DRUGDEX® Consults

RECOMMENDATION, EVIDENCE AND EFFICACY RATINGS

RESPONSE

The Thomson Efficacy, Strength of Evidence and Strength of Recommendation definitions are outlined below:

Table 1. Strength Of Recommendation		
Class I	Recommended	The given test or treatment has been proven to be useful, and should be performed or administered.
Class IIa	Recommended, In Most Cases	The given test, or treatment is generally considered to be useful, and is indicated in most cases.
Class IIb	Recommended, In Some Cases	The given test, or treatment may be useful, and is indicated in some, but not most, cases.
Class III	Not Recommended	The given test, or treatment is not useful, and should be avoided.
Class Indeterminant	Evidence Inconclusive	

Table 2. Strength Of Evidence	
Category A	Category A evidence is based on data derived from: Meta-analyses of randomized controlled trials with homogeneity with regard to the directions and degrees of results between individual studies. Multiple, well-done randomized clinical trials involving large numbers of patients.
Category B	Category B evidence is based on data derived from: Meta-analyses of randomized controlled trials with conflicting conclusions with regard to the directions and degrees of results between individual studies. Randomized controlled trials that involved small numbers of patients or had significant methodological flaws (e.g., bias, drop-out rate, flawed analysis, etc.). Nonrandomized studies (e.g., cohort studies, case-control studies, observational studies).
Category C	Category C evidence is based on data derived from: Expert opinion or consensus, case reports or case series.
No Evidence	

Table 3. Efficacy		
Class I	Effective	Evidence and/or expert opinion suggests that a given drug treatment for a specific indication is effective
Class IIa	Evidence Favors Efficacy	Evidence and/or expert opinion is conflicting as to whether a given drug treatment for a specific indication is effective, but the weight of evidence and/or expert opinion favors efficacy.
Class IIb	Evidence is Inconclusive	Evidence and/or expert opinion is conflicting as to whether a given drug treatment for a specific indication is effective, but the weight of evidence and/or expert opinion argues against efficacy.
Class III	Ineffective	Evidence and/or expert opinion suggests that a given drug treatment for a specific indication is ineffective.

Prolongation of Bleeding Time. Prolongation of bleeding time has been observed with omega-3 fatty acids; however, such prolongation has not exceeded normal limits and was not associated with clinically significant bleeding episodes. The manufacturer states that, although additional blood testing is not required for patients receiving omega-3-acid ethyl esters, patients should be monitored for manifestations of bleeding prior to and during therapy with the drug. (See Drug Interactions: Anticoagulants.)

Specific Populations **Pregnancy.** Category C. (See Users Guide.)

Lactation. Not known whether omega-3-acid ethyl esters are distributed into milk; caution advised if used in nursing women.

Pediatric Use. Safety and efficacy of omega-3-acid ethyl esters have not been established in children younger than 18 years of age.

Geriatric Use. Experience in patients older than 65 years of age is limited. In pooled analyses, no substantial differences in safety and efficacy were observed between patients older than 60 years of age (approximately 25% of the study population) and younger patients.

■ **Common Adverse Effects** Adverse effects reported in 1% or more of patients receiving omega-3-acid ethyl esters include eructation, infection, flu syndrome, dyspepsia, taste perversion, back pain, pain, rash, and angina pectoris.

Drug Interactions

■ **Anticoagulants** Concomitant use of omega-3-acid ethyl esters with anticoagulants have not been adequately evaluated; monitor PT/INR periodically during such concomitant therapy.

■ **Drugs Metabolized by Hepatic Microsomal Enzymes** Free forms of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) at a concentration of 23 μM have been shown to cause modest inhibition of cytochrome P-450 (CYP) isoenzymes 1A2, 2A6, 2C9, 2C19, 2D6, 2E1, and 3A in vitro. However, because free forms of EPA and DHA are undetectable in systemic circulation (less than 1 μM), clinically important interactions with drugs metabolized by the cytochrome P-450 enzyme system are not expected to occur in humans.

Omega-3 fatty acid-containing preparations have been shown to increase hepatic concentrations of cytochrome P-450 and activity of certain cytochrome P-450 isoenzymes in rats. Potential for omega-3-acid ethyl esters to induce cytochrome P-450 activities in humans has not been studied.

Description

Omega-3-acid ethyl esters, a prescription preparation, is a combination consisting predominantly of ethyl esters of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). EPA and DHA, collectively known as marine-derived omega-3 fatty acids (n-3 fatty acids), are long-chain, polyunsaturated fatty acids (PUFAs) that are obtained mainly from marine sources such as fatty fish (e.g., herring, mackerel, salmon, sardines, tuna).

The mechanism of action of omega-3-acid ethyl esters is not completely understood; however, the drug may inhibit diacylglycerol *O*-acyltransferase and increase peroxisomal β-oxidation in the liver. Omega-3-acid ethyl esters may reduce the synthesis of triglycerides and VLDL-cholesterol in the liver because EPA and DHA are poor substrates for the enzymes responsible for triglyceride synthesis; EPA and DHA also inhibit esterification of other fatty acids.

EPA and DHA are absorbed systemically following oral administration as ethyl esters. Oral administration of omega-3-acid ethyl esters results in substantial, dose-dependent increases in EPA content in serum phospholipids and less substantial, non-dose-dependent increases in DHA content. Uptake of EPA and DHA into serum phospholipids in patients receiving omega-3-acid ethyl esters is independent of age. EPA uptake, however, appears to be higher in women than in men. Pharmacokinetic data in pediatric patients currently are not available.

Omega-3-acid ethyl esters is commercially available in the US as a prescription drug. Each 1-g capsule of omega-3-acid ethyl esters contains at least 900 mg of the ethyl esters of omega-3 fatty acids (approximately 465 mg from ethyl esters of EPA and 375 mg from ethyl esters of DHA). Marine-derived omega-3 fatty acids also are commercially available in the US as nonprescription dietary supplements (fish-oil capsules) containing widely variable amounts and ratios of EPA and DHA; the most common fish-oil capsules in the US provide approximately 180 mg of EPA and 120 mg of DHA per capsule.

Advice to Patients

Importance of adherence to National Cholesterol Education Program (NCEP)'s dietary recommendations.

Importance of women informing clinicians if they are or plan to become pregnant or plan to breast-feed.

Importance of informing clinicians of existing or contemplated concomitant therapy, including prescription and OTC drugs, as well as any concomitant illnesses.

Importance of informing patients of other important precautionary information. (See Cautions.)

Overview® (see Users Guide). For additional information on this drug until a more detailed monograph is developed and published, the manufacturer's labeling should be consulted. It is *essential* that the manufacturer's labeling be consulted for more detailed information on usual cautions, precautions, contraindications, potential drug interactions, laboratory test interferences, and acute toxicity.

Preparations

Excipients in commercially available drug preparations may have clinically important effects in some individuals; consult specific product labeling for details.

Omega-3-acid Ethyl Esters

Oral

Capsules, liquid-filled	1 g	**Omacor®**, Reliant

†Use is not currently included in the labeling approved by the US Food and Drug Administration

HYPOTENSIVE AGENTS 24:08

CENTRAL α-AGONISTS 24:08.16

Clonidine
Clonidine Hydrochloride

■ Clonidine hydrochloride, an imidazoline-derivative hypotensive agent, is a selective α_2-adrenergic agonist.

Uses

■ **Hypertension** Clonidine hydrochloride and transdermal clonidine are used alone or in combination with other classes of antihypertensive agents in the management of hypertension. Thiazide diuretics are considered the preferred initial monotherapy for uncomplicated hypertension by the Joint National Committee (JNC 7) on the Prevention, Detection, Evaluation, and Treatment of Hypertension in the US. (See Uses: Hypertension in Adults, in the Thiazides General Statement 40:28.20.)

Although many hypertensive patients may be controlled by clonidine alone, the drug may be more effective when used with a diuretic. Clonidine hydrochloride has been used in conjunction with thiazide diuretics, chlorthalidone, or furosemide, producing a greater reduction in blood pressure than is obtained with either drug alone. Use of a diuretic may aid in overcoming tolerance to clonidine and permit reduction of clonidine dosage.

Clonidine may be useful in some patients who are unable to tolerate other adrenergic blocking agents because of severe postural hypotension. However, the possibility that geriatric patients may not tolerate the adverse cognitive effects of central α_2-adrenergic agonists such as clonidine should be considered. Clonidine hydrochloride has been used with other hypotensive agents such as hydralazine, reserpine, or methyldopa, permitting a reduction in the dosage of each drug and, in some patients, minimizing adverse effects while maintaining blood pressure control. As when clonidine is used alone, satisfactory results are obtained in both supine and standing patients during combined drug therapy; marked fluctuations in blood pressure because of postural changes usually do not occur during combined therapy. As with other hypotensive agents, treatment with clonidine is not curative; upon withdrawal of the drug, blood pressure returns to pretreatment levels or greater. (See Cautions: Withdrawal Effects.)

Transdermal clonidine has been effective in many patients for the management of mild to moderate hypertension when used alone or in combination with an oral thiazide diuretic and has also been successfully substituted for oral clonidine hydrochloride in some patients with mild to moderate hypertension whose therapy included the oral form of the drug. The role of transdermal clonidine relative to oral clonidine hydrochloride remains to be more fully evaluated; transdermal clonidine therapy may prove to be convenient in some patients (e.g., those in whom compliance with a daily dosing regimen may be a problem), but adverse dermatologic reactions may occur frequently.

For additional information on overall principles for treatment of hypertension and overall expert recommendations for such disease, see Uses: Hypertension in Adults, in the Thiazides General Statement 40:28.20.

Hypertensive Crises Oral loading-dose regimens of clonidine hydrochloride† have been effective in rapidly reducing blood pressure in patients with severe hypertension in whom reduction of blood pressure was considered urgent, but not requiring emergency treatment. Hypertensive urgencies are those situations in which it is desirable to reduce blood pressure within a few hours. Such situations include the upper levels of severe hypertension, hypertension with optic disk edema, progressive target organ complications, and severe perioperative hypertension. Hypertensive urgencies can be managed with oral doses of drugs with a relatively rapid onset of action. Excessive falls in blood pressure should be avoided since they may precipitate renal, cerebral, or coronary ischemia.

Clonidine hydrochloride also has been used IV† in the management of acute hypertensive crisis† and in hypertensive episodes during labor†, as well as IM† or subcutaneously† in the management of late-onset toxemia of pregnancy†, with satisfactory results; however, an injectable dosage form is not currently

available in the US. When the drug is administered IV, it must be injected very slowly in order to minimize the possible hypertension that may precede its hypotensive effect.

■ **Pain** Clonidine hydrochloride administered by epidural infusion is used as adjunctive therapy in combination with opiates in the management of severe cancer pain that is not relieved by opiate analgesics alone. Epidural administration of analgesics should be considered only when maximum tolerated doses of opiate and adjunct analgesics administered by other routes (e.g., oral, transdermal, subcutaneous, IV) fail to relieve pain. (See Cautions: Precautions and Contraindications.) Consistent with the drug's mechanism of action, epidural clonidine is more likely to be effective in patients with neuropathic pain rather than somatic or visceral pain.

In a double-blind, placebo-controlled, randomized study, cancer patients with severe intractable pain below the cervical dermatomes not controlled by oral, epidural, or IV opiate analgesics received epidural morphine with either clonidine hydrochloride 30 mcg/hour by continuous epidural infusion or placebo for 14 days. Pain relief, measured by a decrease in use of epidural morphine or a decrease in visual analog pain score, was reported in 45 or 21% of patients receiving epidural clonidine or placebo, respectively. In this study, substantial analgesic effects of clonidine appeared to be restricted to patients with neuropathic pain, characterized as localized, burning, shooting, or electric-like pain in a dermatomal or peripheral nerve distribution.

■ **Pheochromocytoma** Clonidine is not indicated in patients with pheochromocytoma; however, unlike reserpine and guanethidine, it does not cause acute cardiovascular collapse in patients with this condition. Because of clonidine's ability to suppress plasma norepinephrine concentration in healthy individuals via stimulation of central α-adrenergic receptors, the drug has been used as an aid in the diagnosis of pheochromocytoma in hypertensive patients with suggestive symptoms and borderline catecholamine values†; in patients with pheochromocytoma, plasma norepinephrine concentration is generally unchanged following administration of a single oral dose of clonidine, while patients with sympathetic hyperactivity exhibit a decrease in plasma norepinephrine concentration.

■ **Vascular Headaches** Although clonidine has been used in the prophylaxis of migraine headaches†, the efficacy of the drug for this condition is questionable. Results of most studies using α-adrenergic agents (e.g., clonidine) for prevention of migraine headaches indicate that these drugs have limited or no efficacy in most patients, and therefore, some experts state that such use is not recommended. For further information on management and classification of migraine headache, see Vascular Headaches: General Principles in Migraine Therapy, under Uses in Sumatriptan 28:32.28.

■ **Dysmenorrhea** Because clonidine reduces the responsiveness of blood vessels to vasodilators or vasoconstrictors, the drug has been used for the treatment of severe dysmenorrhea†.

■ **Vasomotor Symptoms Associated with Menopause** Clonidine has been used orally and transdermally for the management of vasomotor symptoms† (e.g., hot flashes) associated with menopause. Although limited data indicate that the drug may improve the severity and frequency of vasomotor symptoms in some patients, albeit modestly, the required dosages (exceeding the equivalent of 0.1 mg daily administered orally) may result in increased and, sometimes, intolerable adverse effects. Therefore, some clinicians recommend the use of clonidine for management of vasomotor symptoms mainly in postmenopausal women in whom estrogen replacement therapy is contraindicated or in those with preexisting hypertension.

■ **Opiate Dependence** Clonidine hydrochloride has been used safely and effectively for rapid detoxification in the management of opiate withdrawal in opiate-dependent individuals†, in both inpatient and outpatient settings. The exact role of clonidine and its efficacy compared with other methods of detoxification (e.g., methadone) remain to be clearly determined. Clonidine appears to be most useful as a transitional treatment between opiate dependence and administration of the opiate antagonist naltrexone. Clonidine also may be especially useful when detoxification using methadone is inappropriate, unsuccessful, or unavailable.

■ **Alcohol Dependence** Clonidine also has been used in conjunction with benzodiazepines for the management of alcohol withdrawal†. Clonidine appears to be effective in reducing symptoms of the hyperadrenergic state associated with alcohol withdrawal, including elevated blood pressure, increased heart rate, tremor, sweating, and anxiety. However, clonidine has not been shown to prevent delirium or seizures, and the drug should be used only as an adjunct to benzodiazepines (*not* as monotherapy) for the treatment of alcohol withdrawal (see Uses: Alcohol Withdrawal in the Benzodiazepines General Statement 28:24.08). Some clinicians state that the use of clonidine may be particularly helpful in patients with certain coexisting conditions (e.g., opiate withdrawal).

■ **Smoking Cessation** Clonidine is used for the management of nicotine (tobacco) dependence†. Nicotine dependence is a chronic relapsing disorder that requires ongoing assessment and often repeated intervention. Because effective nicotine dependence therapies are available, every patient should be offered effective treatment, and those who are unwilling to attempt cessation should be provided at least brief interventions designed to increase their motivation to stop tobacco use. The US Public Health Service (USPHS) currently recommends clonidine as a second-line drug for use under the supervision of a clinician. This recommendation is based on evidence from several clinical studies on smoking cessation showing that oral or transdermal clonidine therapy approximately doubles the abstinence rate relative to placebo. Second-line pharmacotherapy (e.g., clonidine, nortriptyline, combined therapy with 2 forms of nicotine replacement) is of a more limited role than first-line pharmacotherapy (i.e., bupropion [as extended-release tablets], nicotine polacrilex gum, transdermal nicotine, nicotine nasal spray, nicotine nasal inhaler) in part because of more concerns about potential adverse effects with second-line drugs than with first-line drugs. The use of second-line pharmacotherapy should be considered after first-line pharmacotherapy was attempted or considered and should be individualized based on patient considerations. Use of second-line pharmacotherapy for smoking cessation should be considered for patients who received first-line drugs but were not able to quit smoking or in whom these drugs are contraindicated. (See Guidelines under Uses: Smoking Cessation, in Nicotine 12:92.)

■ **Glaucoma** Clonidine hydrochloride has been used topically† to reduce intraocular pressure in the treatment of open-angle† (chronic simple) and secondary glaucoma† and hemorrhagic glaucoma associated with hypertension†.

■ **Attention Deficit Hyperactivity Disorder** Clonidine has been used for the treatment of attention deficit hyperactivity disorder† (ADHD). Although pooled data from a retrospective analysis of studies in children with ADHD (with and without comorbid conditions [e.g., developmental delay, conduct or tic disorders]) indicate that the drug has produced a moderate reduction in symptoms of ADHD, stimulants (e.g., methylphenidate, amphetamines) remain the drugs of choice for the management of ADHD because of their greater efficacy compared with that of other drugs (e.g., clonidine). Clonidine generally has been shown to be more effective than placebo in the treatment of core symptoms of ADHD, but the magnitude of its effects is lower than with stimulants and efficacy has been established mainly in children with ADHD and comorbid conditions, especially sleep disturbances. However, because clonidine may improve motor tics in patients with Tourette's syndrome, some experts recommend its use as an adjunct to stimulant therapy in pediatric patients with ADHD whose comorbid tic disorder is not controlled by therapy with a stimulant alone. In pediatric patients without such comorbid psychiatric disorders, use of clonidine for the treatment of ADHD usually is *not* recommended, because of the current lack of evidence establishing safety and efficacy. For a more detailed discussion on the management of ADHD, see Uses: Attention Deficit Hyperactivity Disorder, in Methylphenidate 28:20.04.

■ **Other Uses** Because of its GI effects (see Pharmacology: Other Effects), clonidine hydrochloride has been used with some success in a limited number of patients for the management of diarrhea† of various etiologies (e.g., narcotic bowel syndrome, idiopathic diarrhea associated wtih diabetes).

Dosage and Administration

■ **Administration** Clonidine hydrochloride is administered orally or by epidural infusion, and clonidine is administered percutaneously by topical application of a transdermal system. To ensure overnight blood pressure control with oral administration, the last dose of the day should be administered immediately before retiring. If oral clonidine therapy is to be discontinued, dosage of the drug should be slowly reduced over a period of 2–4 days to avoid the possibility of precipitating the withdrawal syndrome. (See Cautions: Withdrawal Effects.)

Patients receiving transdermal clonidine therapy should be carefully instructed in the use of the transdermal system. To obtain optimum results, patients should also be given a copy of the patient instructions provided by the manufacturer. To expose the adhesive surface of the system, the clear plastic protective strip should be peeled and discarded prior to administration. The transdermal system is applied topically to a dry, hairless area of intact skin on the upper arm or chest by firmly pressing the system with the adhesive side touching the skin. If the system becomes loose during the period of use, an adhesive cover should be applied directly over the system to ensure good adhesion. If the patient develops isolated, mild localized skin irritation before completion of the intended period of use, the system may be removed and replaced with a new system at a different application site. To minimize and/or prevent potential skin irritation, each transdermal system should be applied at a different site (e.g., systems may be applied progressively across the arms and chest in one direction or the other).

Specialized techniques are required for continuous epidural administration of clonidine hydrochloride; the drug should be administered via this route only by qualified individuals familiar with the techniques of administration and patient management problems associated with this route of clonidine administration. Prior to the implantation of a permanent controlled infusion device, screening should be conducted to ensure adequate response to epidural therapy. Chronic epidural analgesia should only be used when adequate pain relief cannot be achieved with less invasive therapies.

The injection for epidural use concentrate containing 500 mcg/mL *must* be diluted prior to use in sodium chloride 0.9% injection to provide a final concentration of 100 mcg/mL.

For continuous epidural infusion of clonidine hydrochloride, a controlled-infusion device is used to administer the drug. Infusion of clonidine into the upper thoracic spinal segments may be associated with substantial decreases in blood pressure. (See Cautions: Cardiovascular Effects.) The manufacturer states that administration of epidural clonidine above the C4 dermatome is

contraindicated because of inadequate safety data supporting such use. Careful monitoring of infusion pump function and inspection of catheter tubing for obstruction or dislodgement is recommended to reduce the risk of inadvertent abrupt withdrawal of epidural clonidine infusion. Clonidine hydrochloride injection for epidural infusion contains no preservatives, and partially used vials of the drug should be discarded. Parenteral drug products should be inspected visually for particulate matter and discoloration whenever solution and container permit.

■ **Dosage** To avoid the possibility of precipitating the withdrawal syndrome, clonidine therapy should *not* be discontinued abruptly. (See Cautions: Withdrawal Effects.)

