\*Whether these observed differences represent true differences in the effects of Levemir and NPH insulin is not known, since these trials were not blinded and the protocols (eg, diet and exercise instructions and monitoring) were not specifically directed at exploring hypotheses related to weight effects of the treatments compared. The clinical significance of the observed differences in weight has not been established.



**Levemir<sup>®</sup>**

insulin detemir (rDNA origin) injection

Lighter years ahead



Reference: 1. IMS Health, IMS MIDAS [12 months ending September 2005].

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131007

September 2006

# Levemir®

insulin detemir (rDNA origin) injection

**Rx ONLY**  
**BRIEF SUMMARY. Please see package insert for prescribing information.**

## INDICATIONS AND USAGE

LEVEMIR is indicated for once- or twice-daily subcutaneous administration for the treatment of adult and pediatric patients with type 1 diabetes mellitus or adult patients with type 2 diabetes mellitus who require basal (long acting) insulin for the control of hyperglycemia.

## CONTRAINDICATIONS

LEVEMIR is contraindicated in patients hypersensitive to insulin detemir or one of its excipients.

## WARNINGS

**Hypoglycemia is the most common adverse effect of insulin therapy, including LEVEMIR. As with all insulins, the timing of hypoglycemia may differ among various insulin formulations.**

**Glycose monitoring is recommended for all patients with diabetes.**

**LEVEMIR is not to be used in insulin infusion pumps.**

**Any change of insulin dose should be made cautiously and only under medical supervision. Changes in insulin strength, timing of dosing, manufacturer, type (e.g., regular, NPH, or insulin analogs), species (animal, human), or method of manufacture (rDNA versus animal-source insulin) may result in the need for a change in dosage. Concomitant oral antidiabetic treatment may need to be adjusted.**

## PRECAUTIONS

### General

Inadequate dosing or discontinuation of treatment may lead to hyperglycemia and, in patients with type 1 diabetes, diabetic ketoacidosis. The first symptoms of hyperglycemia usually occur gradually over a period of hours or days. They include nausea, vomiting, drowsiness, flushed dry skin, dry mouth, increased urination, thirst and loss of appetite as well as acetone breath. Untreated hyperglycemic events are potentially fatal.

LEVEMIR is not intended for intravenous or intramuscular administration. The prolonged duration of activity of insulin detemir is dependent on injection into subcutaneous tissue. Intravenous administration of the usual subcutaneous dose could result in severe hypoglycemia. Absorption after intramuscular administration is both faster and more extensive than absorption after subcutaneous administration.

**LEVEMIR should not be diluted or mixed with any other insulin preparations (see PRECAUTIONS, Mixing of Insulins).**

Insulin may cause sodium retention and edema, particularly if previously poor metabolic control is improved by intensified insulin therapy.

Lipodystrophy and hypersensitivity are among potential clinical adverse effects associated with the use of all insulins.

As with all insulin preparations, the time course of LEVEMIR action may vary in different individuals or at different times in the same individual and is dependent on site of injection, blood supply, temperature, and physical activity.

Adjustment of dosage of any insulin may be necessary if patients change their physical activity or their usual meal plan.

### Hypoglycemia

As with all insulin preparations, hypoglycemic reactions may be associated with the administration of LEVEMIR. Hypoglycemia is the most common adverse effect of insulins. Early warning symptoms of hypoglycemia may be different or less pronounced under certain conditions, such as long duration of diabetes, diabetic nerve disease, use of medications such as beta-blockers, or intensified diabetes control (see PRECAUTIONS, Drug Interactions). Such situations may result in severe hypoglycemia (and, possibly, loss of consciousness) prior to patients' awareness of hypoglycemia.

The time of occurrence of hypoglycemia depends on the action profile of the insulins used and may, therefore, change when the treatment regimen or timing of dosing is changed. In patients being switched from other intermediate or long-acting insulin preparations to once- or twice-daily LEVEMIR, dosages can be prescribed on a unit-to-unit basis; however, as with all insulin preparations, dose and timing of administration may need to be adjusted to reduce the risk of hypoglycemia.

### Renal Impairment

As with other insulins, the requirements for LEVEMIR may need to be adjusted in patients with renal impairment.

### Hepatic Impairment

As with other insulins, the requirements for LEVEMIR may need to be adjusted in patients with hepatic impairment.

### Injection Site and Allergic Reactions

As with any insulin therapy, lipodystrophy may occur at the injection site and delay insulin absorption. Other injection site reactions with insulin therapy may include redness, pain, itching, hives, swelling, and inflammation. Continuous rotation of the injection site within a given area may help to reduce or prevent these reactions. Reactions usually resolve in a few days to a few

weeks. On rare occasions, injection site reactions may require discontinuation of LEVEMIR.

In some instances, these reactions may be related to factors other than insulin, such as irritants in a skin cleansing agent or poor injection technique.

**Systemic allergy:** Generalized allergy to insulin, which is less common but potentially more serious, may cause rash (including pruritus) over the whole body, shortness of breath, wheezing, reduction in blood pressure, rapid pulse, or sweating. Severe cases of generalized allergy, including anaphylactic reaction, may be life-threatening.

### Intercurrent Conditions

Insulin requirements may be altered during intercurrent conditions such as illness, emotional disturbances, or other stresses.

### Information for Patients

LEVEMIR must only be used if the solution appears clear and colorless with no visible particles. Patients should be informed about potential risks and advantages of LEVEMIR therapy, including the possible side effects. Patients should be offered continued education and advice on insulin therapies, injection technique, life-style management, regular glucose monitoring, periodic glycosylated hemoglobin testing, recognition and management of hypo- and hyperglycemia, adherence to meal planning, complications of insulin therapy, timing of dosage, instruction for use of injection devices and proper storage of insulin. Patients should be informed that frequent, patient-performed blood glucose measurements are needed to achieve effective glycemic control to avoid both hyperglycemia and hypoglycemia. Patients must be instructed on handling of special situations such as intercurrent conditions (illness, stress, or emotional disturbances), an inadequate or skipped insulin dose, inadvertent administration of an increased insulin dose, inadequate food intake, or skipped meals. Refer patients to the LEVEMIR "Patient Information" circular for additional information.

As with all patients who have diabetes, the ability to concentrate and/or react may be impaired as a result of hypoglycemia or hyperglycemia.

Patients with diabetes should be advised to inform their health care professional if they are pregnant or are contemplating pregnancy (see PRECAUTIONS, Pregnancy).

### Laboratory Tests

As with all insulin therapy, the therapeutic response to LEVEMIR should be monitored by periodic blood glucose tests. Periodic measurement of HbA<sub>1c</sub> is recommended for the monitoring of long-term glycemic control.

### Drug Interactions

A number of substances affect glucose metabolism and may require insulin dose adjustment and particularly close monitoring.

The following are examples of substances that may reduce the blood-glucose-lowering effect of insulin: corticosteroids, danazol, diuretics, sympathomimetic agents (e.g., epinephrine, albuterol, terbutaline), isoniazid, phenothiazine derivatives, somatropin, thyroid hormones, estrogens, progestogens (e.g., in oral contraceptives).

The following are examples of substances that may increase the blood-glucose-lowering effect of insulin and susceptibility to hypoglycemia: oral antidiabetic drugs, ACE inhibitors, disopyramide, fibrates, fluoxetine, MAO inhibitors, propoxyphene, salicylates, somatostatin analog (e.g., octreotide), and sulfonamide antibiotics.

Beta-blockers, clonidine, lithium salts, and alcohol may either potentiate or weaken the blood-glucose-lowering effect of insulin. Pentamidine may cause hypoglycemia, which may sometimes be followed by hyperglycemia. In addition, under the influence of sympatholytic medicinal products such as beta-blockers, clonidine, guanethidine, and reserpine, the signs of hypoglycemia may be reduced or absent.

The results of *in-vitro* and *in-vivo* protein binding studies demonstrate that there is no clinically relevant interaction between insulin detemir and fatty acids or other protein bound drugs.

### Mixing of Insulins

If LEVEMIR is mixed with other insulin preparations, the profile of action of one or both individual components may change. Mixing LEVEMIR with insulin aspart, a rapid acting insulin analog, resulted in about 40% reduction in AUC<sub>(0-2h)</sub> and C<sub>max</sub> for insulin aspart compared to separate injections when the ratio of insulin aspart to LEVEMIR was less than 50%.

**LEVEMIR should NOT be mixed or diluted with any other insulin preparations.**

**Carcinogenicity, Mutagenicity, Impairment of Fertility**  
 Standard 2-year carcinogenicity studies in animals have not been performed. Insulin detemir tested negative for genotoxic potential in the *in-vitro* reverse mutation test in bacteria, human peripheral blood lymphocyte chromosome aberration test, and the *in-vivo* mouse micronucleus test.

### Pregnancy: Teratogenic Effects: Pregnancy Category C

In a fertility and embryonic development study, insulin detemir was administered to female rats before mating, during mating, and throughout pregnancy at doses up to 300 nmol/kg/day (3 times the recommended human dose, based on plasma Area Under the Curve (AUC) ratios). Doses of 150 and 300 nmol/kg/day produced numbers of litters with visceral anomalies. Doses up to 900 nmol/kg/day (approximately 135 times the recommended human dose based on AUC ratio) were given to rabbits during organogenesis. Drug-dose related increases in the incidence of fetuses with gall bladder abnormalities such as small, bilobed, bifurcated and missing gall bladders were observed at a dose of 900 nmol/kg/day. The rat and rabbit embryofetal development studies that included concurrent human insulin control groups

indicated that insulin detemir and human insulin had similar effects regarding embryotoxicity and teratogenicity.

### Nursing mothers

It is unknown whether LEVEMIR is excreted in significant amounts in human milk. For this reason, caution should be exercised when LEVEMIR is administered to a nursing mother. Patients with diabetes who are lactating may require adjustments in insulin dose, meal plan, or both.

### Pediatric use

In a controlled clinical study, HbA<sub>1c</sub> concentrations and rates of hypoglycemia were similar among patients treated with LEVEMIR and patients treated with NPH human insulin.

### Geriatric use

Of the total number of subjects in intermediate and long-term clinical studies of LEVEMIR, 85 (type 1 studies) and 363 (type 2 studies) were 65 years and older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. In elderly patients with diabetes, the initial dosing, dose increments, and maintenance dosage should be conservative to avoid hypoglycemic reactions. Hypoglycemia may be difficult to recognize in the elderly.

### ADVERSE REACTIONS

Adverse events commonly associated with human insulin therapy include the following:

**Body as Whole:** allergic reactions (see PRECAUTIONS, Allergy).

**Skin and Appendages:** lipodystrophy, pruritus, rash. Mild injection site reactions occurred more frequently with LEVEMIR than with NPH human insulin and usually resolved in a few days to a few weeks (see PRECAUTIONS, Allergy).

### Other:

**Hypoglycemia:** (see WARNINGS and PRECAUTIONS).

In trials of up to 6 months duration in patients with type 1 and type 2 diabetes, the incidence of severe hypoglycemia with LEVEMIR was comparable to the incidence with NPH, and, as expected, greater overall in patients with type 1 diabetes (Table 4).

### Weight gain:

In trials of up to 6 months duration in patients with type 1 and type 2 diabetes, LEVEMIR was associated with somewhat less weight gain than NPH (Table 4). Whether these observed differences represent true differences in the effects of LEVEMIR and NPH insulin is not known, since these trials were not blinded and the protocols (e.g., diet and exercise instructions and monitoring) were not specifically directed at exploring hypotheses related to weight effects of the treatments compared. The clinical significance of the observed differences has not been established.

**Table 4: Safety Information on Clinical Studies**

Treatment	# of subjects	Weight (kg)		Hypoglycemia (events/subject/month)		
		Baseline	End of treatment	Major*	Minor**	
<b>Type 1</b>						
Study A	LEVEMIR	N=276	75.0	75.1	0.045	2.184
	NPH	N=133	75.7	76.4	0.035	3.063
Study C	LEVEMIR	N=492	76.5	76.3	0.029	2.397
	NPH	N=257	76.1	76.5	0.027	2.564
Study D	LEVEMIR	N=232	N/A	N/A	0.076	2.677
	Pediatric NPH	N=115	N/A	N/A	0.083	3.203
<b>Type 2</b>						
Study E	LEVEMIR	N=237	82.7	83.7	0.001	0.306
	NPH	N=239	82.4	85.2	0.006	0.595
Study F	LEVEMIR	N=195	81.8	82.3	0.003	0.193
	NPH	N=200	79.6	80.9	0.006	0.235

\* Major = requires assistance of another individual because of neurologic impairment

\*\* Minor = plasma glucose <56 mg/dL, subject able to deal with the episode him/herself

### OVERDOSAGE

Hypoglycemia may occur as a result of an excess of insulin relative to food intake, energy expenditure, or both. Mild episodes of hypoglycemia usually can be treated with oral glucose. Adjustments in drug dosage, meal patterns, or exercise may be needed. More severe episodes with coma, seizure, or neurologic impairment may be treated with intramuscular/subcutaneous glucagon or concentrated intravenous glucose. After apparent clinical recovery from hypoglycemia, continued observation and additional carbohydrate intake may be necessary to avoid recurrence of hypoglycemia.

**More detailed information is available on request.**

### Rx only

Date of issue: October 19, 2005

Manufactured for Novo Nordisk Inc., Princeton, NJ 08540

Manufactured by Novo Nordisk A/S, 2880 Bagsvaerd, Denmark

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More than powerful reductions in LDL-C

in moderate-risk and high-risk patients

Proof that LIPITOR helps both moderate-risk\* and high-risk\*\* patients

**45%**

relative risk  
reduction seen in  
**ASCOT-LLA<sup>1</sup>**

(P=.0002)

**48%**

relative risk  
reduction seen in  
**CARDS**

(P=.016)

I  my daughter

ASCOT-LLA assessed the effect of LIPITOR 10 mg vs placebo on fatal and nonfatal CHD in 10,305 treated hypertensive patients without previous MI and with TC < 251 mg/dL. All patients had ≥3 CV risk factors such as age ≥55 years, smoking, low HDL-C, or family history of CHD. The primary end point demonstrated a 36% relative risk reduction of nonfatal MI and fatal CHD (P=.0005).

CARDS included 2832 patients aged 40 to 75 years with type 2 diabetes, LDL-C < 160 mg/dL, TG < 600 mg/dL, and no history of CHD, stroke, or other major CV events, and a documented history of ≥1 additional risk factor including retinopathy, albuminuria, hypertension, or current smoking. Patients were randomized to either LIPITOR 10 mg (n=1426) or placebo (n=1410). The primary end point demonstrated a 37% relative risk reduction of major CV events (P=.001).

\*Patients in CARDS had type 2 diabetes, which is considered a CHD risk equivalent according to the NCEP ATP III guidelines.