Hypertension Dosage of clonidine and clonidine hydrochloride must be adjusted according to the patient's blood pressure response and tolerance. Adverse effects such as drowsiness and dry mouth may be minimized by increasing dosage gradually and/or by taking the larger portion of the daily dose at bedtime.

Tolerance to the hypotensive effect of clonidine or clonidine hydrochloride may develop in some patients necessitating increased dosage or concomitant administration of a diuretic to enhance the hypotensive response to the drug.

Oral Dosage. For the management of hypertension, the usual initial oral dosage of clonidine hydrochloride in adults and children 12 years of age and older is 0.1 mg twice daily; geriatric patients may benefit from a lower initial dosage of 0.05 mg twice daily. Most clinicians have reported satisfactory results with administration of the drug in 2 or 3 divided doses daily. Dosage may be increased by 0.1 mg at weekly intervals until the desired response is achieved. When clonidine hydrochloride is used alone, the usual oral maintenance dosage ranges from 0.05–0.4 mg twice daily. The manufacturers report 2.4 mg daily to be the maximum effective dosage in adults and children 12 years of age and older.

When combination therapy is required, the commercially available preparations containing clonidine hydrochloride in fixed combination with chlorthalidone should not be used initially. Dosage should first be adjusted by administering each drug separately. If it is determined that the optimum maintenance dosage corresponds to the ratio in a commercial combination preparation, the fixed combination may be used. However, whenever dosage adjustment is necessary, each drug should be administered separately. Smaller than usual dosages of clonidine hydrochloride may be adequate in patients who are also receiving diuretics or other hypotensive drugs.

Transdermal Dosage. When transdermal clonidine therapy is used for the management of hypertension in adults and children 12 years of age and older, transdermal therapy is initiated with one system delivering 0.1 mg/24 hours applied once every 7 days. Because of interpatient variability in transdermal absorption, it is recommended that this initial dosage be used in all patients, including those who had been receiving oral clonidine hydrochloride therapy, and that dosage subsequently be titrated according to individual requirements; the relationship between the effective dosage of oral clonidine hydrochloride and that of transdermal clonidine is not predictable.

If the desired reduction in blood pressure is not achieved after 1 or 2 weeks with the initial dosage, dosage may be increased by using 2 systems delivering 0.1 mg/24 hours or a larger dosage system. Subsequent dosage adjustments may be made at weekly intervals. The usual dosage range for transdermal clonidine recommended by some experts (e.g., JNC 7) is 0.1–0.3 mg/24 hours applied once every 7 days. Transdermal dosages exceeding 0.6 mg/24 hours (2 systems each delivering 0.3 mg/24 hours) are usually not associated with additional efficacy. In patients who develop localized skin irritation during the intended period of use (7 days), it may be necessary to move the transdermal system to a different site or replace it with another system at shorter intervals (e.g., every 3–5 days). Replacement of the transdermal system following a duration of less than 7 days may be required rarely to maintain blood pressure control.

When transdermal therapy is initiated in patients who have been receiving low dosages of oral clonidine hydrochloride, some clinicians recommend continuing the usual oral dosage the first day the initial transdermal system is applied. When transdermal clonidine therapy is administered to patients already receiving other hypotensive agents, dosage of the other hypotensive agents should be gradually reduced when transdermal therapy is initiated since the hypotensive effect of transdermal clonidine may not begin until 2–3 days after application of the initial system; the other hypotensive agents may have to be continued, particularly in patients with more severe hypertension.

Blood Pressure Monitoring and Treatment Goals. Careful monitoring of blood pressure during initial titration or subsequent upward adjustment in dosage of clonidine hydrochloride is recommended. Large or abrupt reductions in blood pressure generally should be avoided.

Once antihypertensive drug therapy has been initiated, dosage generally is adjusted at approximately monthly intervals (more aggressively in high-risk patients [stage 2 hypertension, comorbid conditions]) if blood pressure control is inadequate at a given dosage; it may take months to control hypertension adequately while avoiding adverse effects of therapy. (For definition of stages of hypertension, see Initial Drug Therapy under Uses: Hypertension in Adults, in the Thiazides General Statement 40:28.20.) Once blood pressure has been stabilized, follow-up visits with the clinician generally can be scheduled at 3- to 6-month intervals, depending on patient status.

Because systolic blood pressure has been shown to be a more precise indicator of cardiovascular risk than diastolic blood pressure (except in patients younger than 50 years of age), the coordinating committee of the National High Blood Pressure Education Program (NHBPEP) recommends using systolic blood pressure as the principal clinical end point for detecting, evaluating, and treating hypertension, especially in middle-aged and geriatric patients. In addition, once the goal systolic blood pressure is attained, most hypertensive patients also will achieve the goal diastolic blood pressure.

The goal of hypertension management and prevention is to achieve and maintain a lifelong systolic blood pressure less than 140 mm Hg and a diastolic blood pressure less than 90 mm Hg if tolerated. Because treatment to lower levels may be particularly useful to prevent stroke, to preserve renal function, and to prevent or slow heart failure progression in hypertensive patients with diabetes mellitus or renal impairment, the goal of hypertension management and prevention in such patients is to achieve and maintain a systolic blood pressure less than 130 mm Hg and a diastolic blood pressure less than 80 mm Hg. Many experts recommend a goal of achieving and maintaining a systolic blood pressure of 125 mm Hg or less and a diastolic blood pressure of 75 mm Hg or less in hypertension management in patients with proteinuria (urinary protein excretion exceeding 1 g per 24 hours) and renal insufficiency (regardless of etiology).

For additional information on initiating and adjusting clonidine hydrochloride dosage in the management of hypertension, see Blood Pressure Monitoring and Treatment Goals under Dosage: Hypertension, in Dosage and Administration in the Thiazides General Statement 40:28.20.

Hypertensive Crises For the management of hypertensive crisis†, clonidine hydrochloride in sodium chloride injection has been administered by IV injection† (currently not commercially available in the US) over a period of 5 minutes at a dose of 0.15–0.3 mg. If IV clonidine is used in the management of a hypertensive emergency, the initial goal of such therapy is to reduce mean arterial blood pressure by no more than 25% within minutes to 1 hour, followed by further reduction *if stable* toward 160/100 to 110 mm Hg within the next 2–6 hours, avoiding excessive declines in pressure that could precipitate renal, cerebral, or coronary ischemia. If this blood pressure is well tolerated and the patient is clinically stable, further gradual reductions toward normal can be implemented in the next 24–48 hours. Patients with aortic dissection should have their systolic pressure reduced to less than 100 mm Hg if tolerated.

For rapid reduction of blood pressure in patients with severe hypertension† in whom reduction of blood pressure was considered urgent but not requiring emergency treatment, clonidine hydrochloride has been administered orally in an initial dose of 0.1–0.2 mg, followed by hourly doses of 0.05–0.2 mg until a total dose of 0.5–0.7 mg had been given or diastolic blood pressure was controlled. Excessive falls in blood pressure should be avoided since they may precipitate renal, cerebral, or coronary ischemia. Thereafter, maintenance dosage of clonidine was adjusted according to the patient's response and tolerance.

For rapid reduction of blood pressure in pediatric patients (1–17 years of age) with severe hypertension† in whom reduction of blood pressure is considered urgent or occasionally requires emergency treatment, some experts recommend an initial oral clonidine hydrochloride dose of 0.05–0.1 mg, which may be repeated up to a total dosage of 0.8 mg.

Pain **Adult Dosage.** When used for the relief of severe, intractable cancer pain that is unresponsive to epidural or spinal opiate analgesia or other more conventional methods of analgesia, the recommended initial dosage of clonidine hydrochloride in adults is 30 mcg/hour, administered by continuous epidural infusion. The dosage may be adjusted based on clinical response and tolerance; however, clinical experience with infusion rates exceeding 40 mcg/hour is limited. Patients should be closely monitored, particularly during the first few days of epidural clonidine therapy.

Pediatric Dosage. The recommended initial dosage of epidural clonidine hydrochloride in pediatric patients is 0.5 mcg/kg of body weight per hour. The dosage of epidural clonidine in pediatric patients should be cautiously adjusted based on clinical response.

Pheochromocytoma As an aid in the diagnosis of pheochromocytoma†, clonidine hydrochloride has been administered orally as a single 0.3-mg dose. To conduct the test, patients should rest in the supine position for 30 minutes, after which time, 2 blood samples for baseline determination of catecholamine concentrations are drawn at 5-minute intervals. The 0. 3-mg dose is then administered and blood samples for catecholamine determinations are drawn at hourly intervals for 3 hours. In patients with pheochromocytoma, plasma norepinephrine concentrations generally remain unchanged following administration of clonidine, whereas plasma norepinephrine concentrations generally decrease in patients without pheochromocytoma.

Vascular Headache The oral dosage of clonidine hydrochloride used in the prophylaxis of migraine† is 0.025 mg 2–4 times a day or up to 0.15 mg daily in divided doses.

Dysmenorrhea For the treatment of dysmenorrhea†, 0.025 mg of clonidine hydrochloride has been administered orally twice daily for 14 days before and during menses.

Vasomotor Symptoms Associated with Menopause **Oral Dosage.** Oral clonidine hydrochloride dosages of 0.025–0.2 mg twice daily have been employed in the management of vasomotor symptoms (e.g., hot flashes) associated with menopause†.

Transdermal Dosage. While comparative efficacy of various transdermal clonidine dosages have not been established, patients in clinical studies have

received one transdermal system delivering 0.1 mg/24 hours applied once every 7 days.

Opiate Dependence For rapid detoxification in the management of opiate withdrawal in opiate-dependent individuals†, various dosage regimens of oral clonidine hydrochloride have been used. Dosage must be carefully individualized according to the patient's response and tolerance, and patients must be closely monitored and supervised. Because of varying sensitivity to clonidine's sedative, hypotensive, and withdrawal-suppressing effects, it may be difficult or impossible to establish a dosage regimen that adequately suppresses withdrawal without producing intolerable adverse effects. Some clinicians administer an initial oral test dose of clonidine hydrochloride of 0.005 or 0.006 mg/kg; if signs and symptoms of withdrawal are suppressed, patients then receive an oral dosage of 0.017 mg/kg daily, given in 3 or 4 divided doses, generally for about 10 days. Alternatively, some clinicians have administered an initial oral dosage of 0.1 mg 3 or 4 times daily, with dosage adjusted by 0.1–0.2 mg per day according to the patient's response and tolerance. Dosage usually ranges from 0.3–1.2 mg daily. When clonidine hydrochloride therapy is discontinued, dosage has been reduced by increments of 50% per day for 3 days and then discontinued, or reduced by 0.1–0.2 mg daily. Clinicians should consult published protocols for more specific information.

Alcohol Dependence While dosages of clonidine hydrochloride in the management of alcohol dependence† have not been established, oral dosages of 0.5 mg twice or 3 times daily have been shown to reduce tremor, heart rate, and blood pressure in patients with alcohol withdrawal.

Smoking Cessation Optimum dosage of oral clonidine hydrochloride or transdermal clonidine for smoking cessation† (nicotine [tobacco] dependence) has not been established, and various regimens have been employed.

Oral Dosage. For use in the cessation of smoking†, the initial adult oral dosage of clonidine hydrochloride is typically 0.1 mg twice daily. Therapy with the drug is initiated on the day set as the date of cessation of smoking or shortly before this date (e.g., up to 3 days prior). Dosage may be increased each week by 0.1 mg daily, if needed. In clinical studies, oral dosages varied from 0.15–0.75 mg daily, without a clear relationship to achievement of cessation of smoking. The duration of oral therapy with clonidine hydrochloride also varied in these studies, ranging from 3–10 weeks.

Transdermal Dosage. When transdermal clonidine is used for the cessation of smoking†, therapy is initiated typically in adults with one system delivering 0.1 mg/24 hours applied once every 7 days. Therapy with the drug is initiated on the day set as the date of cessation of smoking or shortly before this date (e.g., up to 3 days prior). Dosage may be increased at weekly intervals by 0.1 mg/24 hours, if needed. In clinical studies, the transdermal dosage varied from 0.1–0.2 mg/24 hours, without a clear relationship to achievement of cessation of smoking. The duration of transdermal clonidine therapy also varied in these studies, ranging from 3–10 weeks.

Glaucoma In the treatment of glaucoma†, clonidine hydrochloride has been applied topically† in the form of 0.125%, 0.25%, or 0.5% ophthalmic solutions or as a 0.1% ophthalmic ointment. The 0.25% solution appears to provide maximum effectiveness with minimum adverse effects.

Attention Deficit Hyperactivity Disorder For the management of attention deficit hyperactivity disorder (ADHD)†, the initial oral daily dosage of clonidine hydrochloride in pediatric patients is 0.05 mg given as a single dose at bedtime. Thereafter, dosages may be cautiously increased over a period of 2–4 weeks, in order to minimize development of adverse effects (e.g., sedation). Maintenance dosages of clonidine hydrochloride range from 0.05–0.4 mg daily (depending on tolerance and patient's weight). Usually, pediatric patients may receive the maximum tolerated dosages of clonidine hydrochloride for 2–8 weeks in order to assess treatment response, although it should be considered that onset of action of clonidine may be more variable than that associated with stimulants or antidepressants. The American Heart Association (AHA) states that ECG monitoring is not required in pediatric patients receiving clonidine for ADHD; however, several experts recommend weekly office visits during clonidine titration period to monitor both erect and supine blood pressure and heart rate.

Dosage in Renal Impairment Smaller than usual dosages of clonidine or clonidine hydrochloride may be adequate in patients with renal impairment. Dosage should be adjusted according to the degree of renal impairment. Some clinicians suggest that adjustment of clonidine hydrochloride dosage is not necessary in patients with creatinine clearances of 10 mL/minute or greater, but those with lower clearances can receive 50–75% of the usual dosage. Supplemental doses after hemodialysis are not necessary.

Cautions

Adverse effects occurring most frequently during oral clonidine hydrochloride therapy are dry mouth, dizziness, drowsiness and sedation, and constipation; these adverse effects appear to be dose related. Headache, fatigue, and weakness also have been reported. Generally, these adverse effects are mild and tend to diminish with continued therapy or may be relieved by a reduction in dosage. Adverse effects occurring with transdermal clonidine generally appear to be similar to those occurring with oral therapy; however, systemic adverse effects with transdermal clonidine appear to be less severe and possibly may occur less frequently than with oral therapy. Most adverse systemic effects occurring during transdermal therapy have been mild and have tended to diminish with continued treatment. The most frequently occurring adverse effects during transdermal therapy have been dry mouth, drowsiness, and local adverse dermatologic effects. Adverse effects reported most frequently in patients with cancer receiving clonidine by epidural infusion in combination with epidural morphine in a controlled clinical trial included hypotension, postural hypotension, and dry mouth, which occurred in 45, 32, and 16% of patients, respectively.

■ **Nervous System Effects** Drowsiness has been reported in about 33, 13, or 12% of patients receiving oral, epidural, or transdermal clonidine, respectively. In addition to drowsiness, sedation, dizziness, headache, fatigue, and weakness, other adverse nervous system effects of clonidine include lethargy, vivid dreams, nightmares, insomnia, behavioral changes, nervousness, restlessness, anxiety, agitation, irritability, mental depression, visual and auditory hallucinations, delirium, localized numbness, and cerebrovascular accidents.

Depression, which occurs often in patients with cancer, may be exacerbated by the use of epidural clonidine. Therefore, the manufacturer recommends that patients be monitored for signs and symptoms of depression (especially those with a history of affective disorders). Sedation and ventilatory abnormalities, usually mild, have been reported in patients receiving bolus epidural doses of clonidine that were substantially higher than the infusion rate recommended for the treatment of cancer pain. Tolerance to these effects may occur with chronic administration of the drug.

■ **GI Effects** Dry mouth has been reported in about 40, 25, or 13% of patients receiving oral, transdermal, or epidural clonidine, respectively. Nausea and vomiting have occurred in about 5% of patients and anorexia and malaise in about 1% of patients receiving oral clonidine. In addition, parotid pain, parotitis, pseudo-obstruction, abdominal pain, and constipation have occurred rarely in patients receiving oral clonidine. Nausea and vomiting were reported in about 13 and 11%, respectively, of patients receiving clonidine by epidural infusion in combination with epidural morphine for the treatment of intractable cancer pain in a controlled clinical trial. Dry throat, constipation, nausea, dysgeusia, anorexia, and vomiting have been reported in patients receiving transdermal clonidine.

■ **Cardiovascular Effects** Orthostatic symptoms have occurred in about 3% of patients receiving oral clonidine; palpitation and tachycardia, and bradycardia have occurred in about 0.5% of patients receiving oral drug. Rare cases of sinus bradycardia and atrioventricular block, with and without concomitant cardiac glycoside therapy, have been reported. Congestive heart failure, Raynaud's phenomenon, flushes, facial pallor, syncope, chest pain, increases in blood pressure, palpitations, and ECG abnormalities (e.g., arrhythmias, sick sinus syndrome disturbances, sinus node arrest, conduction disturbances such as AV block) also have been reported.

Hypotension occurred in about 45% of patients receiving clonidine by epidural infusion as adjunctive therapy with epidural morphine for the treatment of cancer pain. In a 14-day clinical trial, hypotension usually was reported within the first 4 days of epidural clonidine therapy; however, hypotension also occurred throughout the duration of the study. Hypotension, which can be severe, usually responds to treatment with IV fluids and, if necessary, parenteral ephedrine. Hypotension appears to occur more frequently in women, in patients with a lower body weight, and in patients with higher serum clonidine concentrations.

Decreased heart rate has been reported frequently in patients receiving epidural clonidine, while AV block greater than first degree in severity has been reported rarely. Atropine may be used to treat symptomatic bradycardia when necessary. Increases in heart rate associated with hypovolemia may be masked by clonidine therapy.

■ **Metabolic and Endocrine Effects** Weight gain has been reported in about 1% of patients receiving oral clonidine. Some patients gain weight during the first few days of oral clonidine therapy because of sodium and fluid retention. Sodium retention usually lasts only 3 or 4 days and may be avoided or relieved by administration of a diuretic. Gynecomastia has occurred in about 0.1% of patients receiving oral clonidine during clinical trials, and in up to 0.5% of patients during postmarketing experience with transdermal clonidine. Transient elevation of blood glucose concentration after single large doses of clonidine hydrochloride has been reported; however, no effects on glucose metabolism have been reported during long-term use of the drug, and diabetic patients have remained in control while taking clonidine hydrochloride. Rarely, transient elevation of serum creatine kinase (CK, creatine phosphokinase, CPK) concentrations have been associated with use of the drug.

■ **Dermatologic Effects** Rash has occurred in about 1% of patients; pruritus in about 0.7% of patients; angioedema and urticaria in about 0.5% of patients; and alopecia in about 0.2% of patients receiving oral clonidine.

Dermatologic effects were the most frequently occurring adverse effects in clinical trials of transdermal clonidine. In clinical studies, localized skin reactions (i.e., erythema, pruritus) occurred in up to 50% of patients receiving transdermal clonidine therapy. Localized skin reactions occur more commonly in patients who use an adhesive cover over the transdermal system for the entire 7-day application period. Localized skin reactions usually are readily reversible following removal of the transdermal system and have usually not required discontinuance of transdermal therapy. Allergic contact sensitization to clonidine has occurred in about 20% of patients with transdermal therapy, most frequently in white females and least frequently in black males; the dermatitis

may require discontinuance of transdermal therapy. Although systemic anaphylactic reactions have not been reported to date, subsequent administration of oral clonidine (or continued administration of transdermal clonidine) to patients who experience allergic reactions with transdermal therapy may result in a recurrence of the reaction or development of a generalized rash, urticaria, or angioedema. (See Cautions: Precautions and Contraindications.) Localized vesiculation, hyperpigmentation (at the application site), edema, excoriation, burning, throbbing, blanching, generalized macular rash, urticaria, contact dermatitis, alopecia, and localized hypopigmentation or hyperpigmentation also have occurred in patients receiving transdermal clonidine.

■ **Genitourinary Effects** Decreased sexual activity, impotence, and loss of libido have occurred in about 3% of patients receiving oral clonidine. Nocturia has occurred in about 1% of patients, difficulty in micturition in about 0.2% of patients, and urinary retention in about 0.1% of patients receiving oral clonidine. Impotence/sexual dysfunction has been reported in about 2% of patients receiving transdermal clonidine, and loss of libido or decreased sexual activity and difficulty in micturition have been reported in up to 0.5% of patients receiving transdermal clonidine.