**RESULTS TO TRUST.  
BENEFITS TO LOVE.**



**LIPITOR<sup>®</sup>**  
atorvastatin calcium  
tablets

LIPITOR is indicated to reduce the risk of myocardial infarction, revascularization procedures, angina, and stroke in adult patients with multiple risk factors but without clinically evident CHD; to reduce the risk of myocardial infarction and stroke in patients with type 2 diabetes and without clinically evident CHD, but with multiple risk factors; as an adjunct to diet to reduce elevated total-C, LDL-C, apo B, and TG levels; and to increase HDL-C in patients with primary hypercholesterolemia (heterozygous familial and nonfamilial) and mixed dyslipidemia.

LIPITOR is contraindicated in patients with active liver disease or unexplained persistent elevations of serum transaminases; in women who are or may become pregnant or who are nursing; in patients with hypersensitivity to any component of this medication.

Rare cases of rhabdomyolysis have been reported with LIPITOR and other statins. With any statin, tell patients to promptly report muscle pain, tenderness, or weakness. Discontinue drug if myopathy is suspected, if creatine phosphokinase (CPK) levels rise markedly, or if the patient has risk factors for rhabdomyolysis.

Due to increased risk of myopathy seen with LIPITOR and other statins, physicians should carefully consider combined therapy with fibric acid derivatives, erythromycin, immunosuppressive drugs, azole antifungals, or niacin and carefully monitor patients for signs or symptoms of myopathy early during therapy and when titrating dose of either drug.

It is recommended that liver function tests be performed prior to and 12 weeks following both the initiation of therapy and any elevation of dose, and periodically thereafter. If ALT or AST values >3 x ULN persist, dose reduction or withdrawal is recommended.

In clinical trials, the most common adverse events were constipation, flatulence, dyspepsia, and abdominal pain.

**References:** 1. Data on file, Pfizer Inc, New York, NY. 2. Sverre PS, Dahlöf B, Paulsen O, et al, for the ASCOT investigators. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations in the Anglo-Scandinavian Cardiac Outcomes Trial—Lipid Lowering Arm (ASCOT-LLA): a multicentre randomised controlled trial. *Lancet*. 2002;361:1149-1158. 3. Colhoun HM, Betteridge DJ, Durrington PN, et al, on behalf of the CARDS Investigators. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. *Lancet*. 2004;364:685-696. 4. Grundy SM, Cleeman JI, Merz LN, et al, for the Coordinating Committee of the National Cholesterol Education Program. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. *Circulation*. 2004;110:227-239.

Please see brief summary of prescribing information on adjacent page.

www.LIPITORhcp.com

**LIPITOR®** (Atorvastatin Calcium) Tablets  
**Brief Summary of Prescribing Information**

**CONTRAINDICATIONS:** Active liver disease or unexplained persistent elevations of serum transaminases. Hypersensitivity to any component of this medication. **Pregnancy and Lactation** — Atherosclerosis is a chronic process and discontinuation of lipid-lowering drugs during pregnancy should have little impact on the outcome of long-term therapy of primary hypercholesterolemia. Cholesterol and other products of cholesterol biosynthesis are essential components for fetal development (including synthesis of steroids and cell membranes). Since HMG-CoA reductase inhibitors decrease cholesterol synthesis and possibly the synthesis of other biologically active substances derived from cholesterol, they may cause fetal harm when administered to pregnant women. Therefore, HMG-CoA reductase inhibitors are contraindicated during pregnancy and in nursing mothers. **ATORVASTATIN SHOULD BE ADMINISTERED TO WOMEN OF CHILD-BEARING AGE ONLY WHEN SUCH PATIENTS ARE HIGHLY UNLIKELY TO CONCEIVE AND HAVE BEEN INFORMED OF THE POTENTIAL HAZARDS.** If the patient becomes pregnant while taking this drug, therapy should be discontinued and the patient apprised of the potential hazard to the fetus.

**WARNINGS: Liver Dysfunction** — HMG-CoA reductase inhibitors, like some other lipid-lowering therapies, have been associated with biochemical abnormalities of liver function. **Persistent elevations (>3 times the upper limit of normal [ULN] occurring on 2 or more occasions) in serum transaminases occurred in 0.7% of patients who received atorvastatin in clinical trials.** The incidence of these abnormalities was 0.2%, 0.2%, 0.6%, and 2.3% for 10, 20, 40, and 80 mg, respectively. One patient in clinical trials developed jaundice. Increases in liver function tests (LFT) in other patients were not associated with jaundice or other clinical signs or symptoms. Upon dose reduction, drug interruption, or discontinuation, transaminase levels returned to or near pretreatment levels without sequelae. Eighteen of 30 patients with persistent LFT elevations continued treatment with a reduced dose of atorvastatin. It is recommended that liver function tests be performed prior to and at 12 weeks following both the initiation of therapy and any elevation of dose, and periodically (eg, semiannually) thereafter. Liver enzyme changes generally occur in the first 3 months of treatment with atorvastatin. Patients who develop increased transaminase levels should be monitored until the abnormalities resolve. Should an increase in ALT or AST of >3 times ULN persist, reduction of dose or withdrawal of atorvastatin is recommended. Atorvastatin should be used with caution in patients who consume substantial quantities of alcohol and/or have a history of liver disease. Active liver disease or unexplained persistent transaminase elevations are contraindications to the use of atorvastatin (see CONTRAINDICATIONS). **Skeletal Muscle** — Rare cases of rhabdomyolysis with acute renal failure secondary to myoglobinuria have been reported with atorvastatin and with other drugs in this class. Uncomplicated myalgia has been reported in atorvastatin-treated patients (see ADVERSE REACTIONS). Myopathy, defined as muscle aches or muscle weakness in conjunction with increases in creatine phosphokinase (CPK) values 10 times ULN, should be considered in any patient with diffuse myalgia, muscle tenderness or weakness, and/or marked elevation of CPK. Patients should be advised to report promptly unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever. Atorvastatin therapy should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed or suspected. The risk of myopathy during treatment with drugs in this class is increased with concurrent administration of cyclosporin, fibric acid derivatives, erythromycin, niacin, or azole antifungals. Physicians considering combined therapy with atorvastatin and fibric acid derivatives, erythromycin, immunosuppressive drugs, azole antifungals, or lipid-lowering doses of niacin should carefully weigh the potential benefits and risks and should carefully monitor patients for any signs or symptoms of muscle pain, tenderness, or weakness, particularly during the initial months of therapy and during any periods of upward dosage titration of either drug. Periodic creatine phosphokinase (CPK) determinations may be considered in such situations, but there is no assurance that such monitoring will prevent the occurrence of severe myopathy. Atorvastatin therapy should be temporarily withheld or discontinued in any patient with an acute, serious condition suggestive of a myopathy or having a risk factor predisposing to the development of renal failure secondary to rhabdomyolysis (eg, severe acute infection, hypotension, major surgery, trauma, severe metabolic, endocrine and electrolyte disorders, and uncontrolled seizures).

**PRECAUTIONS: General** — Before instituting therapy with atorvastatin, an attempt should be made to control hypercholesterolemia with appropriate diet, exercise, and weight reduction in obese patients, and to treat other underlying medical problems (see INDICATIONS AND USAGE in full prescribing information). **Information for Patients** — Patients should be advised to report promptly unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever. **Drug Interactions** — The risk of myopathy during treatment with drugs of this class is increased with concurrent administration of cyclosporin, fibric acid derivatives, niacin (nicotinic acid), erythromycin, azole antifungals (see WARNINGS, *Skeletal Muscle*). **Antacid:** When atorvastatin and Meaalox® TC suspension were coadministered, plasma concentrations of atorvastatin decreased approximately 35%. However, LDL-C reduction was not altered. **Antipyrene:** Because atorvastatin does not affect the pharmacokinetics of antipyrine, interactions with other drugs metabolized via the same cytochrome isozymes are not expected. **Colestipol:** Plasma concentrations of atorvastatin decreased approximately 25% when colestipol and atorvastatin were coadministered. However, LDL-C reduction was greater when atorvastatin and colestipol were coadministered than when either drug was given alone. **Cimetidine:** Atorvastatin plasma concentrations and LDL-C reduction were not altered by coadministration of cimetidine. **Digoxin:** When multiple doses of atorvastatin and digoxin were coadministered, steady-state plasma digoxin concentrations increased by approximately 20%. Patients taking digoxin should be monitored appropriately. **Erythromycin:** In healthy individuals, plasma concentrations of atorvastatin increased approximately 40% with coadministration of atorvastatin and erythromycin, a known inhibitor of cytochrome P450 3A4 (see WARNINGS, *Skeletal Muscle*). **Oral Contraceptives:** Coadministration of atorvastatin and an oral contraceptive increased AUC values for norethindrone and ethinyl estradiol by approximately 30% and 20%, respectively. These increases should be considered when selecting an oral contraceptive for a woman taking atorvastatin. **Warfarin:** Atorvastatin had no clinically significant effect on prothrombin time when administered to patients receiving chronic warfarin treatment. **Endocrine Function** — HMG-CoA reductase inhibitors interfere with cholesterol synthesis and theoretically might blunt adrenal and/or gonadal steroid production. Clinical studies have shown that atorvastatin does not reduce basal plasma cortisol concentration or impair adrenal reserve. The effects of HMG-CoA reductase inhibitors on male fertility have not been studied in adequate numbers of patients. The effects, if any, on the pituitary-gonadal axis in premenopausal women are unknown. Caution should be exercised if an HMG-CoA reductase inhibitor is administered concomitantly with drugs that may decrease the levels or activity of endogenous steroid hormones, such as ketoconazole, spironolactone, and cimetidine. **CNS Toxicity** — Brain hemorrhage was seen in a female dog treated for 3 months at 120 mg/kg/day. Brain hemorrhage and optic nerve vacuolation were seen in another female dog that was sacrificed in moribund condition after 11 weeks of escalating doses up to 280 mg/kg/day. The 120 mg/kg dose resulted in a systemic exposure approximately 16 times the human plasma area under the curve (AUC, 0-24 hours) based on the maximum human dose of 80 mg/day. A single toxic convulsion was seen in each of 2 male dogs (one treated at 10 mg/kg/day and one at 120 mg/kg/day) in a 2-year study. No CNS lesions have been observed in mice after chronic treatment for up to 2 years at doses up to 400 mg/kg/day or in rats at doses up to 100 mg/kg/day. These doses were 6 to 11 times (mouse) and 8 to 16 times (rat) the human AUC (0-24) based on the maximum recommended human dose of 80 mg/day. CNS vascular lesions, characterized by perivascular hemorrhages, edema, and mononuclear cell infiltration of perivascular spaces, have been observed in dogs treated with other members of this class. A chemically similar drug in this class produced optic nerve degeneration (Wallerian degeneration of retinogeniculate fibers) in clinically normal dogs in a dose-dependent fashion at a dose that produced plasma drug levels about 30 times higher than the main drug level in humans taking the highest recommended dose. **Carcinogenesis, Mutagenesis, Impairment of Fertility** — In a 2-year carcinogenicity study in rats at dose levels of 10, 30, and 100 mg/kg/day, 2 rare tumors were found in muscle in high-dose females: in one, there was a rhabdomyosarcoma and, in another, there was a fibrosarcoma. This dose represents a plasma AUC (0-24) value of approximately 16 times the mean human plasma drug exposure after an 80 mg oral dose. A 2-year carcinogenicity study in mice given 100, 200, or 400 mg/kg/day resulted in a significant increase in liver adenomas in high-dose males and liver carcinomas in high-dose females. These findings occurred at plasma AUC (0-24) values of approximately 6 times the mean human plasma drug exposure after an 80 mg oral dose. *In vitro*, atorvastatin was not mutagenic or clastogenic in the following tests with and without metabolic activation: the Ames test with *Salmonella typhimurium* and *Escherichia coli*, the HGPRT forward mutation assay in Chinese hamster lung cells, and the chromosomal aberration assay in Chinese hamster lung cells. Atorvastatin was negative in the *in vivo* mouse micronucleus test. Studies in rats performed at doses up to 175 mg/kg (15 times the human exposure) produced no changes in fertility. There was aplasia and aspermia in the epididymis of 2 of 10 rats treated with 100 mg/kg/day of atorvastatin for 3 months (16 times the human AUC at the 80 mg dose); testis weights were significantly lower at 30 and 100 mg/kg and epididymal weight was lower at 100 mg/kg. Male rats given 100 mg/kg/day for 11 weeks prior to mating had decreased sperm motility, sperm head height concentration, and increased abnormal sperm. Atorvastatin caused no adverse effects on semen parameters, or reproductive organ histopathology in dogs given 10, 40, or 120 mg/kg for two years. **Pregnancy Category X:** See CONTRAINDICATIONS. Safety in pregnant women has not been established. Atorvastatin crosses the placenta and reaches a level in fetal liver equivalent to that of maternal plasma. Atorvastatin was not teratogenic in rats at doses up to 300 mg/kg/day or in rabbits at doses up to 100 mg/kg/day. These doses resulted in multiples of about 30 times (rat) or 20 times (rabbit) the human exposure based on surface area (mg/m<sup>2</sup>). In a study in rats given 20, 100, or 225 mg/kg/day, from gestation day 7 through to lactation day 21 (weaning), there was decreased pup survival at birth, neonate, weaning, and maturity in pups of mothers dosed with 225 mg/kg/day. Body weight was decreased on days 4 and 21 in pups of mothers dosed at 100 mg/kg/day; pup body weight was decreased at birth and at days 4, 21, and 91 at 225 mg/kg/day. Pup development was delayed (rotorod performance at 100 mg/kg/day and acoustic startle at