■ **Hepatic Effects** Mild, transient abnormalities in liver function test results have occurred in about 1% of patients during oral clonidine therapy. Hepatitis has been reported rarely; one case of hepatitis without icterus and hyperbilirubinemia occurred in a patient receiving clonidine hydrochloride, chlorthalidone, and papaverine, but a relationship to clonidine has not been established.

■ **Other Adverse Effects** Muscle or joint pain has occurred in about 0.6% of patients and leg cramps in about 0.3% of patients receiving oral clonidine. Dryness of the nasal mucosa; blurred vision; dryness and burning of the eyes; weakly positive Coombs' test results; fever, pallor, thrombocytopenia, and increased sensitivity to alcohol also have been reported in patients receiving oral clonidine.

Fever, malaise, pallor, muscle or joint pain, and leg cramps have been reported in up to 0.5% of patients during postmarketing experience with transdermal clonidine.

In several studies in albino rats receiving oral clonidine hydrochloride for 6 months or longer, the drug produced a dose-dependent increase in the frequency and severity of spontaneous retinal degeneration. Distribution studies in dogs and monkeys showed that clonidine is concentrated in the choroid of the eye. Ophthalmologic examinations performed prior to and periodically during oral clonidine hydrochloride therapy in humans (for 24 months or longer in some) revealed no evidence of drug-induced ophthalmologic abnormalities, except dry eyes, nor was there evidence of altered retinal function as determined by specialized tests such as electroretinography and macular dazzle. Blurred vision and burning and/or dryness of the eyes have been reported in up to 0.5% of patients during postmarketing experience with transdermal clonidine.

Implantable epidural catheters are associated with a risk of infection, including meningitis and/or epidural abscess. The incidence of catheter-related infections is about 5–20%, and depends on several factors, including the clinical status of the patient, type of catheter used, catheter placement technique, quality of catheter care, and duration of catheter placement. The possibility of catheter-related infection should be considered in patients receiving epidural clonidine who develop a fever.

■ **Withdrawal Effects** Abrupt withdrawal of clonidine therapy may result in a rapid increase of systolic and diastolic blood pressures with associated symptoms such as nervousness, agitation, confusion, restlessness, anxiety, insomnia, headache, sweating, palpitation, increased heart rate, tremor, hiccups, stomach pains, nausea, muscle pains, and increased salivation. The exact mechanism(s) of the withdrawal syndrome following discontinuance of α-adrenergic agonists has not been determined but may involve increased concentrations of circulating catecholamines, increased sensitivity of adrenergic receptors, enhanced renin-angiotensin system activity, decreased vagal function, failure of autoregulation of cerebral blood flow, and/or failure of central α_2-adrenergic receptor mechanisms that regulate sympathetic outflow from the CNS and modulate baroreflex function.

Withdrawal syndrome has been reported in about 1% of patients receiving oral clonidine. The clonidine withdrawal syndrome is more pronounced after abrupt cessation of long-term therapy than after short-term (1–2 months) therapy and has usually been associated with previous administration of high oral dosages (greater than 1.2 mg daily) and/or with continuation of concomitant β-adrenergic blocking therapy. In addition, the risk of adverse effects following abrupt discontinuance of clonidine therapy may be increased in patients with a history of hypertension and/or other underlying cardiovascular conditions. (See Cautions: Precautions and Contraindications.) When the drug is discontinued abruptly, symptoms such as restlessness and headache may begin to appear 2–3 hours after a dose is missed and blood pressure may increase substantially within 8–24 hours. In a few patients, blood pressure exceeded pretreatment levels. Rare cases of hypertensive encephalopathy, cerebrovascular accidents, and death occurring after abrupt cessation of clonidine therapy have been reported. It has been postulated that the risk of precipitating the withdrawal syndrome should be reduced substantially with use of transdermal clonidine because of the pharmacodynamics associated with this dosage form; however, withdrawal symptoms have been reported occasionally (in up to 0.5% of patients) following discontinuance of transdermal therapy or when absorption of the drug was impaired because of dermatologic changes (e.g., contact dermatitis) under the transdermal system. In one patient, withdrawal symptoms (severe rebound hypertension, tachycardia, headache, diaphoresis) appeared approximately 36–72 hours after discontinuance of transdermal therapy but responded to sublingual nifedipine and oral clonidine therapy. In a few geriatric patients, blood pressure has increased to levels exceeding baseline approximately 3–7 days after transdermal therapy was discontinued, although other signs of a hyperadrenergic state were not evident.

An excessive rise in blood pressure after oral or transdermal clonidine withdrawal can be reversed and symptoms relieved by resumption of oral clonidine or by combined administration of α- and β-adrenergic blocking agents (e.g., phentolamine or prazosin with atenolol, labetalol, or propranolol). Rebound hypertension may present a particular problem if oral clonidine therapy must be interrupted for surgery. It has been reported that when the drug was discontinued 8 hours or more prior to surgery, hypertension resulted during and after surgery; however, when clonidine was administered 4–6 hours preoperatively, only minor hypertension developed and hypotension requiring treatment did not occur.

The manufacturer of oral clonidine states that because children frequently experience vomiting associated with GI illnesses, they may be particularly susceptible to hypertensive episodes resulting from sudden inability to ingest the drug.

In a controlled clinical trial in cancer patients receiving epidural clonidine as an adjunct to epidural morphine for the treatment of pain, about 10% of patients receiving 720 mcg of clonidine hydrochloride daily experienced rebound hypertension following abrupt discontinuance of the drug; one patient subsequently suffered a cerebrovascular accident. Rebound hypertension following discontinuance of epidural clonidine can be reversed by administration of clonidine or IV phentolamine. In patients who are receiving concomitant therapy with a β-adrenergic blocking agent, the β-blocker should be discontinued several days prior to discontinuance (by gradual tapering) of epidural clonidine.

■ **Precautions and Contraindications** When clonidine hydrochloride is used as a fixed-combination preparation that includes chlorthalidone, the cautions, precautions, and contraindications associated with thiazide diuretics must be considered in addition to those associated with clonidine.

Because of the risk of rebound hypertension, patients receiving clonidine preparations should be warned of the danger of missing doses or stopping the drug without consulting their physician. (See Cautions: Withdrawal Effects.) When discontinuing clonidine therapy, a rapid rise in blood pressure may be minimized or prevented by tapered withdrawal of the drug over 2–4 days. Tapered withdrawal of transdermal clonidine or initiation of a tapered regimen of oral clonidine also is recommended by some clinicians when the transdermal dosage form is discontinued, particularly in geriatric patients. If clonidine therapy is to be discontinued in patients receiving clonidine and a β-adrenergic blocking agent concomitantly, the β-adrenergic blocker should be discontinued several days before clonidine therapy is discontinued. It is recommended that clonidine therapy not be interrupted for surgery; transdermal therapy can be continued throughout the perioperative period and oral therapy should be continued to within 4 hours before surgery. Blood pressure should be carefully monitored during surgery and additional measures to control blood pressure should be available if necessary. If clonidine therapy must be interrupted for surgery, parenteral hypotensive therapy should be administered as necessary, and clonidine therapy should be resumed as soon as possible. If transdermal therapy is initiated during the perioperative period, it must be kept in mind that therapeutic plasma clonidine concentrations are not achieved until 2–3 days after initial application of the transdermal system.

Clonidine transdermal systems should be removed from the site(s) of application prior to attempting defibrillation or cardioversion since altered electrical conductivity and enhanced potential for electrical arcing may occur.

Patients receiving transdermal clonidine therapy should be advised that if the transdermal system begins to loosen from the skin after application, an adhesive cover should be applied directly over the system to ensure good adhesion over the period of application. Patients receiving transdermal therapy who develop moderate or severe localized erythema and/or localized vesicle formation at the application site or who develop a generalized rash should consult their physician promptly about the need to remove the transdermal system. If patients develop isolated, mild localized skin irritation before completion of the intended period of use (7 days), the system may be removed and replaced with a new system at a different application site. In patients who develop localized contact sensitization to clonidine with transdermal therapy, subsequent administration of oral clonidine hydrochloride (or continued administration of transdermal clonidine) may be associated with development of a generalized rash. In patients receiving transdermal therapy who develop an allergic reaction, subsequent administration of oral clonidine hydrochloride also may elicit an allergic reaction (e.g., generalized rash, urticaria, angioedema). Patients receiving transdermal clonidine therapy should be instructed to keep both used and unused transdermal systems out of the reach of children. In addition, these patients should be cautioned that even after use, the transdermal system contains active medication that may be harmful if accidentally applied or ingested by infants or children. (See Acute Toxicity: Manifestations.) Patients should be instructed to handle the used transdermal system carefully (e.g., fold the system in half with the sticky sides together) and to dispose of the system out of the reach of children.

In rare instances, loss of blood pressure control has been reported in patients using transdermal clonidine therapy according to the instructions for use.

Epidural clonidine should be used only in patients with severe cancer pain that has failed to respond to an adequate trial with opiate analgesics. The drug is *not* recommended for the management of obstetric, postpartum, or perioperative pain. Careful monitoring of infusion pump function and inspection of catheter tubing for obstruction or dislodgement is recommended to reduce the risk of accidental abrupt withdrawal of epidural clonidine. Patients should be instructed to notify their clinician immediately in case of inadvertent interruption of epidural clonidine administration. Specialized techniques are required for continuous epidural administration of clonidine hydrochloride; the drug should be administered via this route only by qualified individuals familiar with the techniques of administration and patient management problems associated with this route of clonidine administration. Epidural drug administration is contraindicated in patients receiving anticoagulant therapy, in those with a bleeding diathesis, and in the presence of an injection site infection. Administration of epidural clonidine also is not recommended in most patients with severe cardiovascular disease or in patients who are hemodynamically unstable. The manufacturer states that administration of epidural clonidine above the C4 dermatome is contraindicated because of inadequate safety data supporting such use.

Clonidine should be used with caution in patients with severe coronary insufficiency, recent myocardial infarction, conduction disturbances, cerebrovascular disease, chronic renal failure, Raynaud's disease, or thromboangiitis obliterans. Patients with a history of mental depression require careful supervision while receiving clonidine as they may be subject to further depressive episodes. Patients who engage in potentially hazardous activities such as operating machinery or driving should be warned of the possible sedative effect of the drug. In addition, patients should be informed that clonidine may be additive with, or may potentiate the action of, other CNS depressants such as opiate agonists or other analgesics, barbiturates or other sedatives, anesthetics, or alcohol.

The possibility that clonidine may lower blood pressure in patients receiving the drug for conditions other than hypertension (e.g., smoking cessation, pain management, attention deficit hyperactivity disorder) should be considered, and blood pressure should be monitored as appropriate. In addition, the possibility of rebound hypertension and other withdrawal effects should be considered when the drug is discontinued in such patients; abrupt discontinuance should be avoided.

A dose-dependent increase in the incidence and severity of spontaneously occurring retinal degeneration was observed in albino rats receiving the drug for 6 months or longer, especially those receiving strong exposure to light. Although serious adverse ophthalmologic effects have not been reported in patients receiving clonidine, periodic eye examinations should be performed in patients receiving the drug.

Clonidine is contraindicated in patients with known hypersensitivity to the drug or to any ingredient or component in the formulation.

■ **Pediatric Precautions** Safe use of oral clonidine hydrochloride for the management of attention deficit hyperactivity disorder in children has not been established, but clinical studies are currently under way to determine pediatric safety and efficacy. Safety and efficacy of oral clonidine hydrochloride and clonidine transdermal system for the management of hypertension in children younger than 12 years of age have not been established. For information on overall principles for treatment of hypertension and overall expert recommendations for such disease in pediatric patients, see Uses: Hypertension in Pediatric Patients, in the Thiazides General Statement 40:28.20. The safety and efficacy of clonidine hydrochloride epidural infusion have been established in pediatric patients who are old enough to tolerate placement and management of an epidural catheter, based on evidence from adequate, well-controlled studies in adults and experience with the use of clonidine in pediatric patients for other indications. Epidural clonidine should be used only in pediatric patients with severe, intractable cancer pain that is unresponsive to epidural or spinal opiates and to other conventional analgesic therapy.

Children may be more likely to experience CNS depression associated with clonidine overdosage than adults. In children, signs of toxicity have occurred with clonidine doses as low as 0.1 mg. Rare cases of clonidine toxicity (many involving children) associated with accidental or deliberate mouthing or ingestion of clonidine transdermal systems have been reported.

The manufacturer of oral clonidine states that because children frequently experience vomiting associated with GI illnesses, they may be particularly susceptible to hypertensive episodes resulting from sudden inability to ingest the drug.

■ **Mutagenicity and Carcinogenicity** There was no evidence of clonidine-induced mutagenesis in vitro in the Ames microbial mutagen test. Clonidine was not clastogenic in the mouse micronucleus test. Studies to determine the carcinogenic potential of clonidine were performed in rats receiving oral dosages up to 46 times the maximum recommended human dosage on a mg/kg basis for 132 weeks and in mice receiving up to 70 times the maximum recommended human dosage on a mg/kg basis for up to 78 weeks. These dosages were approximately 9 and 6 times the maximum recommended human daily dosage on a mg/m² basis in rats and mice, respectively.

■ **Pregnancy, Fertility, and Lactation** ***Pregnancy*** Reproduction studies in rabbits using oral clonidine hydrochloride dosages up to about 3 times the maximum recommended human dosage have not revealed evidence of teratogenicity or embryotoxicity. However, in female rats receiving the drug continuously for 2 months prior to mating, an increased incidence of fetal resorptions occurred with oral dosages as low as one-third the maximum recommended human dosage (1/15th the maximum recommended human dosage on a mg/m² basis); resorptions were not increased when these or higher dosages (up to 3 times the maximum recommended human dosage) were administered during days 6–15 of gestation. An increased incidence of fetal resorptions was observed when much higher dosages (40 times the maximum recommended human dosage on a mg/kg basis and 4–8 times the maximum recommended human dosage on a mg/m² basis) were administered to mice and rats during days 1–14 of gestation; the lowest dosage used in the study was 0.5 mg/kg. There are no adequate and controlled studies to date using clonidine in pregnant women, and the drug should be used during pregnancy only when clearly needed.

Smoking cessation programs consisting of behavioral and educational rather than pharmacologic interventions should be tried in pregnant women before drug therapy is considered. Smoking cessation therapy with clonidine, which is a second-line agent, should be used during pregnancy only if the increased likelihood of smoking cessation, with its potential benefits, justifies the potential risk to the fetus and patient of clonidine and possible continued smoking, and first-line pharmacotherapy (e.g., bupropion, nicotine replacement) has failed. Although smoking cessation prior to conception or early in pregnancy is most beneficial, health benefits result from cessation at anytime; therefore, effective smoking cessation interventions should be offered at the first prenatal visit and persist throughout the course of pregnancy for women who continue smoking after conception.

Fertility Reproduction studies in rats using oral clonidine hydrochloride dosages up to 0.15 mg/kg daily (about 3 times the maximum recommended human dosage) have not revealed evidence of impaired fertility; however, fertility in female rats was impaired at oral dosages ranging from 0.5–2 mg/kg daily (about 10–40 times the maximum recommended human oral dosage on a mg/kg basis [2–8 times the maximum recommended human dosage on a mg/m² basis]).

Lactation Since clonidine is distributed into milk, the drug should be used with caution in nursing women. The manufacturer of parenteral clonidine states that because of the potential for serious adverse reactions to clonidine in nursing infants, a decision should be made whether to discontinue nursing or the drug, taking into account the importance of the drug to the woman.

Drug Interactions

■ **CNS Depressants** Clonidine may be additive with, or may potentiate the action of, other CNS depressants such as opiates or other analgesics, barbiturates or other sedatives, anesthetics, or alcohol. Concomitant administration of opiate analgesics with clonidine also may potentiate the hypotensive effects of clonidine.

■ **Psychotherapeutic Agents** Tricyclic antidepressants (i.e., imipramine, desipramine) have reportedly inhibited the hypotensive effect of clonidine. The increase in blood pressure usually occurs during the second week of tricyclic antidepressant therapy, but occasionally may occur during the first several days of concomitant therapy. The possibility of this interaction should be considered in patients receiving clonidine and tricyclic antidepressants concomitantly; blood pressure should be closely monitored during the first several weeks of concurrent therapy, and dosage of clonidine should be increased to adequately control hypertension if necessary. Alternatively, other hypotensive agents that do not interact with tricyclic antidepressants may be substituted, but clonidine therapy should *not* be discontinued abruptly. If tricyclic antidepressant therapy is discontinued in patients receiving clonidine, the hypotensive effect of clonidine may increase; blood pressure should be monitored and dosage of clonidine reduced if necessary. In rats, concurrent administration of clonidine and amitriptyline has produced corneal lesions within 5 days. The effects of tricyclic antidepressants on the analgesic effect of epidural clonidine hydrochloride are not known.

Clonidine withdrawal may result in an excess of circulating catecholamines; therefore, caution should be exercised in concomitant use of drugs which affect the metabolism or tissue uptake of these amines (monoamine oxidase inhibitors or tricyclic antidepressants, respectively).

Acute delirium has been reported in at least one patient receiving fluphenazine concomitantly with oral clonidine. The symptoms resolved following discontinuance of clonidine and recurred upon rechallenge with the drug.

■ **Cardiovascular Drugs** When clonidine is administered with other hypotensive agents, including diuretics, the hypotensive effect of clonidine may be increased. This effect is usually used to therapeutic advantage in antihypertensive therapy; however, careful adjustment of dosage is necessary when these drugs are used concomitantly.

Because clonidine may produce bradycardia and atrioventricular (AV) block, the possibility of additive effects should be considered if it is given concomitantly with other drugs that affect sinus node function or AV nodal conduction (e.g., guanethidine), β-adrenergic blocking agents (e.g., propranolol), calcium-channel blocking agents, or cardiac glycosides.

Because β-adrenergic blocking agents may exacerbate rebound hypertension that may occur following discontinuance of clonidine therapy, β-adrenergic blocking agents should be discontinued several days before gradual withdrawal of clonidine when clonidine therapy is to be discontinued in patients

receiving a β-adrenergic blocking agent and clonidine concurrently. If clonidine therapy is to be replaced by a β-adrenergic blocking agent, administration of the β-adrenergic blocking agent should be delayed for several days after clonidine therapy has been discontinued.

■ **Other Drugs** Epidural clonidine may prolong the duration of the pharmacologic effects, including both sensory and motor blockade, of epidural local anesthetics.

Acute Toxicity

■ **Pathogenesis** The oral LD_{50} of clonidine hydrochloride is 206 and 465 mg/kg in mice and rats, respectively.

■ **Manifestations** Signs and symptoms of overdosage of clonidine include hypotension (which may be profound), transient hypertension, weakness, vomiting, irritability, diminished or absent reflexes, lethargy, somnolence, drowsiness, deep sedation, irritability, skin pallor, hypothermia, decreased or irregular heart rate, dryness of the mouth, constricted pupils with poor reaction to light, respiratory depression, and hypoventilation. Large overdoses may result in reversible cardiac conduction defects or dysrhythmias, apnea, coma, and seizures. Signs and symptoms of clonidine overdosage usually occur within 30–120 minutes after ingestion. Children may be more likely to experience CNS depression associated with clonidine overdosage. In children, signs of toxicity have occurred with oral clonidine doses as low as 0.1 mg. Rare cases of clonidine toxicity (many involving children) associated with accidental or deliberate mouthing or ingestion of clonidine transdermal systems have been reported. In one individual who reportedly ingested 100 mg of clonidine hydrochloride, plasma clonidine concentrations were 60, 90, 370, 120, and 120 ng/mL 1, 1.5, 2, 5.5, and 6.5 hours after ingestion. Signs and symptoms of overdosage in this patient included transient hypertension followed by hypotension, bradycardia, apnea, hallucinations, partial coma, and ventricular premature contractions; the patient recovered following intensive symptomatic and supportive treatment. In a 2-year old infant who apparently ingested clonidine from a used and discarded transdermal system, a serum clonidine concentration determined 24 hours after ingestion was approximately 8 ng/mL (therapeutic range: 0.5–4.5 ng/mL). In this infant, lethargy developed over several hours and was accompanied by bradycardia, hypotension, miosis, and gasping respirations; the patient was monitored in an intensive care unit and recovered over a period of 16 hours without specific treatment.

■ **Treatment** There is no known specific antidote for clonidine overdosage. If signs and symptoms of clonidine overdosage occur in patients receiving transdermal therapy, all transdermal systems should be removed. Following removal of the transdermal system(s), plasma concentrations of clonidine will persist for about 8 hours and then decline slowly over several days. Ipecac-induced emesis and gastric lavage would not be expected to remove significant amounts of clonidine following transdermal exposure. If the transdermal system has been ingested, whole bowel irrigation may be considered, and the administration of activated charcoal and/or cathartic agents may be beneficial.