225 mg/kg/day; pinnae detachment and eye opening at 225 mg/kg/day). These doses correspond to 6 times (100 mg/kg) and 22 times (225 mg/kg) the human AUC at 80 mg/day. Rare reports of congenital anomalies have been received following intrauterine exposure to HMG-CoA reductase inhibitors. There has been one report of severe congenital bony deformity, tracheo-esophageal fistula, and anal atresia (VATER association) in a baby born to a woman who took lovastatin with dextroamphetamine sulfate during the first trimester of pregnancy. LIPITOR should be administered to women of child-bearing potential only when such patients are highly unlikely to conceive and have been informed of the potential hazards. If the woman becomes pregnant while taking LIPITOR, it should be discontinued and the patient advised again as to the potential hazards to the fetus. **Nursing Mothers** — Nursing rat pups had plasma and liver drug levels of 50% and 40%, respectively, of that in their mother's milk. Because of the potential for adverse reactions in nursing infants, women taking LIPITOR should not breast-feed (see CONTRAINDICATIONS). **Pediatric Use** — Safety and effectiveness in patients 10-17 years of age with heterozygous familial hypercholesterolemia have been evaluated in a controlled clinical trial of 6 months duration in adolescent boys and postmenarcheal girls. Patients treated with LIPITOR had an adverse experience profile generally similar to that of patients treated with placebo, the most common adverse experiences observed in both groups, regardless of causality assessment, were infections. **Doses greater than 20 mg have not been studied in this patient population.** In this limited controlled study, there was no detectable effect on growth or sexual maturation in boys or on menstrual cycle length in girls (see CLINICAL PHARMACOLOGY, *Clinical Studies* section in full prescribing information). **ADVERSE REACTIONS, Pediatric Patients** (ages 10-17 years); and **DOSAGE AND ADMINISTRATION, Heterozygous Familial Hypercholesterolemia in Pediatric Patients** (10-17 years of age) in full prescribing information. Adolescent females should be counseled on appropriate contraceptive methods while on LIPITOR therapy (see CONTRAINDICATIONS and PRECAUTIONS, *Pregnancy*). LIPITOR has not been studied in controlled clinical trials involving pre-pubertal patients or patients younger than 10 years of age. Clinical efficacy with doses up to 80 mg/day for 1 year have been evaluated in an uncontrolled study of patients with homozygous FH including 8 pediatric patients (see CLINICAL PHARMACOLOGY, *Clinical Studies: Homozygous Familial Hypercholesterolemia* in full prescribing information). **Geriatric Use** — The safety and efficacy of atorvastatin (10-80 mg) in the geriatric population (>65 years of age) was evaluated in the ACCESS study. In this 54-week open-label trial 1,958 patients initiated therapy with atorvastatin 10 mg. Of these, 835 were elderly (>65 years) and 1,123 were non-elderly. The mean change in LDL-C from baseline after 6 weeks of treatment with atorvastatin 10 mg was -38.2% in the elderly patients versus -34.6% in the non-elderly group. The rates of discontinuation due to adverse events were similar between the two age groups. There were no differences in clinically relevant laboratory abnormalities between the age groups.

**ADVERSE REACTIONS:** LIPITOR is generally well-tolerated. Adverse reactions have usually been mild and transient. In controlled clinical studies of 2502 patients, <2% of patients were discontinued due to adverse experiences attributable to atorvastatin. The most frequent adverse events thought to be related to atorvastatin were constipation, flatulence, dyspepsia, and abdominal pain. **Clinical Adverse Experiences** — Adverse experiences reported in ≥2% of patients in placebo-controlled clinical studies of atorvastatin, regardless of causality assessment, are shown in the following table.

BODY SYSTEM Adverse Event	Adverse Events in Placebo-Controlled Studies (% of Patients)				
	Placebo N = 270	Atorvastatin 10 mg N = 863	Atorvastatin 20 mg N = 36	Atorvastatin 40 mg N = 79	Atorvastatin 80 mg N = 94
<b>BODY AS A WHOLE</b>					
Infection	10.0	10.3	2.8	10.1	7.4
Headache	7.0	5.4	16.7	2.5	6.4
Accidental Injury	3.7	4.0	4.2	1.3	3.2
Flu Syndrome	1.9	2.2	0.0	2.5	3.2
Abdominal Pain	0.7	2.8	0.0	3.8	2.1
Back Pain	3.0	2.8	0.0	3.8	1.1
Allergic Reaction	2.6	0.9	2.8	1.3	0.0
Asthma	1.9	2.2	0.0	3.8	0.0
<b>DIGESTIVE SYSTEM</b>					
Constipation	1.8	2.1	0.0	2.5	1.1
Diarrhea	1.5	2.7	0.0	3.8	5.3
Dyspepsia	4.1	2.3	2.8	1.3	2.1
Flatulence	3.3	2.1	2.8	1.3	1.1
<b>RESPIRATORY SYSTEM</b>					
Sinusitis	2.6	2.8	0.0	2.5	6.4
Pharyngitis	1.5	2.5	0.0	1.3	2.1
<b>SKIN AND APPENDAGES</b>					
Rash	0.7	3.9	2.8	3.8	1.1
<b>MUSCULOSKELETAL SYSTEM</b>					
Arthralgia	1.5	2.0	0.0	5.1	0.0
Myalgia	1.1	3.2	5.6	1.3	0.0

**Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT)** — In ASCOT (see CLINICAL PHARMACOLOGY, *Clinical Studies* in full prescribing information) involving 10,305 participants treated with LIPITOR 10 mg daily (n=5,168) or placebo (n=5,137), the safety and tolerability profile of the group treated with LIPITOR was comparable to that of the group treated with placebo during a median of 3.3 years of follow-up.

**Collaborative Atorvastatin Diabetes Study (CARDS)** — In CARDS (see CLINICAL PHARMACOLOGY, *Clinical Studies* in full prescribing information) involving 2838 subjects with type 2 diabetes treated with LIPITOR 10 mg daily (n=1428) or placebo (n=1410), there was no difference in the overall frequency of adverse events or serious adverse events between the treatment groups during a median follow-up of 3.9 years. No cases of rhabdomyolysis were reported.

The following adverse events were reported, regardless of causality assessment in patients treated with atorvastatin in clinical trials. The events in italics occurred in ≥2% of patients and the events in plain type occurred in <2% of patients.

**Body as a Whole:** Chest pain, face edema, fever, neck rigidity, malaise, photosensitivity reaction, generalized edema. **Digestive System:** Nausea, gastroenteritis, liver function tests abnormal, colitis, vomiting, gastritis, dry mouth, rectal hemorrhage, esophagitis, eructation, glossitis, mouth ulceration, anorexia, increased appetite, stomatitis, biliary pain, chelitis, duodenal ulcer, dysphagia, enteritis, melena, gum hemorrhage, stomach ulcer, tenesmus, ulcerative stomatitis, hepatitis, pancreatitis, cholestatic jaundice. **Respiratory System:** Rhinitis, rhinitis, pneumonia, dyspnea, asthma, epistaxis. **Nervous System:** Insomnia, dizziness, paresthesia, somnolence, amnesia, abnormal dreams, libido decreased, emotional lability, incoordination, peripheral neuropathy, torticollis, facial paralysis, hyperkinesia, depression, hypesthesia, hypertension. **Musculoskeletal System:** Arthralgia, leg cramps, bursitis, tenosynovitis, myasthenia, tendinopathy, myositis. **Skin and Appendages:** Pruritus, contact dermatitis, alopecia, dry skin, sweating, acne, urticaria, eczema, seborrhea, skin ulcer. **Urogenital System:** Urinary tract infection, hematuria, albuminuria, urinary frequency, cystitis, impotence, dysuria, kidney calculus, nocturia, epididymitis, fibrocystic breast, vaginal hemorrhage, breast enlargement, metrorrhagia, nephritis, urinary incontinence, urinary retention, urinary urgency, abnormal ejaculation, uterine hemorrhage. **Special Senses:** Amblyopia, tinnitus, dry eyes, refraction disorder, eye hemorrhage, deafness, glaucoma, parosmia, taste loss, taste perversion. **Cardiovascular System:** Palpitation, vasodilatation, syncope, migraine, postural hypotension, pleuritis, arrhythmia, angina pectoris, hypertension. **Metabolic and Nutritional Disorders:** Peripheral edema, hyperglycemia, creatine phosphokinase increased, gout, weight gain, hypoglycemia. **Hemic and Lymphatic System:** Eosinophilia, anemia, lymphadenopathy, thrombocytopenia, petechia. **Postintroduction Reports** — Adverse events associated with LIPITOR therapy reported since market introduction, that are not listed above, regardless of causality assessment, include the following: anaphylaxis, angioneurotic edema, bullous rashes (including erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis), rhabdomyolysis, and fatigue. **Pediatric Patients (ages 10-17 years)** — In a 26-week controlled study in boys and postmenarcheal girls (n=140), the safety and tolerability profile of LIPITOR 10 to 20 mg daily was generally similar to that of placebo (see CLINICAL PHARMACOLOGY, *Clinical Studies* section in full prescribing information and PRECAUTIONS, *Pediatric Use*).

**OVERDOSAGE:** There is no specific treatment for atorvastatin overdosage. In the event of an overdose, the patient should be treated symptomatically, and supportive measures instituted as required. Due to extensive drug binding to plasma proteins, hemodialysis is not expected to significantly enhance atorvastatin clearance.

Please see full prescribing information for additional information about LIPITOR.

Ⓢ, only

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# HELP THEM QUIT

**QUIT RATES SUPERIOR TO ZYBAN® AT 12 WEEKS  
IN HEAD-TO-HEAD CLINICAL TRIALS (P=.0001)<sup>1,2\*</sup>**

**44%** of subjects who received CHANTIX 1 mg bid quit smoking by the end of 12 weeks vs:

- Approximately 30% of subjects who received Zyban 150 mg bid
- Approximately 17.5% of subjects who received placebo

## **WELL-STUDIED TOLERABILITY AND SAFETY PROFILE**

- The most common adverse events associated with CHANTIX were nausea, sleep disturbance, constipation, flatulence, and vomiting
- Nausea was reported by approximately 30% of subjects treated with CHANTIX 1 mg bid, with approximately a 3% discontinuation rate during 12 weeks of treatment

## **GET QUIT™ SUPPORT PLAN**

- A personalized behavioral support program developed by experts specifically for your CHANTIX patients

**TURN MORE SMOKERS INTO QUITTERS**

**CHANTIX™**  
*(varenicline) TABLETS*

\*Results from 2 identically designed, 52-week (12 weeks pharmacotherapy, 40 weeks nonpharmacotherapy follow-up), randomized, double-blind, parallel-group, multicenter clinical trials (study 4: N=1022; study 5: N=1023) in which CHANTIX 1 mg bid was compared with Zyban 150 mg bid and placebo for efficacy and safety in smoking cessation. For trial inclusion, subjects must have smoked at least 10 cigarettes per day over the past year, with no period of abstinence greater than 3 months, and must have been bupropion naive. The primary efficacy end point in both trials was the carbon monoxide (CO)-confirmed 4-week continuous abstinence rate for weeks 9 through 12, defined as the percentage of subjects who reported no smoking (not even a puff) or use of any nicotine-containing products confirmed by an exhaled CO measurement of 10 ppm or less at each clinic visit. (Studies 4 and 5 from the CHANTIX package insert.)<sup>1-4</sup>

**Subjects were provided with an educational booklet on smoking cessation and received up to 10 minutes of smoking cessation counseling at each clinic visit in accordance with Agency for Healthcare Research and Quality guidelines.<sup>1</sup>**

# CHANTIX<sup>®</sup> (varenicline) TABLETS



Before prescribing, please consult  
Full Prescribing Information.

## INDICATIONS AND USAGE

CHANTIX is indicated as an aid to smoking cessation treatment.

## PRECAUTIONS

**General:** Nausea was the most common adverse event associated with CHANTIX treatment. Nausea was generally described as mild or moderate and often transient; however, for some subjects, it was persistent over several months. The incidence of nausea was dose-dependent. Initial dose titration was beneficial in reducing the occurrence of nausea. Nausea was reported by approximately 30% of patients treated with CHANTIX 1 mg BID after an initial week of dose titration. In patients taking CHANTIX 0.5 mg BID, the incidence of nausea was 16% following initial titration. Approximately 3% of subjects treated with CHANTIX 1 mg BID in studies involving 12 weeks of treatment discontinued treatment prematurely because of nausea. For patients with intolerable nausea, dose reduction should be considered. **Effect of smoking cessation:** Physiological changes resulting from smoking cessation, with or without treatment with CHANTIX, may alter the pharmacokinetics or pharmacodynamics of some drugs, for which dosage adjustment may be necessary (examples include theophylline, warfarin and insulin).

**Drug Interactions:** Based on varenicline characteristics and clinical experience to date, CHANTIX has no clinically meaningful pharmacokinetic drug interactions. (See Full Prescribing Information, CLINICAL PHARMACOLOGY, Drug-Drug Interactions).

**Carcinogenesis, Mutagenesis, Impairment of Fertility:** Carcinogenesis: Lifetime carcinogenicity studies were performed in CD-1 mice and Sprague-Dawley rats. There was no evidence of a carcinogenic effect in mice administered varenicline by oral gavage for 2 years at doses up to 20 mg/kg/day (47 times the maximum recommended human daily exposure based on AUC). Rats were administered varenicline (1, 5, and 15 mg/kg/day) by oral gavage for 2 years. In male rats (n = 65 per sex per dose group), incidences of fibrosarcoma (tumor of the brown fat) were increased at the mid dose (1 tumor, 5 mg/kg/day, 23 times the maximum recommended human daily exposure based on AUC) and maximum dose (2 tumors, 15 mg/kg/day, 67 times the maximum recommended human daily exposure based on AUC). The clinical relevance of this finding to humans has not been established. There was no evidence of carcinogenicity in female rats.

**Mutagenesis:** Varenicline was not genotoxic, with or without metabolic activation, in the following assays: Ames bacterial mutation assay, mammalian CHO/KGPR assay, and tests for cytogenetic aberrations in vivo in rat bone marrow and in vitro in human lymphocytes.

**Impairment of Fertility:** There was no evidence of impairment of fertility in either male or female Sprague-Dawley rats administered varenicline succinate up to 15 mg/kg/day (67 and 36 times the maximum recommended human daily exposure based on AUC at 1 mg BID, respectively). However, a decrease in fertility was noted in the offspring of pregnant rats who were administered varenicline succinate at an oral dose of 15 mg/kg/day (36 times the maximum recommended human daily exposure based on AUC at 1 mg BID). This decrease in fertility in the offspring of treated female rats was not evident at an oral dose of 3 mg/kg/day (9 times the maximum recommended human daily exposure based on AUC at 1 mg BID).

**Pregnancy:** Pregnancy Category C. Varenicline succinate was not teratogenic in rats and rabbits at oral doses up to 15 and 30 mg/kg/day, respectively (36 and 67 times the maximum recommended human daily exposure based on AUC at 1 mg BID, respectively). **Human data:** Varenicline succinate has been shown to have an adverse effect on the fetus in animal reproduction studies. Administration of varenicline succinate to pregnant rabbits resulted in reduced fetal weights at an oral dose of 30 mg/kg/day (50 times the human AUC at 1 mg BID); this reduction was not evident following treatment with 10 mg/kg/day (23 times the maximum recommended human daily exposure based on AUC). In addition, in the offspring of pregnant rats treated with varenicline succinate there were decreases in fertility and increases in auditory startle response at an oral dose of 15 mg/kg/day (36 times the maximum recommended human daily exposure based on AUC at 1 mg BID). There are no adequate and well-controlled studies in pregnant women. CHANTIX should be used during pregnancy only if the potential benefits justifies the potential risk to the fetus. **Nursing mothers:** Although it is not known whether this drug is excreted in human milk, animal studies have demonstrated that varenicline can be transferred to nursing pups. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from CHANTIX, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. **Labor and delivery:** The potential effects of CHANTIX on labor and delivery are not known. **Pediatric Use:** Safety and effectiveness of CHANTIX in pediatric patients have not been established; therefore, CHANTIX is not recommended for use in patients under 18 years of age. **Geriatric Use:** A combined single and multiple-dose pharmacokinetic study demonstrated that the pharmacokinetics of 1 mg varenicline given QD or BID to 16 healthy elderly male and female smokers (aged 65-75 yrs) for 7 consecutive days was similar to that of younger subjects. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. Varenicline 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 (see DOSAGE AND ADMINISTRATION, Special Populations, Patients with Impaired renal function). No dosage adjustment is recommended for elderly patients (see DOSAGE AND ADMINISTRATION, Special Populations).