In acute overdosage with oral clonidine, gastric lavage may be indicated following recent and/or large ingestions; administration of an activated charcoal slurry and/or cathartic agents may be beneficial. Because clonidine overdosage may result in the rapid development of CNS depression, induction of emesis using ipecac syrup is not recommended. If the patient is comatose, having seizures, or lacks the gag reflex, gastric lavage may be performed if an endotracheal tube with cuff inflated is in place to prevent aspiration of gastric contents. Supportive and symptomatic treatment should be initiated and an adequate airway established and maintained since respiratory depression or apnea may ensue. Supportive care may include atropine sulfate for symptomatic bradycardia, IV fluids and/or vasopressor agents for hypotension, and vasodilators for hypertension. Patients with hypotension also may be placed in Trendelenburg's position; IV infusion of dopamine may be useful for severe, persistent hypotension. The manufacturers state that administration of tolazoline has yielded inconsistent results and is not recommended as first-line therapy for clonidine overdosage. Hypertension has been managed with IV furosemide or diazoxide or α-adrenergic blocking agents (e.g., phentolamine). Additional information on the efficacy of α-adrenergic blockers in the treatment of clonidine overdosage is necessary. Naloxone may be a useful adjunct for the management of respiratory depression, hypotension, and/or coma associated with clonidine overdosage; because paradoxical hypertension occasionally has been reported with the use of naloxone, blood pressure should be monitored. Seizures can be managed with IV administration of a benzodiazepine (e.g., diazepam). Although forced diuresis has been suggested to enhance the elimination of clonidine, there is no current evidence to support this procedure for clonidine overdosage; in addition, forced diuresis may potentiate clonidine-induced hypotension. Hemodialysis is of limited value in the treatment of clonidine overdosage, since a maximum of 5% of circulating drug is removed.

Pharmacology

■ **Cardiovascular Effects** Clonidine appears to stimulate α_2-adrenergic receptors in the CNS (mainly in the medulla oblongata), causing inhibition, but not blockade, of sympathetic vasomotor centers. Cardiovascular reflexes remain intact, and normal homeostatic mechanisms and hemodynamic responses to exercise are maintained. The central effects of the drug result in reduced peripheral sympathetic nervous system activity, reduced peripheral and renovascular resistance, reduction of systolic and diastolic blood pressure, and bradycardia. Peripheral venous pressure remains unchanged. It has been postulated that the hypotensive response to clonidine may result from reduced angiotensin II generation because of inhibition of renin release or from reduced stimulation of medullary vasomotor centers responsive to circulating angiotensin II; however, the exact relationship between the action of the drug in reducing renin activity and excretion of aldosterone and catecholamines and the hypotensive effect of the drug has not been fully elucidated.

Clonidine reduces blood pressure to essentially the same extent in both supine and standing patients; therefore, orthostatic effects are mild and infrequently encountered. However, the underlying hemodynamic effects differ with position of the patient. Administration of a single dose of clonidine hydrochloride to supine patients results in a reduction in cardiac output and decreased stroke volume. Total peripheral resistance remains unchanged. In patients in the standing position or at a 45° tilt, a smaller decrease in cardiac output occurs and total peripheral resistance is decreased, but stroke volume is maintained. Prolonged therapy results in circulatory adjustments, so that the hypotensive effect of the drug largely results from reduced peripheral resistance. Rapid IV, but not oral or IM, administration of clonidine produces direct stimulation of peripheral α_2-adrenergic receptors, resulting in transient vasoconstriction and a rise in systolic and diastolic blood pressure.

Urinary excretion of catecholamines is decreased during clonidine hydrochloride therapy; however, unlike reserpine, clonidine does not deplete catecholamines from the heart or other tissues. Abrupt withdrawal of clonidine following prolonged oral administration may cause increased urinary excretion of catecholamines and rebound of systolic and diastolic blood pressure.

Blood volume, as determined using iodinated I 131 serum albumin, is not substantially affected by clonidine. Circulation time is prolonged during use of the drug.

■ **Analgesic Effect** Epidurally administered α_2-agonists, including clonidine, produce anagesia by mimicking the activation of descending pain-suppressing pathways arising from supraspinal control centers (i.e., cortex, thalamus, and brainstem) and terminating in the dorsal horn of the spinal cord. Stimulation of spinal α_2-adrenergic receptors by clonidine inhibits sympathetically mediated ascending pain pathways that are activated by nociceptive stimuli and prevents transmission of pain signals to the brain. Activation of α_2-adrenergic receptors by α_2-adrenergic agonists also stimulates acetylcholine release and inhibits the release of substance P, an inflammatory neuropeptide. Clonidine-mediated analgesia is dose-dependent and is limited to regions of the body that are innervated by spinal segments containing analgesic concentrations of the drug. Analgesia resulting from clonidine therapy is not antagonized by opiate antagonists.

■ **Renal and Metabolic Effects** Acute or chronic administration of clonidine hydrochloride produces no substantial change in renal blood flow, renal plasma flow, or glomerular filtration rate. In standing patients, renal vascular resistance is substantially reduced. The moderate reduction in renal blood flow and glomerular filtration rate produced by head-up tilting are unchanged by administration of the drug. The increased renal vascular resistance which normally occurs after tilting does not occur in patients receiving clonidine.

Sodium and chloride excretion are markedly reduced after initial administration of clonidine hydrochloride; however, potassium excretion is not substantially changed. Sodium retention probably results from enhanced tubular reabsorption being stimulated by decreased renal perfusion pressure and generally persists for only 3–4 days after which natriuresis occurs. Renal vein plasma renin activity and aldosterone excretion rate are consistently reduced as a result of centrally mediated sympathetic inhibition.

■ **Other Effects** Acute administration of clonidine stimulates release of growth hormone in children and adults, but the drug does not produce sustained elevation of growth hormone during chronic administration.

The sedative effect of clonidine is thought to result from central α_2-agonist activity. The decrease in salivation induced by clonidine appears to result from both central and peripheral mechanisms, probably involving the drug's α_2-agonist activity. The peripheral mechanism of decreased salivation may involve inhibition of cholinergic transmission via stimulation of α_2-adrenergic receptors.

Clonidine has been shown to decrease GI motility and control diarrhea in animals, probably secondary to the drug's α_2-agonist activity. Clonidine has also been shown to increase intestinal absorption of sodium and chloride, with a secondary passive increase in water absorption.

IV or topical administration of clonidine hydrochloride in patients with glaucoma decreases intraocular pressure, reportedly by decreasing production of aqueous humor. It has been reported that when only one eye is treated topically with clonidine, ocular pressure in the untreated eye is also reduced.

Clonidine has been shown to reduce the signs and symptoms of opiate withdrawal in individuals physically dependent on opiates. Clonidine appears to reduce the severity of opiate withdrawal symptoms by stimulating central presynaptic α_2-adrenergic receptors; the stimulation results in attenuation in noradrenergic activity in the CNS, which may be responsible for the behavioral symptoms of opiate withdrawal.

Pharmacokinetics

■ **Absorption** Clonidine hydrochloride is well absorbed from the GI tract. The drug may also be absorbed when applied topically to the eye. Clon-

idine is well absorbed percutaneously following topical application of a transdermal system to the arm or chest. Plasma clonidine concentrations of 2 ng/mL have been detected 1 hour after administration of a single 0.39-mg oral dose of radiolabeled drug. Peak plasma concentrations following oral administration occur in approximately 3–5 hours.

Following initial application of a transdermal system of clonidine, the initial release of the drug saturates skin sites beneath the system; therapeutic plasma concentrations are attained within 2–3 days. To provide the concentration gradient necessary for controlled release and percutaneous absorption of drug, clonidine transdermal systems contain an excess amount of drug. Following removal of the systems in one study in healthy adults, analysis of residual concentration of drug in transdermal systems that initially contained 2.5 mg of clonidine per 3.5 cm^2 surface area indicated that release of clonidine averaged 48 and 65% after 7 and 11 days of wear, respectively, following topical application to the upper outer arm and averaged 70% after 11 days of wear following topical application to the chest. When given in dosages that produce comparable blood pressure reduction, steady-state plasma clonidine concentrations attained with the transdermal systems are generally similar to trough concentrations attained with twice-daily oral dosing regimens of the drug. Mean steady-state plasma clonidine concentrations of 0.39, 0.84, or 1.12 ng/mL have been reported following topical application of the 3.5-, 7-, or 10.5-cm^2 transdermal system (see Preparations), respectively, to the upper outer arm of healthy adults. Percutaneous absorption of the drug from the upper arm or chest is similar, but less drug is absorbed from the thigh. Replacement of the transdermal system at a different site at weekly intervals continuously maintains therapeutic plasma clonidine concentrations. Following discontinuance of transdermal therapy, therapeutic plasma drug concentrations persist for about 8 hours and then decline slowly over several days; over this time period, blood pressure returns gradually to pretreatment levels. If a transdermal system of clonidine is not removed after 7 days as recommended, absorption of the drug from the system may continue; if an additional system is then applied, higher plasma drug concentrations may result and, if an additional system is not applied, plasma drug concentrations may not decrease substantially for at least 2–4 more days while the system is still being worn.

Reduction in blood pressure is maximal at plasma clonidine concentrations less than 2 ng/mL. Blood pressure begins to decrease within 30–60 minutes after an oral dose of clonidine hydrochloride; the maximum decrease occurs in approximately 2–4 hours. The hypotensive effect lasts up to 8 hours. Following administration of clonidine by slow IV injection† in patients with acute hypertensive crisis, a hypotensive effect occurred within minutes, peaked in 30–60 minutes, and lasted more than 4 hours.

Following epidural administration of a single bolus dose of clonidine in healthy individuals and patients with cancer, clonidine is rapidly absorbed into the systemic circulation. A mean peak plasma clonidine concentration of 4.4 ng/mL (range: 3–5.8 ng/mL) was reported on average 19 minutes following epidural administration of 700 mcg of clonidine hydrochloride given over 5 minutes in healthy individuals. Mean peak plasma concentrations of clonidine were reported to be higher in women than in men. Following continuous epidural infusion of clonidine hydrochloride (30 mcg/hour for 14 days in addition to administration of morphine sulfate for patient-controlled analgesia [PCA]) in cancer patients, mean steady-state plasma concentrations were approximately 2.2 and 2.4–2.5 ng/mL on days 7 and 14 of dosing, respectively. Accumulation of clonidine does not appear to occur following continuous epidural infusion of the drug in adult cancer patients.

Following epidural administration of a single dose of clonidine hydrochloride, near maximal analgesia occurs within 30–60 minutes. Onset and duration of the analgesic effect of a single epidural dose of clonidine do not correlate with plasma drug concentrations; rather, analgesic effects appear to correlate with drug concentration in the CSF. Although the CSF is not the presumed site of action of clonidine-mediated analgesia, the drug appears to diffuse rapidly from the CSF to the dorsal horn. A lumbar CSF concentration of 130 ng/mL reportedly was associated with a 95% maximal analgesic effect in healthy individuals.

■ **Distribution** Animal studies indicate that clonidine is widely distributed into body tissues; tissue concentrations of the drug are higher than plasma concentrations. The mean volume of distribution of clonidine is reported to be 2.1 L/kg. After oral administration, highest concentrations of the drug are found in the kidneys, liver, spleen, and GI tract. High concentrations of the drug also appear in the lacrimal and parotid glands. Clonidine is concentrated in the choroid of the eye and is also distributed into the heart, lungs, testes, adrenal glands, fat, and muscle. The lowest concentration occurs in the brain. Clonidine is distributed into CSF. Following epidural infusion, clonidine is rapidly and extensively distributed into CSF and readily partitions into the plasma via epidural veins. In vitro, clonidine is approximately 20–40% bound to plasma proteins, mainly albumin. Clonidine crosses the placenta and is distributed into milk. In one lactating woman who received approximately 0.04 mg of oral clonidine hydrochloride twice daily and 25 mg of oral dihydralazine 3 times daily, clonidine concentrations were 0.33 ng/mL in a plasma sample obtained 1 hour after a dose and 0.6 ng/mL in a milk sample obtained 2.5 hours after a dose; the drug was not detected in the plasma of the infant 1 hour after nursing.

■ **Elimination** The plasma half-life of clonidine is 6–20 hours in patients with normal renal function. The half-life in patients with impaired renal function has been reported to range from 18–41 hours. The elimination half-life of the drug may be dose dependent, increasing with increasing dose.

Clonidine hydrochloride is metabolized in the liver. In humans, 4 metabolites have been detected but only one, the inactive *p*-hydroxyclonidine, has been identified.

In humans, 40–60% of an orally administered dose of clonidine hydrochloride is excreted in urine as unchanged drug within 24 hours. Following IV administration of radiolabeled clonidine, 72% of the administered dose is excreted in urine within 96 hours; about 40–50% is excreted as unchanged drug. In humans, less than 10% of a dose usually is excreted as *p*-hydroxyclonidine. Approximately 20% of the dose is excreted in feces, probably via enterohepatic circulation. Approximately 85% of a single dose is excreted within 72 hours, and excretion is complete after 5 days. Following IV administration of clonidine, renal clearance of the drug averages 133 mL/minute. In patients undergoing hemodialysis, only 5% of a dose was removed into the dialysate. Following continuous epidural infusion of clonidine hydrochloride (30 mcg/hour for 14 days in addition to morphine sulfate administered for patient-controlled analgesia [PCA]) in cancer patients, mean total body clearance of the drug was approximately 279 and 272 mL/minute on days 7 and 14 of dosing, respectively.

Chemistry and Stability

■ **Chemistry** Clonidine hydrochloride, an imidazoline-derivative hypotensive agent, is a selective α_2-adrenergic agonist. Clonidine is commercially available as the base and as the hydrochloride salt. Clonidine hydrochloride occurs as a white, crystalline powder that has a bitter taste and is freely soluble in water and soluble in alcohol. Clonidine hydrochloride also is commercially available as a clear, colorless, preservative-free aqueous sterile solution. Sodium hydroxide and/or hydrochloric acid may be added during manufacture of the injection to adjust the pH to 5–7.

The commercially available transdermal system of clonidine consists of an outer layer of pigmented polyester film; a drug reservoir of clonidine, mineral oil, polyisobutylene, and colloidal silicon dioxide; a microporous polypropylene membrane that controls the rate of diffusion of the drug; and a final adhesive layer that provides an initial release of drug and contains those ingredients found in the reservoir. The adhesive layer is covered by a protective slit release liner which is removed prior to application.

■ **Stability** The commercially available transdermal system of clonidine should be stored at a temperature less than 30°C. Clonidine hydrochloride tablets should be stored in tight, light-resistant containers at a controlled room temperature of 25°C, but may be exposed to temperatures ranging from 15–30°C. Commercially available clonidine hydrochloride tablets have an expiration date of 42 months following the date of manufacture. Commercially available clonidine hydrochloride injection should be stored at controlled room temperature of 25°C, but may be exposed to temperatures ranging from 15–30°C. The injection contains no preservatives; any unused portion should be discarded.

Preparations

Excipients in commercially available drug preparations may have clinically important effects in some individuals; consult specific product labeling for details.

Clonidine

Topical		
Transdermal System	0.1 mg/24 hours (2.5 mg/3.5 cm^2)	**Catapres-TTS®**, Boehringer Ingelheim
	0.2 mg/24 hours (5 mg/7 cm^2)	**Catapres-TTS®**, Boehringer Ingelheim
	0.3 mg/24 hours (7.5 mg/10.5 cm^2)	**Catapres-TTS®**, Boehringer Ingelheim

Clonidine Hydrochloride

Oral		
Tablets	0.1 mg*	**Catapres®** (scored), Boehringer Ingelheim
		Clonidine Hydrochloride Tablets
	0.2 mg*	**Catapres®** (scored), Boehringer Ingelheim
		Clonidine Hydrochloride Tablets
	0.3 mg*	**Catapres®** (scored), Boehringer Ingelheim
		Clonidine Hydrochloride Tablets
Parenteral		
For injection, concentrate, for epidural use	500 mcg/mL	**Duraclon®**, Xanodyne

Injection, for epidural use	100 mcg/mL	Duraclon*, Xanodyne

*available from one or more manufacturer, distributor, and/or repackager by generic (nonproprietary) name

Clonidine Hydrochloride and Chlorthalidone

Oral		
Tablets	0.1 mg Clonidine Hydrochloride and Chlorthalidone 15 mg	Clorpres* (scored), Mylan
	0.2 mg Clonidine Hydrochloride and Chlorthalidone 15 mg	Clorpres* (scored), Mylan
	0.3 mg Clonidine Hydrochloride and Chlorthalidone 15 mg	Clorpres* (scored), Mylan

†Use is not currently included in the labeling approved by the US Food and Drug Administration

Guanabenz Acetate

■ Guanabenz acetate is a centrally active hypotensive agent that is structurally and pharmacologically related to clonidine.

Uses

■ **Hypertension** Guanabenz is used alone or in combination with other classes of antihypertensive agents in the management of hypertension. Thiazide diuretics, however, are considered the preferred initial monotherapy for uncomplicated hypertension by the Joint National Committee (JNC 7) on the Prevention, Detection, Evaluation, and Treatment of Hypertension in the US. (See Uses: Hypertension in Adults, in the Thiazides General Statement 40:28.20.)

The efficacy of guanabenz in hypertensive patients is similar to that of other adrenergic agonists such as clonidine, methyldopa, or β-adrenergic blocking agents (e.g., pindolol, propranolol). As with other hypotensive agents, treatment with guanabenz is not curative; after withdrawal of the drug, blood pressure returns to pretreatment levels or greater.

Although many hypertensive patients may be controlled by guanabenz alone, the drug may be more effective when used with a diuretic. Guanabenz has been used in conjunction with thiazide diuretics, producing a greater reduction in blood pressure than that obtained with either drug alone. Concomitant use with a diuretic may permit dosage reduction of either or both drugs and minimize adverse effects while maintaining blood pressure control. However, the possibility that geriatric patients may not tolerate the adverse cognitive effects of central α_2-adrenergic agonists such as guanabenz should be considered.

Guanabenz may be particularly useful in hypertensive patients whose baseline catecholamine concentrations are markedly elevated and whose hypertension is characterized by increased sympathetic activity. Guanabenz also may be useful in the treatment of hypertension that is predominantly of the systolic form, commonly occurring in patients 60 years of age and older, although thiazide diuretics generally are preferred for the treatment of isolated systolic hypertension in geriatric adults because of established cardiovascular benefits (e.g., stroke reduction). Because guanabenz does not appear to induce sodium retention, the drug is useful in patients who develop secondary renal- or cardiac-induced sodium retention during therapy with clonidine or methyldopa. Guanabenz has been used in diabetic hypertensive patients with no adverse effect on control or therapy of diabetes; the drug also has been effective in hypertensive patients with chronic obstructive pulmonary disease (COPD), including asthma, chronic bronchitis, or emphysema.

For additional information on overall principles for treatment of hypertension and overall expert recommendations for such disease, see Uses: Hypertension in Adults, in the Thiazides General Statement 40:28.20.

■ **Other Uses** Guanabenz has been used alone or in combination with naltrexone in the management of opiate withdrawal† in patients physically dependent on opiates and undergoing detoxification. Guanabenz has also been used as an analgesic in a limited number of patients with chronic pain†; use of the drug permitted a reduction in opiate dosage or discontinuance of opiate therapy in these patients, but additional study is necessary.

Dosage and Administration

■ **Administration** Guanabenz acetate is administered orally. To ensure overnight blood pressure control and minimize daytime drowsiness, the last dose of the day should be administered at bedtime. Guanabenz has also been given as a single daily dose administered at bedtime to minimize adverse effects.

If guanabenz therapy is to be discontinued, dosage of the drug should be slowly reduced over several days to avoid the possibility of precipitating the withdrawal syndrome. (See Cautions: Withdrawal Effects.)

■ **Dosage** Dosage of guanabenz acetate is expressed in terms of guanabenz.

Hypertension Dosage of guanabenz must be adjusted according to the patient's blood pressure response and tolerance. Additional dosage adjustment may be necessary in hypertensive patients with hepatic impairment.

Adult Dosage. The initial adult dosage of guanabenz, when administered alone or in combination with a thiazide diuretic, is 2–4 mg twice daily. Dosage may be increased by 4- or 8-mg increments daily at 1- to 2-week intervals or longer until the desired blood pressure response is achieved. The usual maintenance dosage of guanabenz ranges from 4–16 mg twice daily. The maximum dosage studied in patients with hypertension to date and recommended by the manufacturer and most clinicians is 32 mg twice daily, but such dosages are rarely necessary.