## Information for Patients:

- Patients should be instructed to set a date to quit smoking and to initiate CHANTIX treatment one week before the quit date.
- Patients should be advised that CHANTIX should be taken after eating, and with a full glass of water.
- Patients should be instructed how to titrate CHANTIX, beginning at a dose of 0.5 mg/day. Prescribers should explain that one 0.5 mg tablet should be taken daily for the first three days, and that for the next four days, one 0.5 mg tablet should be taken in the morning and one 0.5 mg tablet should be taken in the evening.
- Patients should be advised that, after the first seven days, the dose should be increased to one 1 mg tablet in the morning and one 1 mg tablet in the evening.
- Patients should be encouraged to continue to attempt to quit if they have early lapses after quit day.
- Patients should be informed that nausea and insomnia are side effects of CHANTIX and are usually transient; however, patients should be advised that if they are persistently troubled by these symptoms, they should notify the prescribing physician so that a dose reduction can be considered.
- Patients should also be provided with educational materials and necessary counseling to support an attempt at quitting smoking.
- Patients should be informed that some medications may require dose adjustment after quitting smoking.
- Patients intending to become pregnant or planning to breast-feed an infant should be advised of the risks of smoking and risks and benefits of smoking cessation with CHANTIX.

## ADVERSE REACTIONS

During the premarketing development of CHANTIX, over 4500 individuals were exposed to CHANTIX, with over 450 treated for at least 24 weeks and approximately 100 for a year. Most study participants were treated for 12 weeks or less. In Phase 2 and 3 placebo-controlled studies, the treatment discontinuation rate due to adverse events in patients dosed with 1 mg BID was 12% for CHANTIX compared to 10% for placebo in studies of three months' treatment. In this group, the discontinuation rates for the most common adverse events in CHANTIX treated patients were as follows: nausea (3% vs. 0.5% for placebo), headache (0.6% vs. 0.9% for placebo), insomnia (1.2% vs. 1.1% for placebo), and abnormal dreams (0.3% vs. 0.2% for placebo). Adverse Events were categorized using the Medical Dictionary for Regulatory Activities (MedDRA, Version 7.1).

The most common adverse events associated with CHANTIX (>5% and twice the rate seen in placebo-treated patients) were nausea, sleep disturbance, constipation, flatulence, and vomiting. Smoking cessation, with or without treatment, is associated with nicotine withdrawal symptoms.

The most common adverse event associated with CHANTIX treatment is nausea. For patients treated to the maximum recommended dose of 1 mg BID following initial dose titration, the incidence of nausea was 30% compared with 10% in patients taking a comparable placebo regimen. In patients taking CHANTIX 0.5 mg BID following initial titration, the incidence was 16% compared with 11% for placebo. Nausea was generally described as mild or moderate and often transient; however, for some subjects, it was persistent throughout the treatment period.

Table 3 shows the adverse events for CHANTIX and placebo in the 12 week fixed dose studies with titration in the first week (Studies 2 (titrated arm only), 4, and 5). MedDRA High Level Group Terms (HLGT) reported in ≥ 5% of patients in the CHANTIX 1 mg BID dose group, and more commonly than in the placebo group, are listed, along with subordinate Preferred Terms (PT) reported in ≥ 1% of CHANTIX patients (and at least 0.5% more frequent than placebo). Closely related Preferred Terms such as "insomnia", "initial insomnia", "middle insomnia", "early morning awakening" were grouped, but individual patients reporting two or more grouped events are only counted once.

Table 3: Common Treatment Emergent AEs (%) in the Fixed-Dose, Placebo-Controlled Studies (≥1% in the 1 mg BID CHANTIX Group, and 1 mg BID CHANTIX at least 0.5% more than Placebo)

SYSTEM ORGAN CLASS High Level Group Term Preferred Term	CHANTIX 0.5 mg BID N=129	CHANTIX 1mg 1mg BID N=521	Placebo N=805
<b>GI Signs and Symptoms</b>			
Nausea	16	30	10
Abdominal Pain*	5	7	5
Flatulence	9	6	3
Dyspepsia	5	5	3
Vomiting	1	5	2
<b>GI Motility/Defecation Conditions</b>			
Constipation	5	8	3
Gastroesophageal reflux disease	1	1	0
Salivary Gland Conditions			
Dry mouth	4	6	4

(Table 3 continued)

<b>Sleep Disorders/Disturbances</b>			
Insomnia**	19	18	13
Abnormal dreams	9	13	5
Sleep disorder	2	5	3
Nightmares	2	1	0
<b>Headaches</b>			
Headache	19	15	13
<b>Neurological Disorders NEC</b>			
Dysgeusia	8	5	4
Somnolence	3	3	2
Lethargy	2	1	0
<b>General Disorders NEC</b>			
Fatigue/Malaise/Asthenia	4	7	6
<b>Respiratory Disorders NEC</b>			
Rhinorrhea	0	1	0
Dyspnea	2	1	1
Upper Respiratory Tract Disorder	7	5	4
<b>Epidermal and Dermal Conditions</b>			
Rash	1	3	2
Pruritis	0	1	1
<b>Appetite/General Nutrit. Disorders</b>			
Increased appetite	4	3	2
Decreased appetite/Anorexia	1	2	1

\* Includes PTs Abdominal (pain, pain upper, pain lower, discomfort, tenderness, distension) and Stomach (discomfort  
\*\* Includes PTs Insomnia/Initial Insomnia/Middle Insomnia/Early morning awakening

The overall pattern, and the frequency of adverse events during the longer-term trials was very similar to that described in Table 3, though several of the most common events were reported by a greater proportion of patients. Nausea, for instance, was reported in 40% of patients treated with CHANTIX 1 mg BID in a one-year study, compared to 6% of placebo-treated patients.

Following is a list of treatment-emergent adverse events reported by patients treated with CHANTIX during all clinical trials. The listing does not include those events already listed in the previous tables or elsewhere in labeling, those events for which a drug cause was remote, those events which were so general as to be uninformative, and those events reported only once which did not have a substantial probability of being acutely life-threatening. **BLOOD AND LYMPHATIC SYSTEM DISORDERS:** Infrequent: Anemia, Lymphadenopathy. Rare: Leukocytosis, Thrombocytopenia, Splenomegaly. **CARDIAC DISORDERS:** Infrequent: Angina pectoris, Arrhythmia, Bradycardia, Ventricular extrasystoles; Myocardial infarction, Palpitations, Tachycardia. Rare: Atrial fibrillation, Cardiac flutter, Coronary artery disease, Cor pulmonale, Acute coronary syndrome, EAR AND LABYRINTH DISORDERS: Infrequent: Tinnitus, Vertigo. Rare: Deafness, Meniere's disease. **ENDOCRINE DISORDERS:** Infrequent: Thyroid gland disorders. **EYE DISORDERS:** Infrequent: Conjunctivitis, Dry eye, Eye irritation, Vision blurred, Visual disturbance, Eye pain. Rare: Acquired night blindness, Blindness transient, Cataract subcapsular, Ocular vascular disorder, Photophobia, Vitreous floaters. **GASTROINTESTINAL DISORDERS:** Frequent: Diarrhea, Gastroenteritis, Dysphagia, Enterocolitis, Eructation, Gastritis, Gastrointestinal hemorrhage, Mouth ulceration, Esophagitis. Rare: Gastric ulcer, Intestinal obstruction, Pancreatitis acute. **GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS:** Frequent: Chest pain, Influenza like illness, Edema, Thirst. Infrequent: Chest discomfort, Chills, Pyrexia. **HEPATOBIILIARY DISORDERS:** Infrequent: Gall bladder disorder. **IMMUNE SYSTEM DISORDERS:** Infrequent: Hypersensitivity. Rare: Drug hypersensitivity. **INVESTIGATIONS:** Frequent: Liver function test abnormal, Weight increased. Infrequent: Electrocardiogram abnormal, Muscle enzyme increased, Urine analysis abnormal. **METABOLISM AND NUTRITION DISORDERS:** Infrequent: Diabetes mellitus, Hypertolemia, Hypokalemia, Hypoglycemia. **MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS:** Frequent: Arthralgia, Back pain, Muscle cramp, Musculoskeletal pain, Myalgia. Infrequent: Arthritis, Osteoporosis. Rare: Myositis. **NEUROUS SYSTEM DISORDERS:** Frequent: Disturbance in attention, Dizziness, Sensory disturbance. Infrequent: Amnesia, Migraine, Parosmia, Psychomotor hyperactivity, Restless legs syndrome, Syncope, Tremor. Rare: Balance disorder, Cerebrovascular accident, Convulsion, Dysarthria, Facial palsy, Mental impairment, Multiple sclerosis, Nystagmus, Psychomotor skills impaired, Transient ischemic attack, Visual field defect. **PSYCHIATRIC DISORDERS:** Frequent: Anxiety, Depression, Emotional disorder, Irritability, Restlessness. Infrequent: Aggression, Apathy, Disorientation, Dissociation, Libido decreased, Mood swings, Thinking abnormal. Rare: Bradycardia, Euphoric mood, Hallucination, Psychotic disorder, Suicidal ideation. **RENAL AND URINARY DISORDERS:** Frequent: Polyuria. Infrequent: Nephrolithiasis, Nicturia, Urine abnormality, Urinary syndrome. Rare: Renal failure acute, Urinary retention. **REPRODUCTIVE SYSTEM AND BREAST DISORDERS:** Frequent: Menstrual disorder. Infrequent: Erectile dysfunction. Rare: Sexual dysfunction. **RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS:** Frequent: Epistaxis, Respiratory disorders. Infrequent: Asthma. Rare: Pneumia, Pulmonary embolism. **SKIN AND SUBCUTANEOUS TISSUE DISORDERS:** Frequent: Hyperhidrosis. Infrequent: Ache, Dermatitis, Dry skin, Eczema, Erythema, Paresthesia, Urticaria. Rare: Photosensitivity reaction. **VASCULAR DISORDERS:** Frequent: Hot flush, Hypertension. Infrequent: Hypotension, Peripheral ischemia, Thrombosis.

## DRUG ABUSE AND DEPENDENCE

**Controlled Substance Class:** Varenicline is not a controlled substance. **Humans:** Fewer than 1 out of 1000 patients reported euphoria in clinical trials with CHANTIX. At higher doses (greater than 2 mg), CHANTIX produced more frequent reports of gastrointestinal disturbances such as nausea and vomiting. There is no evidence of dose-escalation to maintain therapeutic effects in clinical studies, which suggests that tolerance does not develop. Abrupt discontinuation of CHANTIX was associated with an increase in irritability and sleep disturbances in up to 3% of patients. This suggests that, in some patients, varenicline may produce mild physical dependence which is not associated with addiction. In a human laboratory abuse liability study, a single oral dose of 1 mg varenicline did not produce any significant positive or negative subjective responses in smokers. In non-smokers, 1 mg varenicline produced an increase in some positive subjective effects, but this was accompanied by an increase in negative adverse effects, especially nausea. A single oral dose of 3 mg varenicline uniformly produced unpleasant subjective responses in both smokers and non-smokers. **Animals:** Studies in rodents have shown that varenicline produces behavioral responses similar to those produced by nicotine. In rats trained to discriminate nicotine from saline, varenicline produced full generalization to the nicotine cue. In self-administration studies, the degree to which varenicline substitutes for nicotine is dependent upon the requirement of the task. Rats trained to self-administer nicotine under easy conditions continued to self-administer varenicline to a degree comparable to that of nicotine, however, in a more demanding task, rats self-administered varenicline to a lesser extent than nicotine. Varenicline pretreatment also reduced nicotine self-administration.

## OVERDOSAGE

In case of overdose, standard supportive measures should be instituted as required. Varenicline has been shown to be dialyzed in patients with end stage renal disease (see Full Prescribing Information, CLINICAL PHARMACOLOGY, Pharmacokinetics, Pharmacokinetics in Special Patient Populations), however, there is no experience in dialysis following overdose.

## DOSAGE AND ADMINISTRATION

**Usual Dosage for Adults:** Smoking cessation therapies are more likely to succeed for patients who are motivated to stop smoking and who are provided additional advice and support. Patients should be provided with appropriate educational materials and counseling to support the quit attempt. The patient should set a date to stop smoking. CHANTIX dosing should start one week before this date. CHANTIX should be taken after eating and with a full glass of water. The recommended dose of CHANTIX is 1 mg twice daily following a 1-week titration as follows:

Days 1-3:	0.5 mg once daily
Days 4-7:	0.5 mg twice daily
Days 8-End of treatment:	1 mg twice daily

Patients who cannot tolerate adverse effects of CHANTIX may have the dose lowered temporarily or permanently. Patients should be treated with CHANTIX for 12 weeks. For patients who have successfully stopped smoking at the end of 12 weeks, an additional course of 12 weeks treatment with CHANTIX is recommended to further increase the likelihood of long-term abstinence. Patients who do not succeed in stopping smoking during 12 weeks of initial therapy, or who relapse after treatment, should be encouraged to make another attempt once factors contributing to the failed attempt have been identified and addressed.

## Special Populations

**Patients with Impaired renal function:** No dosage adjustment is necessary for patients with mild to moderate renal impairment. For patients with severe renal impairment, the recommended starting dose of CHANTIX is 0.5 mg once daily. Patients may then titrate as needed to a maximum dose of 0.5 mg twice a day. For patients with End-stage renal disease undergoing hemodialysis, a maximum dose of 0.5 mg once daily may be administered if tolerated well (See Full Prescribing Information, CLINICAL PHARMACOLOGY, Pharmacokinetics, Pharmacokinetics in Special Populations, Renal Impairment). **Dosing in elderly patients and patients with impaired hepatic function:** No dosage adjustment is necessary for patients with hepatic impairment. 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 (See PRECAUTIONS, Geriatric Use). **Use in children:** Safety and effectiveness of CHANTIX in pediatric patients have not been established; therefore, CHANTIX is not recommended for use in patients under 18 years of age.

Rx only

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