Pediatric Dosage. In children 12 years of age and older, the maintenance dosage of guanabenz has been 4–24 mg daily (0.08–0.2 mg/kg daily), administered in 2 divided doses. Initial dosages of the drug in these children ranged from 0.5–4 mg daily and were increased in increments of 0.5–2 mg daily, depending on patient weight, age, response, and tolerance.

Blood Pressure Monitoring and Treatment Goals. Careful monitoring of blood pressure during initial titration or subsequent upward adjustment in dosage of guanabenz is recommended. Large or abrupt reductions in blood pressure generally should be avoided.

Once antihypertensive drug therapy has been initiated, dosage generally is adjusted at approximately monthly intervals (more aggressively in high-risk patients [stage 2 hypertension, comorbid conditions]) if blood pressure control is inadequate at a given dosage; it may take months to control hypertension adequately while avoiding adverse effects of therapy. (For definition of stages of hypertension, see Initial Drug Therapy under Uses: Hypertension in Adults, in the Thiazides General Statement 40:28.20.) Once blood pressure has been stabilized, follow-up visits with the clinician generally can be scheduled at 3- to 6-month intervals, depending on patient status.

Because systolic blood pressure has been shown to be a more precise indicator of cardiovascular risk than diastolic blood pressure (except in patients younger than 50 years of age), the coordinating committee of the National High Blood Pressure Education Program (NHBPEP) recommends using systolic blood pressure as the principal clinical end point for detecting, evaluating, and treating hypertension, especially in middle-aged and geriatric patients. In addition, once the goal systolic blood pressure is attained, most hypertensive patients also will achieve the goal diastolic blood pressure.

The goal of hypertension management and prevention is to achieve and maintain a lifelong systolic blood pressure less than 140 mm Hg and a diastolic blood pressure less than 90 mm Hg if tolerated. Because treatment to lower levels may be particularly useful to prevent stroke, to preserve renal function, and to prevent or slow heart failure progression in hypertensive patients with diabetes mellitus or renal impairment, the goal of hypertension management and prevention in such patients is to achieve and maintain a systolic blood pressure less than 130 mm Hg and a diastolic blood pressure less than 80 mm Hg. Many experts recommend a goal of achieving and maintaining a systolic blood pressure of 125 mm Hg or less and a diastolic blood pressure of 75 mm Hg or less in hypertension management in patients with proteinuria (urinary protein excretion exceeding 1 g per 24 hours) and renal insufficiency (regardless of etiology).

For additional information on initiating and adjusting guanabenz dosage in the management of hypertension, see Blood Pressure Monitoring and Treatment Goals under Dosage: Hypertension, in Dosage and Administration in the Thiazides General Statement 40:28.20.

Opiate Withdrawal A guanabenz dosage of 4 mg twice daily has been used in the management of opiate withdrawal† in patients physically dependent on opiates and undergoing detoxification; if necessary to control signs and symptoms of withdrawal, dosage has been increased to 4 mg 4 times daily.

Cautions

Overall, the frequency of adverse effects produced by guanabenz is similar to or greater than that produced by clonidine and by methyldopa. Adverse effects of guanabenz generally are mild, appear to be dose related, usually occur within the first 2 weeks of therapy, and tend to diminish with continued therapy or may be relieved by a reduction in dosage. Adverse nervous system effects (e.g., sedation) and dry mouth occur most frequently during guanabenz therapy. Although adverse effects of the drug generally are not severe, discontinuance of guanabenz therapy has been necessary in about 10–15% of patients, principally because of intolerable sedation or dry mouth. The manufacturer states that the incidence of the most frequently reported adverse effects was similar in patients receiving guanabenz or placebo in some studies.

■ **Nervous System Effects** Sedation (e.g., drowsiness, tiredness) occurs in about 20% of patients at a guanabenz dosage of 8 mg daily and in about 40% at a dosage of 8 mg twice daily. Dizziness, weakness, and headache occur in about 12–17, 10, and 5% of patients receiving the drug, respectively. Other adverse nervous system effects, including anxiety, irritability, tremor, ataxia, mental depression, insomnia, and numbness, occur in up to 3% of patients receiving guanabenz but have not been directly attributed to the drug.

■ **GI Effects** Dry mouth occurs in 30–40% of patients receiving guanabenz. Other GI effects, including nausea, epigastric pain, diarrhea, vomiting, constipation, anorexia, abdominal discomfort, and dysgeusia, occur in up to 3% of patients receiving the drug.

Clonidine

Dosing & Indications

- **Adult Dose**
  - Essential hypertension: (transderm patch), initial, 0.1 mg/day TRANSDERMAL patch applied once every 7 days to upper outer arm or chest; titrate up by 0.1 mg/day TRANSDERMAL patch increments every one to two weeks as needed; MAX 0.6 mg/day every 7 days
  - Essential hypertension: when discontinuing therapy, gradually decrease the dose over 2 to 4 days to reduce the risk of withdrawal symptoms
  - Hot sweats: 0.1 mg/day TRANSDERMAL PATCH every 7 days
- **Pediatric Dose**
  - safety and efficacy in children have not been established
  - Attention deficit hyperactivity disorder: initial, 0.05 mg ORALLY once daily at bedtime; increase by 0.05 mg every 3 days until a 3 or 4 times daily dosing schedule is reached (mean dose 0.23 to 0.24 mg/day); MAX dose 0.6 mg/day (clinical study dosing)
- **Dose Adjustments**
  - renal impairment: lower initial dose is recommended
  - geriatric: lower initial doses are recommended since elderly patients may experience more troublesome orthostatic hypotension and impairment of motor function and thought processes
  - hemodialysis: no dosage supplementation of clonidine is required following hemodialysis
- **FDA Labeled Indications**
  - Essential hypertension
    - ◇ FDA Approval:
      Adult, yes
      Pediatric, no
    - ◇ Efficacy:
      Adult, Effective
      Pediatric, Evidence favors efficacy
    - ◇ Strength of Recommendation:
      Adult, Class IIb
      Pediatric, Class IIb
    - ◇ Strength of Evidence:
      Adult, Category B
      Pediatric, Category C
- **Non-FDA Labeled Indications**
  - Attention deficit hyperactivity disorder
    - ◇ FDA Approval:
      Adult, no
      Pediatric, no

- Efficacy:
  Pediatric, Evidence is inconclusive
- Strength of Recommendation:
  Pediatric, Class IIb
- Strength of Evidence:
  Pediatric, Category B

- Hot sweats
  - FDA Approval:
    Adult, no
    Pediatric, no
  - Efficacy:
    Adult, Evidence favors efficacy
  - Strength of Recommendation:
    Adult, Class IIb
  - Strength of Evidence:
    Adult, Category B
- Ischemic foot ulcer; Adjunct
  - FDA Approval:
    Adult, no
    Pediatric, no
  - Efficacy:
    Adult, Evidence favors efficacy
  - Strength of Recommendation:
    Adult, Class IIb
  - Strength of Evidence:
    Adult, Category B
- Nicotine dependence
  - FDA Approval:
    Adult, no
    Pediatric, no
  - Efficacy:
    Adult, Evidence favors efficacy
  - Strength of Recommendation:
    Adult, Class IIb
  - Strength of Evidence:
    Adult, Category A
- Opioid withdrawal

- FDA Approval:
  Adult, no
  Pediatric, no

- Efficacy:
  Adult, Evidence favors efficacy
  Pediatric, Evidence favors efficacy

- Strength of Recommendation:
  Adult, Class IIb
  Pediatric, Class IIb

- Strength of Evidence:
  Adult, Category B
  Pediatric, Category C

- Tic disorder

  - FDA Approval:
    Adult, no
    Pediatric, no

  - Efficacy:
    Pediatric, Evidence favors efficacy

  - Strength of Recommendation:
    Pediatric, Class IIb

  - Strength of Evidence:
    Pediatric, Category B

Contraindications/Warnings

- **Contraindications**
  - hypersensitivity to clonidine or any component of the product

- **Precautions**
  - abrupt discontinuation may result in symptoms of withdrawal (eg, agitation, headache, tremor, rapid rise of blood pressure); increased risk with higher doses or concomitant beta-blocker use; gradual reduction of dosage is recommended when therapy is discontinued
  - conduction abnormalities and/or concomitant use of other sympatholytic drugs; postmarketing cases of severe bradycardia have been reported
  - contact dermatitis with transdermal system; substitution of oral clonidine may result in generalized rash
  - defibrillation or cardioversion; increased risk of arcing due to altered electrical current; remove transdermal clonidine before attempting defibrillation or cardioversion
  - magnetic resonance imaging (MRI), aluminum in patch has caused skin burns at application site; remove transdermal clonidine before undergoing MRI
  - surgery; continue use throughout perioperative period; monitoring recommended

- **Pregnancy Category**
  - C (FDA)
  - B3 (AUS)

- **Breast Feeding**
  - Micromedex: Milk effects are possible.

Drug Interactions

- **Major**
  - ◇ Acebutolol (theoretical)
  - ◇ Amitriptyline (probable)
  - ◇ Amoxapine (probable)
  - ◇ Atenolol (theoretical)
  - ◇ Betaxolol (theoretical)
  - ◇ Bevantolol (theoretical)
  - ◇ Bisoprolol (theoretical)
  - ◇ Carteolol (theoretical)
  - ◇ Celiprolol (theoretical)
  - ◇ Clomipramine (probable)
  - ◇ Desipramine (probable)
  - ◇ Dilevalol (theoretical)
  - ◇ Diltiazem (theoretical)
  - ◇ Dothiepin (probable)
  - ◇ Doxepin (probable)
  - ◇ Esmolol (theoretical)
  - ◇ Imipramine (probable)
  - ◇ Levobunolol (theoretical)
  - ◇ Lofepramine (probable)
  - ◇ Metipranolol (theoretical)
  - ◇ Metoprolol (theoretical)
  - ◇ Mirtazapine (probable)
  - ◇ Nadolol (theoretical)
  - ◇ Nebivolol (theoretical)
  - ◇ Nortriptyline (probable)
  - ◇ Oxprenolol (theoretical)
  - ◇ Penbutolol (theoretical)
  - ◇ Pindolol (theoretical)
  - ◇ Propranolol (theoretical)
  - ◇ Protriptyline (theoretical)
  - ◇ Sotalol (theoretical)
  - ◇ Tertatolol (theoretical)
  - ◇ Timolol (theoretical)
  - ◇ Trimipramine (probable)
  - ◇ Verapamil (probable)
- **Moderate**
  - ◇ Cyclosporine (probable)
  - ◇ Fluphenazine (probable)
  - ◇ Mepivacaine (probable)
  - ◇ Naloxone (probable)
  - ◇ Yohimbine (probable)

Adverse Effects

- **COMMON**

- ◇ Dermatologic: Contact dermatitis (5% to 47%), Erythema (26%), Pruritus
- ◇ Gastrointestinal: Xerostomia (25%)
- ◇ Neurologic: Dizziness (2%), Headache (5%), Sedated (3%), Somnolence (12%)
- ◇ Other: Fatigue (6%)

- **SERIOUS**
  - ◇ Cardiovascular: Atrioventricular block

Name Info

- **US Trade Names**
  - Catapres-TTS-1
  - Catapres-TTS-2
  - Catapres-TTS-3
  - Nexiclon XR
- **Class**
  - Alpha-2 Adrenergic Agonist
  - Antihypertensive
- **Regulatory Status**
  - RX
- **Generic Availability**
  - Yes

Mechanism of Action/Pharmacokinetics

- **Mechanism of Action**
  - Clonidine stimulates alpha 2-adrenergic receptors in the brain resulting in reduced sympathetic outflow from the CNS and decreased peripheral resistance, renal vascular resistance, heart rate, and blood pressure.
- **Pharmacokinetics**
  - **Absorption**
    - ◇ Bioavailability, Transdermal: 60%
  - **Distribution**
    - ◇ Vd: 2.1 L/kg
    - ◇ Protein binding, 20% to 40%
  - **Metabolism**
    - ◇ Hepatic: 40% to 60%
  - **Excretion**
    - ◇ Fecal: 22%
    - ◇ Renal: 40% to 60% unchanged

- ◇ Dialyzable: No (hemodialysis)

- **Elimination Half Life**

  - ◇ Normal subjects, 12.7 to 13.7 hours
  - ◇ Renal impairment, 41 hours

Administration/Monitoring

- **Administration**

  - Topical

    - ◇ Topical: apply patch to hairless area of intact skin on upper outer arm or chest; rotate patch location
    - ◇ Topical: fold used patch in half with sticky sides together and discard
    - ◇ Topical: if patch loosens during 7-day wearing, secure with adhesive cover

- **Monitoring**

  - hypertension: normalized blood pressure
  - ADHD: improvement of mental and behavioral symptoms
  - hypertension: heart rate, respiratory rate
  - ADHD: thorough examination prior to initiating therapy for ADHD diagnosis
  - ADHD: palpitations, near syncope, or syncope; may be indicative of a cardiac condition
  - ADHD: complete family and patient cardiovascular history to determine potential risk factors associated with sudden cardiac death (SCD)
  - ADHD: detailed physical examination and medication history to detect cardiac conditions associated with SCD
  - ADHD: further evaluation if family history, patient history or physical exam is suggestive of cardiac disease during initial visit or at follow up visits, and if indicated, consult pediatric cardiologist
  - ADHD: continued evaluation of patient for cardiac symptoms and changes in family history
  - ADHD: blood pressure and heart rate; baseline and at 1 to 3 months, every 6 to 12 months thereafter, and when patient is weaned from drug

How Supplied

- Generic
  - ◇ Transdermal Patch, Extended Release: 0.1 MG/24 HR, 0.2 MG/24 HR, 0.3 MG/24 HR

- Catapres-TTS-1
  - ◇ Transdermal Patch, Extended Release: 0.1 MG/24 HR

- Catapres-TTS-2
  - ◇ Transdermal Patch, Extended Release: 0.2 MG/24 HR

- Catapres TTS-3
  - ◇ Transdermal Patch, Extended Release: 0.3 MG/24 HR

- Catapres-TTS-3
  - ◇ Transdermal Patch, Extended Release: 0.3 MG/24 HR

Toxicology

- **Clinical Effects**

- CLONIDINE
  - USES: Used primarily for the treatment of hypertension and attention deficit hyperactivity disorder (ADHD); less often for detoxification from opioid, ethanol, or nicotine. PHARMACOLOGY: Clonidine stimulates the presynaptic alpha-2 receptor in the brain, leading to inhibition of norepinephrine release, and it also stimulates the imidazoline receptor; both of these actions decrease sympathetic outflow. TOXICOLOGY: Stimulation of peripheral postsynaptic alpha-2 receptors after overdose can cause initial transient hypertension. Excessive stimulation of presynaptic alpha-2 receptors in the lower brainstem and medulla decreases plasma norepinephrine concentrations, causing hypotension and bradycardia. EPIDEMIOLOGY: Clonidine ingestion is common, but severe poisoning is rare. MILD TO MODERATE TOXICITY: CNS depression, miosis, heart conduction abnormality, hypertension. SEVERE TOXICITY: Apnea, respiratory depression, coma, bradycardia, hypothermia, hypotension, early transient hypertension. ADVERSE EFFECTS: Confusion, hallucinations, dry mouth, hypotension, nausea, vomiting, constipation, pruritus, contact dermatitis, tinnitus, dizziness, nervousness, and sedation are the most common adverse effects. Atrioventricular block, minor dysrhythmias, Raynaud phenomenon, and congestive heart failure are also reported. Rebound hypertension develops with abrupt withdrawal.

- **Treatment of Exposure**

  - CLONIDINE

    - Support: MANAGEMENT OF MILD TO MODERATE TOXICITY: There is no specific treatment. Hypotension should be treated with intravenous boluses of crystalloid. Bradycardia is typically mild and usually doesn't require any treatment. Bradycardia, hypotension and CNS depression often respond to physical stimulation. Naloxone has been used to reverse CNS depression with inconsistent success. MANAGEMENT OF SEVERE TOXICITY: Severe bradycardia associated with hypotension and not responsive to physical stimulation should be treated with standard dose of atropine or cardiac pacing. Norepinephrine or dopamine may be beneficial in patients with severe bradycardia and hypotension not responding to physical stimulation, naloxone, intravenous crystalloid, and atropine. Patients with significant CNS and/or respiratory depression should be intubated. If hypertension is severe (associated with end organ effects) and prolonged, treatment should be initiated with an infusion of sodium nitroprusside.
    - Decontamination: PREHOSPITAL: GI decontamination is not recommended because of the potential risk of altered mental status. With dermal exposure, remove clonidine patches and wash exposed skin. HOSPITAL: Induced emesis and gastric lavage are not indicated. Activated charcoal binds clonidine and may be given for patients who present early after significant ingestions. Whole bowel irrigation should be used for symptomatic patients who have ingested a clonidine patch.
    - Airway management: Intubate patients with depressed mental status and who are unable to protect their airway and those with significant respiratory depression.
    - Antidote: There is no antidote for clonidine. Although some patients have responded to naloxone (reversal of altered mental status, respiratory depression or apnea, and miosis), not all patients respond. Naloxone should be administered to patients with significant CNS or respiratory depression. Tolazoline (an alpha-2 adrenergic antagonist) has been suggested as an antidote, but there is little clinical experience with its use and most patients do well with supportive care.
    - Intrathecal injection: Intrathecal overdose of clonidine has not been reported; however, clonidine can be administered intrathecally, therefore the potential for overdose exists. Support blood pressure with fluids and pressors. Intubate and ventilate as needed. Immediately empty the intrathecal pump. Cerebrospinal fluid (CSF) drainage should be performed immediately followed by CSF exchange. Keep the patient upright if possible. Immediately drain at least 20 mL CSF; drainage of up to 70 mL has been tolerated in adults. Follow with CSF exchange (remove serial 20 mL aliquots CSF and replace with equivalent volumes of warmed, preservative free normal saline or lactated ringers).
    - Monitoring of patient: Clonidine is not routinely detected by the urine drug screen and the serum level is not clinically useful. Evaluation of respiratory function with pulse oximetry and

cardiac function with ECG and frequent vital signs are important. Most patients with mild symptoms do not require additional testing.
- Enhanced elimination procedure: Although clonidine has pharmacokinetic characteristics suggesting it is amenable to hemodialysis, there is no clinical experience with its use, and overdose is rarely severe enough to warrant emergent hemodialysis.
- Patient disposition: HOME CRITERIA: Asymptomatic children with inadvertent clonidine tablet ingestions may be monitored at home if the ingestion is: Less than 0.1 mg clonidine for a child 4-years-old or younger, 0.2 mg clonidine or less in a child aged 5 to 8 years, or less than 0.4 mg clonidine in a child older than 8 years of age. Children taking clonidine therapeutically who inadvertently receive no more than double their therapeutic dose may be observed at home if asymptomatic. OBSERVATION CRITERIA: Symptomatic patients, those with deliberate ingestions, children who have chewed or ingested clonidine patches or ophthalmic preparations, and children with tablet ingestions greater than the amounts listed above should be sent to a healthcare facility for observation and treatment. Most patients who ingest clonidine will manifest symptoms rapidly, typically within 30 to 90 minutes, so a 4-hour observation period is adequate for asymptomatic patients. Patients who ingest a clonidine patch may have delayed onset of symptoms. ADMISSION CRITERIA: Patients with bradycardia, CNS depression, respiratory depression, heart block, and hemodynamic instability or other serious symptoms should be admitted to an intensive care setting.

- **Range of Toxicity**

- CLONIDINE
  - TOXICITY: ADULTS: Mild toxicity may occur at just above the therapeutic range. PEDIATRIC: As little as 0.1 mg has produced toxicity in children. Toddlers have developed toxicity after chewing a single used clonidine patch or ingesting small volumes of ophthalmic preparations. THERAPEUTIC DOSE: ADULT: The adult therapeutic dose is 0.1 mg twice daily and the maximum dose is 2.4 mg/day. PEDIATRIC: The pediatric dose for hypertension is 5 to 10 mcg/kg/day, up to 0.9 mg/day.

Clinical Teaching

- Patient should avoid activities requiring mental alertness until drug effects are realized, as drug may cause somnolence.
- This drug may cause local erythema, vesicle formation at site, nausea, and vomiting.
- If patch loosens during 7-day application period, patient should secure with adhesive cover.
- Advise patient against sudden discontinuation of drug, as rebound hypertension may result.
- Patient should not drink alcohol or use other CNS depressants while taking this drug.
- Advise patient to notify healthcare worker of patch or remove patch before MRI procedure.

Last Modified: March 25, 2013

Images & Imprints

Ingredients: Clonidine (0.1 MG/24 HR)
Color: Pink
Shape: Square
Imprint: LOGO B131
NDC: 00597-0031-12

Ingredients: Clonidine (0.2 MG/24 HR)
Color: Pink
Shape: Square
Imprint: LOGO/B132
NDC: 00597-0032-12, 52959-0679-12

Ingredients: Clonidine (0.3 MG/24 HR)
Color: Pink
Shape: Square
Imprint: LOGO/B133
NDC: 00597-0033-34, 54868-0533-00, 55887-0488-04

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  - http://online.statref.com/Document.aspx?fxId=6&docId=410
- Location In Title:
  - DRUGPOINTS® SYSTEM
    "C" Monographs
    Clonidine

■ **Other Serotonergic Agents** Potential pharmacologic interaction (potentially life-threatening serotonin syndrome) with other drugs or herbal supplements affecting serotonergic neurotransmission, including tramadol and St. John's Wort; use with caution. Concurrent administration of serotonin precursors (such as tryptophan) not recommended. (See Serotonin Syndrome under Warnings/Precautions: Warnings, in Cautions.)

■ **Pimozide** Potential pharmacodynamic interaction (increased QT_c intervals have been observed when pimozide and racemic citalopram have been concurrently administered); effects on escitalopram have not been evaluated. Pharmacokinetics of racemic citalopram (AUC and peak plasma concentrations) were not affected by pimozide. Concomitant use of pimozide with escitalopram is contraindicated.

■ **Other CNS-Active Drugs** Potential pharmacologic interaction with other centrally acting drugs.

■ **Alcohol** Concomitant use not recommended.

■ **Cimetidine** Potential pharmacokinetic interaction (increased AUC and peak plasma concentrations of citalopram have been observed; effects on escitalopram have not been evaluated); clinical importance of this interaction is unknown.

■ **Theophylline** Pharmacokinetics of theophylline were not affected by racemic citalopram. The effect of theophylline on the pharmacokinetics of racemic citalopram, however, has not been evaluated.

■ **Digoxin** Pharmacokinetic interaction unlikely based on studies with racemic citalopram.

■ **Electroconvulsive Therapy** The combined use of electroconvulsive therapy and escitalopram has not been evaluated.

Description

Escitalopram, a selective serotonin-reuptake inhibitor (SSRI), is a bicyclic phthalane-derivative antidepressant. Escitalopram is the *S*-enantiomer of citalopram, an SSRI that occurs as a 50:50 racemic mixture of the *R*- and *S*-enantiomers. Escitalopram and citalopram differ structurally from other SSRIs (e.g., fluoxetine, fluvoxamine, paroxetine, sertraline) and other currently available antidepressants (e.g., monoamine oxidase inhibitors, tricyclic and tetracyclic antidepressants). Escitalopram is at least 100-fold more potent as an inhibitor of the reuptake of serotonin (5-hydroxytryptamine [5-HT]) at the presynaptic membranes and the 5-HT neuronal firing rate than the *R*-enantiomer and is twice as potent as the racemic mixture. However, further studies are needed to determine whether these differences result in any clinical superiority of escitalopram compared with citalopram.

Like other SSRIs, escitalopram's antidepressant effect is believed to involve potentiation of serotonin activity in the CNS. Escitalopram appears to have little or no effect on reuptake of other neurotransmitters such as norepinephrine and dopamine. In vitro studies also have demonstrated that escitalopram possesses little or no affinity for α- or β-adrenergic, dopamine D_{1-5}, histamine H_{1-3}, GABA-benzodiazepine, muscarinic M_{1-5}, or 5-HT_{1-7} receptors or various ion channels (e.g., calcium, chloride, potassium, sodium channels).

Escitalopram is extensively metabolized, principally by the hepatic cytochrome P-450 (CYP) 2C19 and 3A4 isoenzymes. The principal metabolites are less potent inhibitors of serotonin reuptake, suggesting that the metabolites do not substantially contribute to the antidepressant activity of escitalopram.

Advice to Patients

Risk of suicidality; importance of patients, family, and caregivers being alert to and immediately reporting emergence of suicidality, worsening depression, or unusual changes in behavior, especially during the first few months of therapy or during periods of dosage adjustment. (See Worsening of Depression and Suicidality Risk under Warnings/Precautions: Warnings, in Cautions.) FDA recommends providing written patient information (medication guide) explaining risks of suicidality each time the drug is dispensed.

Risk of psychomotor impairment; importance of exercising caution while operating hazardous machinery, including automobile driving, until they gain experience with the drug's effects.

Importance of informing patients of risk of serotonin syndrome with concurrent use of escitalopram and 5-HT_1 receptor agonists (also called triptans), tramadol, or other serotonergic agents. Importance of seeking immediate medical attention if symptoms of serotonin syndrome develop.

Risks associated with concomitant use of escitalopram with alcohol or racemic citalopram.

Importance of informing clinicians of existing or contemplated concomitant therapy, including prescription and OTC drugs or herbal supplements, as well as any concomitant illnesses (e.g., bipolar disorder) or personal or family history of suicidality or bipolar disorder. Risk of bleeding associated with concomitant use of escitalopram with aspirin or other nonsteroidal anti-inflammatory agents, warfarin, or other drugs that affect coagulation.

Importance of women informing clinicians if they are or plan to become pregnant or plan to breast-feed.

Importance of continuing escitalopram therapy even if improvement is evident within 1–4 weeks, unless directed otherwise by their clinician.

Importance of informing patients of other important precautionary information. (See Cautions.)

Overview* (see Users Guide). For additional information on this drug until a more detailed monograph is developed and published, the manufacturer's labeling should be consulted. It is *essential* that the manufacturer's labeling be consulted for more detailed information on usual cautions, precautions, contraindications, potential drug interactions, laboratory test interferences, and acute toxicity.

Preparations

Excipients in commercially available drug preparations may have clinically important effects in some individuals; consult specific product labeling for details.

Escitalopram Oxalate

Oral		
Solution	5 mg (of escitalopram) per 5 mL	**Lexapro®**, Forest
Tablets, film-coated	5 mg (of escitalopram)	**Lexapro®**, Forest
	10 mg (of escitalopram)	**Lexapro®** (scored), Forest
	20 mg (of escitalopram)	**Lexapro®** (scored), Forest

Fluoxetine Hydrochloride

■ Fluoxetine, a selective serotonin-reuptake inhibitor (SSRI), is an antidepressant.

Uses

Fluoxetine is used in the treatment of major depressive disorder, obsessive-compulsive disorder, premenstrual dysphoric disorder, and bulimia nervosa. In addition, fluoxetine has been used for the treatment of depression associated with bipolar disorder†; obesity†; anorexia nervosa†; panic disorder† with or without agoraphobia; myoclonus†; cateplexy†; alcohol dependence†; and premature ejaculation†.

■ **Major Depressive Disorder** Fluoxetine is used in the treatment of major depressive disorder. The efficacy of fluoxetine for long-term use (i.e., longer than 5–6 weeks) as an antidepressant has not been established by controlled studies, but the drug has been used in some patients for substantially longer periods (e.g., up to 4 years or longer) without apparent loss of clinical effect or increased toxicity. If fluoxetine is used for extended periods, the need for continued therapy should be reassessed periodically.

A major depressive episode implies a prominent and relatively persistent depressed or dysphoric mood that usually interferes with daily functioning (nearly every day for at least 2 weeks). According to DSM-IV criteria, a major depressive episode includes at least 5 of the following 9 symptoms (with at least one of the symptoms being either depressed mood or loss of interest or pleasure): depressed mood most of the day as indicated by subjective report (e.g., feels sad or empty) or observation made by others; markedly diminished interest or pleasure in all, or almost all, activities most of the day; significant weight loss (when not dieting) or weight gain (e.g., a change of more than 5% of body weight in a month), or decrease or increase in appetite; insomnia or hypersomnia; psychomotor agitation or retardation (observable by others, not merely subjective feelings of restlessness or being slowed down); fatigue or loss of energy; feelings of worthlessness or excessive or inappropriate guilt (not merely self-reproach or guilt about being sick); diminished ability to think or concentrate or indecisiveness (either by subjective account or as observed by others); and recurrent thoughts of death, recurrent suicidal ideation without a specific plan, or a suicide attempt or specific plan for committing suicide.

Treatment of major depressive disorder generally consists of an acute phase (to induce remission), a continuation phase (to preserve remission), and a maintenance phase (to prevent recurrence). Various interventions (e.g., psychotherapy, antidepressant drug therapy, electroconvulsive therapy [ECT]) are used alone or in combination to treat major depressive episodes. Treatment should be individualized and the most appropriate strategy for a particular patient is determined by clinical factors such as severity of depression (e.g., mild, moderate, severe), presence or absence of certain psychiatric features (e.g., suicide risk, catatonia, psychotic or atypical features, alcohol or substance abuse or dependence, panic or other anxiety disorder, cognitive dysfunction, dysthymia, personality disorder, seasonal affective disorder), and concurrent illness (e.g., asthma, cardiac disease, dementia, seizure disorder, glaucoma, hypertension). Demographic and psychosocial factors as well as patient preference also are used to determine the most effective treatment strategy.

While use of psychotherapy alone may be considered as an initial treatment strategy for patients with mild to moderate major depressive disorder (based on patient preference and presence of clinical features such as psychosocial stressors), combined use of antidepressant drug therapy and psychotherapy may be useful for initial treatment of patients with moderate to severe major depressive disorder with psychosocial issues, interpersonal problems, or a comorbid axis II disorder. In addition, combined use of antidepressant drug therapy and psychotherapy may be beneficial in patients who have a history of

poor compliance or only partial response to adequate trials of either antidepressant drug therapy or psychotherapy alone.

Antidepressant drug therapy can be used alone for initial treatment of patients with mild major depressive disorder (if preferred by the patient) and usually is indicated alone or in combination with psychotherapy for initial treatment of patients with moderate to severe major depressive disorder (unless ECT is planned). ECT is not generally used for initial treatment of uncomplicated major depression, but is recommended as first-line treatment for severe major depressive disorder when it is coupled with psychotic features, catatonic stupor, severe suicidality, food refusal leading to nutritional compromise, or other situations when a rapid antidepressant response is required. ECT also is recommended for patients who have previously shown a positive response or a preference for this treatment modality and can be considered for patients with moderate or severe depression who have not responded to or cannot receive antidepressant drug therapy. In certain situations involving depressed patients unresponsive to adequate trials of several individual antidepressant agents, adjunctive therapy with another agent (e.g., buspirone, lithium) or concomitant use of a second antidepressant agent (e.g., bupropion) has been used; however, such combination therapy is associated with an increased risk of adverse reactions, may require dosage adjustments, and (if not contraindicated) should be undertaken only after careful consideration of the relative risks and benefits. (See Drug Interactions: Drugs Associated with Serotonin Syndrome, see Drug Interactions: Tricyclic and Other Antidepressants, and see Drug Interactions: Lithium.)

Efficacy of fluoxetine for the management of major depression has been established principally in outpatient settings; the drug's antidepressant efficacy in hospital or institutional settings has not been adequately studied to date. Most patients evaluated in clinical studies with fluoxetine had major depressive episodes of at least moderate severity, had no evidence of bipolar disorder, and had experienced either single or recurrent episodes of depressive illness. Limited evidence suggests that mildly depressed patients may respond less well to fluoxetine than moderately depressed patients. There also is some evidence that patients with atypical depression (which usually is characterized by atypical signs and symptoms such as hypersomnia and hyperphagia), a history of poor response to prior antidepressant therapy, chronic depressive symptomatology with or without episodic worsening of depressive symptoms, a longer duration of depression in the current episode, and/or a younger age of onset of depression may be more likely to respond to fluoxetine than to tricyclic antidepressant therapy.

Considerations in Choosing Antidepressants A variety of antidepressant drugs are available for the treatment of major depressive disorder, including selective serotonin-reuptake inhibitors (e.g., citalopram, escitalopram, fluoxetine, paroxetine, sertraline), tricyclic antidepressants (e.g., amitriptyline, amoxapine, desipramine, doxepin, imipramine, nortriptyline, protriptyline, trimipramine), monoamine oxidase (MAO) inhibitors (e.g., phenelzine, tranylcypromine), and other antidepressants (e.g., bupropion, duloxetine, maprotiline, nefazodone, trazodone, venlafaxine). Most clinical studies have shown that the antidepressant effect of usual dosages of fluoxetine in patients with moderate to severe depression is greater than that of placebo and comparable to that of usual dosages of tricyclic antidepressants, maprotiline, other selective serotonin-reuptake inhibitors (e.g., paroxetine, sertraline), and other antidepressants (e.g., trazodone). Fluoxetine appears to be as effective as tricyclic antidepressants in reducing most of the signs and symptoms associated with major depressive disorder, including depression, anxiety, cognitive disturbances, and somatic symptoms. However, in some studies, the drug did not appear to be as effective as tricyclic antidepressants or trazodone in reducing sleep disturbances associated with depression. In geriatric patients with major depressive disorder, fluoxetine appears to be as effective as and to cause fewer overall adverse effects than doxepin. The onset of action of fluoxetine appears to be comparable to that of tricyclic antidepressants, although the onset of action has been variably reported to be somewhat faster or slower than that of tricyclic antidepressants in some studies.

Because response rates in patients with major depression are similar for most currently available antidepressants, the choice of antidepressant agent for a given patient depends principally on other factors such as potential adverse effects, safety or tolerability of these adverse effects in the individual patient, psychiatric and medical history, patient or family history of response to specific therapies, patient preference, quantity and quality of available clinical data, cost, and relative acute overdose safety. No single antidepressant can be recommended as optimal for all patients because of substantial heterogeneity in individual responses and in the nature, likelihood, and severity of adverse effects. In addition, patients vary in the degree to which certain adverse effects and other inconveniences of drug therapy (e.g., cost, dietary restrictions) affect their preferences.

In the large-scale Sequenced Treatment Alternatives to Relieve Depression (STAR*D) effectiveness trial, patients with major depressive disorder who did not respond to or could not tolerate therapy with one SSRI (citalopram) were randomized to switch to extended-release ("sustained-release") bupropion, sertraline, or extended-release venlafaxine as a second step of treatment (level 2). Remission rates as assessed by the 17-item Hamilton Rating Scale for Depression (HRSD-17) and the Quick Inventory of Depressive Symptomology—Self Report (QIDS-SR-16) were approximately 21 and 26% for extended-release bupropion, 18 and 27% for sertraline, and 25 and 25% for extended-release venlafaxine therapy, respectively; response rates as assessed by the QIDS-SR-16 were 26, 27, and 28% for extended-release bupropion, sertraline, and extended-release venlafaxine therapy, respectively. These results suggest that after unsuccessful initial treatment of depressed patients with an SSRI, approximately 25% of patients will achieve remission after therapy is switched to another antidepressant, and either another SSRI (e.g., sertraline) or an agent from another class (e.g., bupropion, venlafaxine) may be reasonable alternative antidepressants in patients not responding to initial SSRI therapy.

Patient Tolerance Considerations. Because of differences in the adverse effect profile between selective serotonin-reuptake inhibitors and tricyclic antidepressants, particularly less frequent anticholinergic effects, cardiovascular effects, and weight gain with selective serotonin-reuptake inhibitors, these drugs may be preferred in patients in whom such effects are not tolerated or are of potential concern. The decreased incidence of anticholinergic effects associated with fluoxetine and other selective serotonin-reuptake inhibitors compared with tricyclic antidepressants is a potential advantage, since such effects may result in discontinuance of the drug early during therapy in unusually sensitive patients. In addition, some anticholinergic effects may become troublesome during long-term tricyclic antidepressant therapy (e.g., persistent dry mouth may result in tooth decay). Although serotonin-reuptake inhibitors share the same overall tolerability profile, certain patients may tolerate one drug in this class better than another. In an open study, most patients who had discontinued fluoxetine therapy because of adverse effects subsequently tolerated sertraline therapy. Antidepressants other than selective serotonin-reuptake inhibitors may be preferred in patients in whom certain adverse GI effects (e.g., nausea, anorexia) or nervous system effects (e.g., anxiety, nervousness, insomnia, weight loss) are not tolerated or are of concern, since such effects appear to occur more frequently with fluoxetine and other drugs in this class.

Pediatric Considerations. The clinical presentation of depression in children and adolescents can differ from that in adults and generally varies with the age and developmental stages of the child. Younger children may exhibit behavioral problems such as social withdrawal, aggressive behavior, apathy, sleep disruption, and weight loss; adolescents may present with somatic complaints, self esteem problems, rebelliousness, poor performance in school, or a pattern of engaging in risky or aggressive behavior.

Data from controlled clinical studies evaluating various antidepressant agents in children and adolescents are less extensive than with adults, and many of these studies have methodologic limitations (e.g., nonrandomized or uncontrolled, small sample size, short duration, nonspecific inclusion criteria). However, there is some evidence that the response to antidepressants in pediatric patients may differ from that seen in adults, and caution should be used in extrapolating data from adult studies when making treatment decisions for pediatric patients. Results of several studies evaluating tricyclic antidepressants (e.g., amitriptyline, desipramine, imipramine, nortriptyline) in preadolescent and adolescent patients with major depression indicate a lack of overall efficacy in this age group.

Based on the lack of efficacy data regarding use of tricyclic antidepressants and MAO inhibitors in pediatric patients and because of the potential for life-threatening adverse effects associated with the use of these drugs, many experts consider selective serotonin-reuptake inhibitors, including fluoxetine, the drugs of choice when antidepressant therapy is indicated for the treatment of major depressive disorder in children and adolescents. However, the US Food and Drug Administration (FDA) states that, while efficacy of fluoxetine has been established in pediatric patients, efficacy of other newer antidepressants (i.e., citalopram, duloxetine, escitalopram, fluvoxamine, mirtazapine, nefazodone, paroxetine, sertraline, venlafaxine) was not conclusively established in clinical trials in pediatric patients with major depressive disorder. In addition, FDA now warns that antidepressants increase the risk of suicidal thinking and behavior (suicidality) in children and adolescents with major depressive disorder and other psychiatric disorders. (See Cautions: Pediatric Precautions.) FDA currently states that anyone considering using an antidepressant in a child or adolescent for any clinical use must balance the potential risk of therapy with the clinical need. (See Cautions: Precautions and Contraindications.)

Geriatric Considerations. The response to antidepressants in geriatric patients is similar to that reported in younger adults, but depression in geriatric patients often is not recognized and is not treated. In geriatric patients with major depressive disorder, selective serotonin-reuptake inhibitors appear to be as effective as tricyclic antidepressants (e.g., amitriptyline) but may cause fewer overall adverse effects than these other agents. Geriatric patients appear to be especially sensitive to anticholinergic (e.g., dry mouth, constipation, vision disturbance), cardiovascular, orthostatic hypotensive, and sedative effects of tricyclic antidepressants. The low incidence of anticholinergic effects associated with fluoxetine compared with tricyclic antidepressants also is a potential advantage in geriatric patients, since such effects (e.g., constipation, dry mouth, confusion, memory impairment) may be particularly troublesome in these patients. Some clinicians state that selective serotonin-reuptake inhibitors including fluoxetine may be preferred for treating depression in geriatric patients in whom the orthostatic hypotension associated with many antidepressants (e.g., tricyclics) potentially may result in injuries (such as severe falls). However, despite the fewer cardiovascular and anticholinergic effects associated with selective serotonin-reuptake inhibitors, these drugs did not show any advantage over tricyclic antidepressants with regard to hip fracture in a case-control study. In addition, there was little difference in the rates of falls between nursing home residents receiving selective serotonin-reuptake inhibitors and those receiving tricyclic antidepressants in a retrospective study. Therefore, all geriatric individuals receiving either type of antidepressant should be considered at increased risk of falls and appropriate measures should be taken.

Patients with dementia of the Alzheimer's type (Alzheimer's disease, presenile or senile dementia) often present with depressive symptoms, such as depressed mood, appetite loss, insomnia, fatigue, irritability, and agitation. Most experts recommend that patients with dementia of the Alzheimer's type and depressive symptoms be considered as candidates for pharmacotherapy even if they fail to meet the criteria for a major depressive syndrome. The goals of such therapy are to improve mood, functional status (e.g., cognition), and quality of life. Although patients may present with depressed mood alone, the possibility of more extensive depressive symptomatology should be considered. Therefore, patients should be monitored carefully for indices of major depression, suicidal ideation, and neurovegetative signs since safety measures (e.g., hospitalization for suicidality) and more vigorous and aggressive therapy (e.g., relatively high dosages, multiple drug trials) may be needed in some patients.

If pharmacotherapy is initiated for depressive symptoms in Alzheimer's patients, most experts recommend selective serotonin-reuptake inhibitors such as fluoxetine, citalopram, escitalopram, sertraline, or paroxetine as first-line therapy because of their favorable adverse effect profile in this population compared with other currently available antidepressants (e.g., tricyclic antidepressants, MAO inhibitors). Although evidence of efficacy from controlled studies currently is limited, the available evidence and experience with the use of antidepressants in patients with dementia of the Alzheimer's type and associated depressive manifestations indicate that depressive symptoms (including depressive mood alone and with neurovegetative changes) in such patients are responsive to antidepressant therapy. In some patients, cognitive deficits may partially or fully resolve during antidepressant therapy, but the extent of response will be limited to the degree of cognitive impairment that is directly related to depression.

Cardiovascular Considerations. The relatively low incidence of adverse cardiovascular effects, including orthostatic hypotension and conduction disturbances, associated with fluoxetine and other selective serotonin-reuptake inhibitors may be advantageous in patients in whom cardiovascular effects associated with tricyclic antidepressants may be hazardous. However, most clinical studies of fluoxetine for the management of depression did not include individuals with cardiovascular disease (e.g., those with a recent history of myocardial infarction or unstable heart disease), and further experience in such patients is necessary to confirm the reported relative lack of cardiotoxicity with the drug. (See Cautions: Precautions and Contraindications.)

Sedative Considerations. Because fluoxetine and other selective serotonin-reuptake inhibitors generally are less sedating than some other antidepressants (e.g., tricyclics), some clinicians state that these drugs may be preferable in patients who do not require the sedative effects associated with many antidepressant agents; however, an antidepressant with more prominent sedative effects may be preferable in some patients (e.g., those with insomnia).

Suicidal Risk Considerations. Suicide is a known risk of depression and certain other psychiatric disorders, and these disorders themselves are the strongest predictors of suicide. However, there has been a long-standing concern that antidepressants may have a role in inducing worsening of depression and the emergency of suicidal thinking and behavior (suicidality) in certain patients during the early phases of treatment. FDA states that antidepressants increased the risk of suicidality in short-term studies in children, adolescents, and young adults (18–24 years of age) with major depressive disorder and other psychiatric disorders. (See Cautions: Pediatric Precautions.) It currently is unknown whether the suicidality risk extends to longer-term antidepressant use (i.e., beyond several months); however, there is substantial evidence from placebo-controlled maintenance trials in adults with major depressive disorder that antidepressants can delay the recurrence of depression. Because the risk of suicidality in depressed patients may persist until substantial remission of depression occurs, appropriate monitoring and close observation of patients of all ages who are receiving antidepressant therapy are recommended. (See Cautions: Precautions and Contraindications.)

Dosing Interval Considerations. Fluoxetine can be administered once weekly as delayed-release capsules for continuing management of major depressive disorder. Whether the weekly regimen is equivalent to daily therapy with conventional preparations for preventing relapse has not been established. In a double-blind study in adults who responded to daily fluoxetine therapy for major depressive disorder, the relapse rate for continuing therapy with fluoxetine 20-mg conventional capsules administered daily, fluoxetine 90-mg delayed-release capsules administered once weekly, or placebo was 26, 37, or 50%, respectively.

Other Considerations. Fluoxetine has been effective for the treatment of depression in adults with human immunodeficiency virus (HIV) infection. In one randomized, placebo-controlled study, analysis of patients who completed the study showed a statistically significant benefit in patients receiving fluoxetine compared with those receiving placebo. However, results of intent-to-treat analysis did not show a statistically significant benefit in those receiving the antidepressant, possibly because of a high attrition rate and substantial placebo response. There was no evidence that the degree of immunosuppression affected the response to antidepressant therapy.

Fluoxetine has been effective when used in combination with lithium in a limited number of patients with refractory depression who had not responded to prior therapy (including tricyclic antidepressants and MAO inhibitors administered alone or in combination with lithium), suggesting that lithium may potentiate the antidepressant activity of fluoxetine. (See Drug Interactions: Lithium.) In the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) level 2 trial, patients with major depressive disorder who did not respond to or could not tolerate therapy with citalopram (another SSRI) were randomized to receive either extended-release ("sustained-release") bupropion or buspirone therapy in addition to citalopram. Although both extended-release bupropion and buspirone were found to produce similar remission rates, extended-release bupropion produced a greater reduction in the number and severity of symptoms and a lower rate of drug discontinuance than buspirone in this large-scale, effectiveness trial. These results suggest that augmentation of SSRI therapy with extended-release bupropion may be useful in some patients with refractory depression.

Fluoxetine has been used safely for the management of depression in at least one patient with established susceptibility to malignant hyperthermia, suggesting that the drug may be useful in depressed patients susceptible to malignant hyperthermia and in whom tricyclics and MAO inhibitors are potentially hazardous; however, additional experience is necessary to confirm this preliminary finding.

Because fluoxetine possesses anorectic and weight-reducing properties, some clinicians state that the drug may be preferred in obese patients and/or patients in whom the increase in appetite, carbohydrate craving, and weight gain associated with tricyclic antidepressant therapy may be undesirable (e.g., potentially hazardous to the patient's health; result in possible discontinuance of or noncompliance with therapy). However, the possibility that some patients with concurrent eating disorders or those who may desire to lose weight may misuse fluoxetine for its anorectic and weight-reducing effects should be considered. (See Uses: Eating Disorders and also see Chronic Toxicity.)

■ **Obsessive-Compulsive Disorder** Fluoxetine is used in the treatment of obsessive-compulsive disorder in adults and pediatric patients 7 years of age and older when the obsessions or compulsions cause marked distress, are time consuming, or interfere substantially with social or occupational functioning. Obsessions are recurrent and persistent ideas, thoughts, impulses, or images that, at some time during the disturbance, are experienced as intrusive and inappropriate (i.e., "ego dystonic") and that cause marked anxiety or distress but that are not simply excessive worries about real-life problems. Compulsions are repetitive, intentional behaviors (e.g., hand washing, ordering, checking) or mental acts (e.g., praying, counting, repeating words silently) performed in response to an obsession or according to rules that must be applied rigidly (e.g., in a stereotyped fashion). Although the behaviors or acts are aimed at preventing or reducing distress or preventing some dreaded event or situation, they either are not connected in a realistic manner with what they are designed to neutralize or prevent or are clearly excessive. At some time during the course of the disturbance, the patient, if an adult, recognizes that the obsessions or compulsions are excessive or unreasonable; children may not make such a recognition.

The efficacy of fluoxetine for the management of obsessive-compulsive disorder has been established in several multicenter, placebo-controlled studies, including 2 studies of 13 weeks' duration in adults and one study of 13 weeks' duration in children and adolescents 7–17 years of age. Patients in these studies had moderate to severe obsessive-compulsive disorder with average baseline total scores on the Yale-Brown Obsessive-Compulsive Scale (YBOCS) of 22–26 in adults and 25–26 in children and adolescents (measured in the Children's Yale-Brown Obsessive-Compulsive Scale [CY-BOCS]).

In 2 fixed-dose studies of 13 weeks' duration, adults receiving fluoxetine dosages of 20, 40 and 60 mg daily experienced substantially greater reductions in the YBOCS total score than those receiving placebo. Mean reductions in total scores on the YBOCS in fluoxetine-treated patients were approximately 4–6 units in one study and 4–9 units in the other study compared with a 1-unit reduction in patients receiving placebo. In these 2 studies, a positive clinical response (much or very much improved on the Clinical Global Impressions improvement scale) occurred in 36–47 or 11% of patients receiving fluoxetine or placebo, respectively. While there was no indication of a dose-response relationship for effectiveness in one study, a dose-response relationship was observed in the other study, with numerically better responses in patients receiving 40 or 60 mg of fluoxetine daily compared with those receiving 20 mg of the drug daily. No age- or gender-related differences in outcome were noted in either of these studies.

In another randomized, placebo-controlled study of 13 weeks' duration, children and adolescents 7–17 years of age with obsessive-compulsive disorder who received mean fluoxetine dosages of approximately 25 mg daily (range: 10–60 mg daily) demonstrated substantially greater reductions in the CY-BOCS total score than those receiving placebo. In this study, a positive clinical response (much or very much improved on the Clinical Global Impressions improvement scale) occurred in approximately 55–58 or 9–19% of patients receiving fluoxetine or placebo, respectively. In addition, 49% of patients who received fluoxetine were classified as responders (i.e., patients with a 40% or greater reduction in their CY-BOCS total score from baseline) compared with 25% of those who received placebo. Subgroup analyses on outcome did not suggest any differential responsiveness on the basis of age or gender.

Results from comparative studies to date suggest fluoxetine and other selective serotonin-reuptake inhibitors (e.g., fluvoxamine, paroxetine, sertraline) are as effective or somewhat less effective than clomipramine in the management of obsessive-compulsive disorder. In a pooled analysis of separate short-term (10–13 weeks) studies comparing clomipramine, fluoxetine, fluvoxamine, or sertraline with placebo, clomipramine was calculated as being more effective (as determined by measures on the YBOC scale) than selective serotonin-reuptake inhibitors, although all drugs were superior to placebo.

Many clinicians consider a selective serotonin-reuptake inhibitor (e.g., fluoxetine, fluvoxamine, paroxetine, sertraline) or clomipramine to be the drugs of choice for the pharmacologic treatment of obsessive-compulsive disorder. The decision whether to initiate therapy with a selective serotonin-reuptake inhibitor or clomipramine often is made based on the adverse effect profile of these drugs. For example, some clinicians prefer clomipramine in patients who may not tolerate the adverse effect profile of selective serotonin-reuptake inhibitors (nausea, headache, overstimulation, sleep disturbances) while selective serotonin-reuptake inhibitors may be useful alternatives in patients unable to tolerate the adverse effects associated with clomipramine therapy (anticholinergic effects, cardiovascular effects, sedation). Consideration of individual patient characteristics (age, concurrent medical conditions), pharmacokinetics of the drug, potential drug interactions, and cost of therapy may also influence decisions regarding use of selective serotonin-reuptake inhibitors or clomipramine as first-line therapy in patients with obsessive-compulsive disorder. Although not clearly established, it has been suggested that the mechanism of action of fluoxetine and other drugs (e.g., clomipramine) used in the management of obsessive-compulsive disorder may be related to their serotonergic activity.

Other Disorders with an Obsessive-Compulsive Component

Experience in a limited number of patients suggests that fluoxetine also reduces obsessive-compulsive symptoms associated with Tourette's disorder† (Gilles de la Tourette's syndrome); however, the drug did not appear to be effective in suppressing motor and vocal tics associated with the condition.

Trichotillomania† (an urge to pull out one's hair) has some features in common with those of obsessive-compulsive disorder and some studies have suggested that antiobsessional agents such as selective serotonin-reuptake inhibitors and clomipramine may be useful in treating this condition. Successful treatment with fluoxetine has been reported in some patients with trichotillomania, including in 2 short-term, open studies in which dosages of up to 80 mg daily were given. However, fluoxetine's efficacy in the management of this disorder was not demonstrated in 2 double-blind, placebo-controlled, crossover studies. In addition, behavioral therapy was found to be more effective than fluoxetine in treating trichotillomania in a short-term, controlled study. Further studies are needed to more clearly determine the role of fluoxetine and other serotonin-reuptake blockers in the management of this condition.

■ **Premenstrual Dysphoric Disorder** Fluoxetine is used in the treatment of premenstrual dysphoric disorder (previously late luteal phase dysphoric disorder). DSM-IV criteria for premenstrual dysphoric disorder (PMDD) require that in most menstrual cycles of the previous year at least 5 of the following 11 symptoms must have been present for most of the time during the last week of the luteal phase (with at least one of the symptoms being the first 4 listed): marked depressed mood, feelings of hopelessness, or self-deprecating thoughts; marked anxiety, tension, feelings of being "keyed up" or on "edge"; marked affective lability (e.g., feeling suddenly sad or tearful or increased sensitivity to rejection); persistent and marked anger or irritability or increased interpersonal conflicts; decreased interest in usual activities (e.g., work, school, friends, hobbies); a subjective sense of difficulty in concentrating; lethargy, easy fatigability, or marked lack of energy; marked change in appetite, overeating, or specific food cravings; hypersomnia or insomnia; a subjective sense of being overwhelmed or out of control; and other physical symptoms, such as breast tenderness or swelling, headaches, joint or muscle pain, a sensation of "bloating" or weight gain. Such symptoms should begin to remit within a few days of the onset of menses (follicular phase) and are always absent in the week following menses. The presence of this cyclical pattern of symptoms must be confirmed by at least 2 consecutive months of prospective daily symptom ratings. PMDD should be distinguished from the more common premenstrual syndrome (PMS) by prospective daily ratings and the strict criteria listed above.

There is some evidence that serotonergic agents (e.g., fluoxetine, paroxetine) have greater efficacy compared with non-serotonergic agents (e.g., bupropion, maprotiline) in relieving the physical and/or emotional symptoms of PMDD. In published studies, the response rates to fluoxetine therapy in women with PMDD appear to be similar to those described in patients with depression, panic disorder, and obsessive-compulsive disorder. However, unlike the onset of action of fluoxetine in other psychiatric conditions (6–8 weeks), some clinicians have observed a rapid onset of response to fluoxetine (approximately 2–4 weeks) in women with PMDD, suggesting that the mechanism of action of these agents in PMDD is not mediated by the drug's antidepressant or antiobsessive effects. In addition, use of fluoxetine in the treatment of PMDD does not appear to produce the sustained remission typically seen in the treatment of major depressive disorder. PMDD symptoms recur soon after discontinuance of fluoxetine therapy (e.g., within 2 menstrual cycles), even in women who have received the drug for more than 1 year. It has been suggested that a past history of major depression may be associated with a partial or absent response to lower dosages of fluoxetine therapy. Because patients on oral contraceptives were excluded from most clinical studies to date, efficacy of fluoxetine used in conjunction with oral contraceptives for the treatment of PMDD has not been determined.

The efficacy of fluoxetine for the management of PMDD has been established in 3 randomized, placebo-controlled (1 intermittent- and 2 continuous-dosing) studies of 3 or 6 months' duration in adult women who met DSM-III-R or DSM-IV criteria for PMDD. One study involved over 300 women (20–40 years of age) who were randomized to receive either fluoxetine (at fixed dosages of 20 or 60 mg daily) or placebo continuously throughout the full menstrual cycle, beginning on the first day of their cycle. In this study, fixed doses of fluoxetine were shown to be substantially more effective than placebo in decreasing the mean total of 3 visual analog scale scores (tension, irritability, dysphoria); total scores decreased by 36–39% on 20 or 60 mg of fluoxetine and 7% on placebo. However, marked (greater than 50% reduction from baseline) improvement in total luteal phase visual analog scale scores occurred only in 18% of patients receiving 60 mg of fluoxetine and in 6 or 4% of those receiving 20 mg of fluoxetine or placebo, respectively. Fluoxetine therapy appeared to be well tolerated in patients receiving dosages of 20 mg daily, but approximately 33% of women receiving 60 mg daily discontinued the drug because of adverse reactions and 86% of those receiving this dosage who remained in the study reported one or more adverse effects attributable to the drug.

In a second double-blind, placebo-controlled, crossover study, women with PMDD who received flexible doses of fluoxetine (20–60 mg daily; mean dosage of 27 mg daily) throughout the menstrual cycle for a total of 3 cycles had an average visual analog scale total score (follicular to luteal phase increase) that was 3.8 times lower than that of patients receiving placebo. However, results of another double-blind, parallel study indicated that the response rate in women receiving fluoxetine 20 mg daily or bupropion 300 mg daily continuously for 2 cycles was not substantially superior to placebo on the clinical global impressions scale.

The efficacy of intermittent dosing (defined as initiation of daily dosage 14 days prior to the anticipated onset of menstruation and continuing through the first full day of menses) was established in a double-blind, parallel group study of 3 months' duration. In this study, women receiving intermittent dosing of 20 mg daily dosages of fluoxetine had substantially greater improvements on the Daily Record of Severity of Problems, a patient-rated instrument that mirrors the diagnostic criteria for PMDD as identified in the DSM-IV, than those receiving placebo. Further studies are needed to evaluate the comparative efficacy of continuous and intermittent dosing regimens.

■ **Eating Disorders** Fluoxetine is used in the treatment of bulimia nervosa; the drug also has been used in a limited number of patients with other eating disorders (e.g., anorexia nervosa).

Although DSM-IV criteria provide guidelines for establishing a diagnosis of a specific eating disorder, the symptoms frequently occur along a continuum between those of anorexia nervosa and bulimia nervosa. The primary features in both anorexia nervosa and bulimia nervosa are weight preoccupation and excessive self-evaluation (i.e., disturbed perception) of body weight and shape, and many patients exhibit a mixture of both anorexic and bulimic behaviors.

The American Psychiatric Association (APA) states that psychiatric management forms the foundation of treatment for patients with eating disorders and should be instituted for all patients in combination with other specific treatment modalities (e.g., nutritional rehabilitation and pharmacotherapy). Because patients with eating disorders often exhibit comorbid conditions and/or associated psychiatric features that may compromise clinical outcome, treatment programs should identify and address all comorbid conditions before initiating therapy. Clinicians should recognize that patients with concurrent diabetes mellitus often underdose their insulin in order to lose weight, and that pregnant patients with disturbed eating behaviors (e.g., inadequate nutritional intake, binge eating, purging, abuse of teratogenic medications) may be at high risk for fetal or maternal complications. Results from several studies indicate that patients with associated psychiatric features such as substance abuse/dependence or personality disorder may require longer-term therapy than those without these comorbid conditions. Although the presence of depression at initial presentation has no predictive value for treatment outcome, many clinicians suggest that severe depression can impair the patient's involvement in and/or response to psychotherapy, and such patients should receive initial pharmacologic therapy to improve mood symptoms.

Bulimia Nervosa Fluoxetine is used in the management of binge-eating and self-induced vomiting behaviors in patients with moderate to severe bulimia nervosa (e.g., at least 3 bulimic episodes per week for 6 months).

According to DSM-IV, bulimia nervosa is characterized by recurrent episodes of binge eating and recurrent inappropriate compensatory behaviors to prevent weight gain (e.g., self-induced vomiting; misuse of laxatives, diuretics, enemas, or other medications; fasting; excessive exercise) and binge eating and compensatory behaviors both occur at least twice a week for 3 months.

Treatment strategies for bulimia nervosa include psychosocial interventions, nutritional counseling and rehabilitation, and pharmacotherapy. The primary goals in treating bulimia nervosa are to reduce binge eating and purging. Although antidepressants initially were used only in bulimic patients who were clinically depressed, evidence from recent studies indicates that nondepressed patients also respond to these agents, and that the presence of depression is not predictive of therapeutic response. Therefore, antidepressants are included as one component of initial treatment regimens for patients with bulimia nervosa. Because selective serotonin-reuptake inhibitors have a more favorable adverse effects profile, these drugs usually are preferred and may be especially useful for patients with symptoms of depression, anxiety, obsessions, or certain impulse disorder symptoms or for those who previously failed to achieve optimal response to psychosocial therapy. Other antidepressants also may be used to reduce the symptoms of binge eating and purging and help prevent relapse. However, the APA cautions against the use of tricyclic antidepressants in patients who are suicidal and cautions against use of MAO inhibitors in those with chaotic binge eating and purging.

The APA states that in patients who fail to respond to initial antidepressant therapy, it may be necessary to assess whether the patient has taken the drug shortly before vomiting or to determine whether effective drug concentrations have been achieved. Although only limited data are available regarding use of antidepressants for maintenance therapy, there appears to be a high rate of relapse during the treatment phase and an even higher rate following discontinuance of therapy. However, limited data indicate that the rate of relapse appears to correlate with the time at which drug therapy is initiated. In one small, open-label study, patients who received drug treatment within 13 weeks of diagnosis were more likely to exhibit sustained recovery during the first year than those who did not receive pharmacotherapy. Furthermore, continuing cognitive behavior therapy following discontinuance of drug therapy appears to prevent relapse in patients with bulimia nervosa. Additional study is needed to determine the effects of sequential use of psychotherapy and pharmacotherapy in the treatment of bulimia nervosa.

The efficacy of fluoxetine for the management of bulimia nervosa has been established in several multicenter, placebo-controlled studies, including 2 studies of 8 weeks' duration (using fluoxetine dosages of 20 or 60 mg daily) and one study of 16 weeks' duration (using fluoxetine dosages of 60 mg once daily) in patients with moderate to severe bulimia nervosa with median binge eating and self-induced vomiting of 7–10 and 5–9 times a week, respectively. In these studies, fluoxetine given in dosages of 60 mg daily (but not in dosages of 20 mg daily) was substantially more effective than placebo in reducing the number of binge-eating and self-induced vomiting episodes weekly. The superiority of fluoxetine compared with placebo was evident as early as within 1 week of therapy and persisted throughout each study period. The drug-related reduction in bulimic episodes appeared to be independent of baseline depression as assessed by the Hamilton Depression Rating Scale. The beneficial effect of fluoxetine therapy (compared with placebo), as measured by median reductions in the frequency of bulimic behaviors at the end of therapy compared with baseline, ranged from 1–2 and 2–4 episodes per week for binge eating and self-induced vomiting, respectively. The magnitude of clinical effect was related to baseline frequency of bulimic behaviors since greater reductions in such behaviors were observed in patients with higher baseline frequencies. Although binge eating and purging resolved completely in some patients who received fluoxetine therapy, the majority of fluoxetine-treated patients only experienced a partial reduction in the frequency of bulimic behaviors.

In an uncontrolled study in patients with bulimia nervosa, fluoxetine substantially reduced the frequency of binge eating and self-induced vomiting but did not affect bodily dissatisfaction in patients receiving 60–80 mg of the drug for 4 weeks; in several patients, therapeutic effects of the drug appeared to be maintained during chronic therapy. In another uncontrolled study, fluoxetine reduced the frequency of binge eating and self-induced vomiting in several patients with bulimia nervosa who were unresponsive to previous therapy with imipramine. The drug also reportedly improved bulimic symptoms, expanded food preferences, and resulted in weight gain in one underweight patient with anorexia nervosa and bulimia who was unresponsive to or unable to tolerate previous therapy for her eating disorder (including tricyclic antidepressants, monoamine oxidase inhibitors, bupropion, nomifensine, or lithium). In addition, fluoxetine used in combination with lithium was effective in improving bulimic symptoms in a patient with major depression and bulimia who was unresponsive to prior therapy.

The efficacy of fluoxetine for long-term use in the treatment of bulimia nervosa has been established in a placebo-controlled study of up to 52 weeks' duration in patients who responded to an initial single-blind, 8-week acute treatment phase with fluoxetine 60 mg daily for bulimia nervosa. In this study, fluoxetine decreased the likelihood of relapse and improved the clinical outcome. However, symptoms of bulimia gradually worsened over time in patients in both the fluoxetine and placebo groups in this study, suggesting that fluoxetine alone may not be an adequate maintenance treatment after acute response in some patients with bulimia nervosa. Additional management strategies, such as psychotherapy, may be required to augment or to sustain initial improvement in this condition.

Pending further accumulation of data, most clinicians recommend that antidepressant therapy, including fluoxetine, be continued for at least 6–12 months in patients with bulimia nervosa before attempting to discontinue therapy. If fluoxetine is used for extended periods, the need for continued therapy with the drug should be reassessed periodically.

Anorexia Nervosa Fluoxetine has been used in a limited number of patients with anorexia nervosa†. According to DSM-IV, anorexia nervosa is characterized by refusal to maintain body weight at or above a minimally normal weight for age and height (e.g., weight loss leading to maintenance of body weight less than 85% of that expected or failure to make expected weight gain during periods of growth, leading to body weight less than 85% of that expected); intense fear of gaining weight or becoming fat (even though underweight); disturbance in the perception of body weight and shape, undue influence of body weight or shape on self-evaluation, or denial of the seriousness of the current low body weight; and amenorrhea in postmenarcheal females (i.e., absence of at least 3 consecutive menstrual cycles). Patients with anorexia nervosa often exhibit depressive (e.g., depressed mood, social withdrawal, irritability, insomnia, and diminished interest in sex) and obsessive-compulsive symptoms that may be associated with or exacerbated by undernutrition.

The APA recommends that a program of nutritional rehabilitation, including vitamin (e.g., potassium and phosphorus) supplementation, be established for all patients who are significantly underweight. The APA states that pharmacologic measures (e.g., antidepressants) may be considered in patients with anorexia nervosa to maintain weight and normal eating behaviors; to treat psychiatric symptoms associated with the disorder (e.g., depression, anxiety, or obsessive-compulsive symptoms); and to prevent relapse. However, such therapy should not be used as the sole or primary treatment for anorexia nervosa. Because associated psychiatric symptoms of anorexia nervosa (e.g., depression) often improve with weight gain, the APA states that the decision to initiate antidepressant therapy should be deferred until weight gain has been restored, and that the choice of an antidepressant agent depends on the remaining symptoms. According to the APA, selective serotonin-reuptake inhibitors commonly are considered in patients with anorexia nervosa whose depressive, obsessive, or compulsive symptoms persist in spite of or in the absence of weight gain.

Although there are few well-controlled, clinical studies of antidepressants for the treatment of anorexia nervosa, data from one study indicate that weight-restored patients with anorexia nervosa who received fluoxetine (40 mg daily) after hospital discharge had less weight loss, depression, and fewer rehospitalizations for anorexia nervosa during the subsequent year than those who received placebo. However, it should be noted that fluoxetine has been misused for its anorectic and weight-reducing effects in a patient with a history of chronic depression, anorexia nervosa, and laxative abuse who was receiving the drug for the treatment of depression; therefore, the misuse potential of fluoxetine in depressed patients with concurrent eating disorders or in other patients who may desire to lose weight should be considered. (See Chronic Toxicity.)

■ **Panic Disorder** Fluoxetine is used in the treatment of panic disorder with or without agoraphobia. Panic disorder is characterized by the occurrence of unexpected panic attacks and associated concern about having additional attacks, worry about the implications or consequences of the attacks, and/or a clinically important change in behavior related to the attacks.

According to DSM-IV, panic disorder is characterized by recurrent unexpected panic attacks, which consist of a discrete period of intense fear or discomfort in which 4 (or more) of the following symptoms develop abruptly and reach a peak within 10 minutes: palpitations, pounding heart, or accelerated heart rate; sweating; trembling or shaking; sensations of shortness of breath or smothering; feeling of choking; chest pain or discomfort; nausea or abdominal distress; feeling dizzy, unsteady, lightheaded, or faint; derealization (feelings of unreality) or depersonalization (being detached from oneself); fear of losing control; fear of dying; paresthesias (numbness or tingling sensations); and chills or hot flushes.

The efficacy of fluoxetine for the management of panic disorder with or without agoraphobia has been established by 2 randomized, double-blind, placebo-controlled studies in adult outpatients who met DSM-IV criteria for panic disorder with or without agoraphobia. These studies were of 12 weeks' duration and used a flexible dosing schedule. Fluoxetine therapy in both studies was initiated in a dosage of 10 mg daily for the first week and then the dosage was escalated to 20–60 mg daily depending on clinical response and tolerability. In these studies, 42–62% of patients receiving fluoxetine were free from panic attacks at week 12 compared with 28–44% of those receiving placebo. The mean fluoxetine dosage in one of these studies was approximately 30 mg daily.

The optimum duration of fluoxetine therapy required to prevent recurrence of panic disorder has not been established to date. The manufacturer states that the efficacy of fluoxetine for long-term use (i.e., longer than 12 weeks) has not been demonstrated in controlled studies. However, in a 10-week, placebo-controlled, fixed-dose study, patients responding to fluoxetine 10 or 20 mg daily were randomized to receive continued therapy with their previous fluoxetine dosage or placebo during a 6-month continuation phase. The patients who received an additional 6 months of fluoxetine therapy in this study demonstrated continued clinical improvement.. The manufacturer and some clinicians state that panic disorder is a chronic condition and requires several months or longer of sustained therapy. Therefore, it is reasonable to continue therapy in responding patients. The manufacturer recommends, however, that patients be reassessed periodically to determine the need for continued therapy.

Panic disorder can be treated with cognitive and behavioral psychotherapy and/or pharmacologic therapy. There are several classes of drugs that appear to be effective in the pharmacologic management of panic disorder, including tricyclic antidepressants (e.g., imipramine, clomipramine), monamine oxidase (MAO) inhibitors (e.g., phenelzine), selective serotonin-reuptake inhibitors, and benzodiazepines (e.g., alprazolam, clonazepam). When choosing among the available drugs, clinicians should consider their acceptance and tolerability by patients; their ability to reduce or eliminate panic attacks, reduce clinically important anxiety and disability secondary to phobic avoidance, and ameliorate other common comorbid conditions (such as depression); and their ability to prevent relapse during long-term therapy. Because of their better tolerability when compared with other agents (such as the tricyclic antidepressants and benzodiazepines), the lack of physical dependence problems commonly associated with benzodiazepines, and efficacy in panic disorder with comorbid conditions (e.g., depression, other anxiety disorders such as obsessive-compulsive disorder, alcoholism), many clinicians prefer selective serotonin-reuptake inhibitors as first-line therapy in the management of panic disorder. If selective serotonin-reuptake inhibitor therapy is ineffective or is not tolerated, use of a tricyclic antidepressant or a benzodiazepine is recommended.

■ **Bipolar Disorder** Fluoxetine has been used for the short-term treatment of acute depressive episodes† in a limited number of patients with bipolar depression† (bipolar disorder, depressed). In one poorly controlled study, fluox-

etine was more effective than imipramine, and each drug was more effective than placebo in the management of depression in patients with bipolar disorder; fluoxetine appeared to be particularly effective in reducing anxiety and somatic symptoms in these patients. However, because the drug has been reported to cause manic reactions in some patients, the possibility that hypomanic or manic attacks may be precipitated in patients with bipolar disorder must be considered. In addition, some experts have reported an association between use of antidepressants and the development of rapid cycling and mixed affective states in patients with bipolar disorder, suggesting that such use may worsen the overall course of bipolar disorder in these patients. Consequently, the American Psychiatric Association (APA) does not recommend use of antidepressant monotherapy in patients with bipolar disorder. Initiation or optimization of dosages of maintenance agents (i.e., lithium, lamotrigine) are considered first-line therapies for the management of acute episodes of depression in patients with bipolar disorder. While the addition of either lamotrigine, bupropion, or paroxetine currently is recommended as the next step for patients who fail to respond to optimum dosages of maintenance agents, the APA states that other selective serotonin-reuptake inhibitors (e.g., fluoxetine) can be used as an alternative to these agents. For further information on the management of bipolar disorder, see Uses: Bipolar Disorder, in Lithium Salts 28:28.

Fluoxetine also is used in combination with olanzapine for the treatment of acute depressive episodes in patients with bipolar disorder. In 2 randomized, double-blind studies of 8 weeks' duration comparing a fixed combination of fluoxetine and olanzapine (Symbyax®) with olanzapine monotherapy and placebo, the fixed combination (flexible daily dosages of 6 mg olanzapine and 25 or 50 mg of fluoxetine or of 12 mg of olanzapine and 50 mg of fluoxetine) was more effective than olanzapine monotherapy (5–20 mg daily) or placebo in improvement in depressive symptoms as assessed by the Montgomery-Asberg Depression Rating Scale (MADRS). Although the manufacturer states that efficacy beyond 8 weeks' duration remains to be established, patients have received the fixed combination for up to 24 weeks in clinical trials. Clinicians who elect to extend therapy beyond 8 weeks should reevaluate the risks and benefits of continued therapy periodically.

■ **Obesity** Fluoxetine has been used in a limited number of patients for the short-term management of exogenous obesity†. In a controlled study, obese (i.e., more than 20% overweight), nondepressed individuals receiving fluoxetine (average dosage: 64.9 mg daily), benzphetamine hydrochloride (average dosage: 97 mg daily), or placebo concurrently with reduced food intake and increased exercise for 8 weeks lost an average of about 4.8, 4, and 1.7 kg, respectively. Fluoxetine-treated patients who usually experienced carbohydrate cravings reportedly lost more weight during this study than those who did not experience such cravings. (See Pharmacology: Effects on Appetite and Body Weight.)

In a study evaluating the safety of fluoxetine therapy in the management of exogenous obesity, the drug was generally well tolerated. The adverse effect profile of the drug in nondepressed obese patients appeared to differ somewhat from that in depressed patients receiving similar dosages of the drug; obese patients reportedly had a higher incidence of fatigue and a lower incidence of nausea, anxiety, and tremor. Unlike amphetamines, the potential for addiction to or abuse of fluoxetine appears to be minimal (see Chronic Toxicity), and tolerance to the drug's anorectic and weight-reducing effects has not been reported to date following short-term administration. However, long-term studies are necessary to fully determine whether tolerance develops during chronic fluoxetine therapy and to fully establish the relative efficacy and safety of fluoxetine in the management of exogenous obesity.

■ **Cataplexy** Fluoxetine has been used for the symptomatic management of cataplexy† in a limited number of patients with cataplexy and associated narcolepsy. In one study, the drug appeared to be as effective as clomipramine in reducing the number of cataplexy attacks in patients concurrently receiving CNS stimulants (e.g., dextroamphetamine) for the symptomatic management of associated narcolepsy.

■ **Alcohol Dependence** Like some other selective serotonin-reuptake inhibitors (e.g., citalopram, zimeldine [not commercially available in the US]), fluoxetine has been used in the management of alcohol dependence†. However, studies of selective serotonin-reuptake inhibitors have generally shown modest effects on alcohol consumption. In a limited number of early-stage problem drinkers (who drank an average of about 8 drinks daily prior to therapy), alcohol consumption was reduced by an average of 17% in patients receiving 60 mg of fluoxetine daily; however, response showed considerable interindividual variability, and alcohol consumption was not altered substantially in problem drinkers receiving 40 mg of the drug daily. It has been suggested that the clinical effects of selective serotonin-reuptake inhibitors in the management of alcohol dependence may only be transient. In patients with mild to moderate alcohol dependence, alcohol consumption is substantially decreased for only the first 1–4 weeks of fluoxetine therapy or first 12 weeks of citalopram therapy. Additional study is required to fully determine the safety and efficacy of fluoxetine in the management of alcohol dependence. (See Pharmacology: Effects on Alcohol Intake and also see Drug Interactions: Alcohol.)

■ **Myoclonus** Fluoxetine has been used for the management of intention myoclonus†, including postanoxic action myoclonus† and progressive action myoclonus†, in a limited number of patients. Although fluoxetine alone was not effective in improving myoclonus, speech abnormalities, gait abnormalities, or overall performance on neurological examination in such patients, the drug did appear to potentiate the therapeutic effects of combined oxitriptan (l-5-hydroxytryptophan, l-5HTP) and carbidopa therapy in some patients. In addition, fluoxetine reportedly reduced the dosage requirement of oxitriptan and the incidence of adverse GI effects (e.g., diarrhea, abdominal cramps) associated with such therapy. Fluoxetine used in combination with oxitriptan also has exhibited antimyoclonic activity in animals. (See Pharmacology: Other Effects.) However, because toxic effects have been reported in some patients concurrently receiving fluoxetine and tryptophan, a serotonergic agent that is structurally similar to oxitriptan (see Tryptophan and Other Serotonin Precursors under Drug Interactions: Drugs Associated with Serotonin Syndrome), further study and experience are needed to fully determine the safety and efficacy of combined therapy with fluoxetine and oxitriptan-carbidopa in the management of intention myoclonus.

■ **Premature Ejaculation** Like some other serotonin-reuptake inhibitors, fluoxetine has been used with some success in the treatment of premature ejaculation†. In a placebo-controlled study, fluoxetine produced substantial improvements compared with placebo in time to ejaculation and was well tolerated in most patients. However, in a comparative study, patients receiving either clomipramine or sertraline reported a greater increase in mean intravaginal ejaculation latency time and a greater patient sexual satisfaction rating than those receiving either fluoxetine or placebo. Although the mechanism of action of selective serotonin-reuptake inhibitors in delaying ejaculation is unclear, it has been suggested that these drugs may be particularly useful in patients who fail or refuse behavioral or psychotherapeutic treatment or when partners are unwilling to cooperate with such therapy.

Dosage and Administration

■ **Administration** Fluoxetine hydrochloride is administered orally without regard to meals.

Fluoxetine hydrochloride conventional capsules, tablets, and solution are administered once or twice daily; the delayed-release capsules are administered once weekly. For the initial management of depression, obsessive-compulsive disorder, premenstrual dysphoric disorder, or bulimia nervosa, the drug generally is administered once daily in the morning. If the dosage exceeds 20 mg daily, the manufacturer and some clinicians state that fluoxetine should be administered in 2 divided doses daily (preferably in the morning and at noon). However, limited evidence suggests that no clinically important differences in either the efficacy or incidence of adverse effects exist with once-daily (in the morning) versus twice-daily (in the morning and at noon) administration of the drug. If sedation occurs during fluoxetine therapy, administering the second dose at bedtime rather than at noon may be useful. Because fluoxetine and its active metabolites have relatively long half-lives, the drug has been administered less frequently than once daily (e.g., every 2–7 days), particularly during maintenance therapy. Fluoxetine delayed-release capsules are administered once weekly as maintenance therapy in the management of major depressive disorder in patients who have responded to daily administration of the drug. Some clinicians have suggested that conventional fluoxetine preparations administered less frequently than once daily (i.e., three 20-mg capsules once weekly) may also be effective as maintenance therapy in the management of major depressive disorder, but such dosing regimens should be considered investigational at this time and require additional study to confirm their safety and efficacy.

Because of the prolonged elimination of fluoxetine and its active metabolite from the body, missing a dose of the drug once steady-state concentrations have been achieved is unlikely to result in substantial alterations in plasma fluoxetine or norfluoxetine concentrations.

■ **Dosage** Dosage of fluoxetine hydrochloride is expressed in terms of fluoxetine.

In titrating dosage of or discontinuing fluoxetine therapy, the prolonged elimination half-life of fluoxetine and norfluoxetine should be considered. Several weeks will be required before the full effect of such alterations is realized.

Withdrawal symptoms, including dysphoric mood, irritability, agitation, dizziness, anxiety, confusion, headache, lethargy, emotional lability, insomnia, hypomania, and sensory disturbances (e.g., paresthesias such as electric shock sensations), have been reported following discontinuance of fluoxetine and other selective serotonin-reuptake inhibitors, particularly upon abrupt discontinuance. While these events are generally self-limiting, there have been reports of serious discontinuance symptoms. If fluoxetine is to be discontinued, the manufacturer recommends that the dosage be tapered gradually and the patient closely monitored for these manifestations. Abrupt discontinuance should be avoided whenever possible. If intolerable symptoms occur following a decrease in the dose or upon discontinuance of therapy, fluoxetine therapy may be reinstituted at the previously prescribed dosage. Subsequently, the clinician may continue decreasing the dose but at a more gradual rate. Plasma concentrations of fluoxetine and norfluoxetine (the principal metabolite) decline gradually after cessation of therapy, which may minimize the risk of withdrawal symptoms.

Patients receiving fluoxetine should be monitored for possible worsening of depression, suicidality, or unusual changes in behavior, especially at the beginning of therapy or during periods of dosage adjustment. (See Cautions: Precautions and Contraindications.)

Major Depressive Disorder **Adult Dosage.** For the management of major depression, the recommended initial dosage of fluoxetine in adults is 20 mg daily. However, some clinicians suggest that fluoxetine therapy be initiated

with lower dosages (e.g., 5 mg daily or 20 mg every 2 or 3 days). Although symptomatic relief may be apparent within the first 1–3 weeks of fluoxetine therapy, optimum antidepressant effect usually requires at least 4 weeks or more of therapy with the drug. If insufficient clinical improvement is apparent after several weeks of fluoxetine therapy at 20 mg daily, an increase in dosage may be considered. Efficacy of fluoxetine for major depression was demonstrated in clinical trials employing 10–80 mg daily. Studies comparing fluoxetine 20, 40, and 60 mg daily to placebo indicate that a dosage of 20 mg daily is sufficient to obtain a satisfactory response in most adults with major depression. Fluoxetine dosages up to 80 mg daily have been administered in some patients, and dosages as low as 5 mg daily may be effective in some patients with depression. In addition, in a study in moderately depressed patients, increasing the dosage of fluoxetine from 20 mg to 40 or 60 mg daily did not result in substantial improvement in depression but was associated with an increase in certain adverse effects (e.g., nausea, anxiety, diarrhea, dry mouth, weight loss). The manufacturer states that the maximum dosage of fluoxetine in adults with major depression should not exceed 80 mg daily; however, somewhat higher dosages (e.g., 100–120 mg daily) occasionally have been used in patients who did not respond adequately to lower dosages.

When fluoxetine hydrochloride delayed-release capsules are used for the continuing management of major depressive disorder, the recommended dosage of fluoxetine is 90 mg once weekly beginning 7 days after the last dose of fluoxetine 20 mg daily. If a satisfactory response is not maintained with once weekly administration, consideration may be given to reestablishing a daily dosage schedule.

As with the use of fluoxetine for other indications, lower dosages or less frequent dosing regimens should be considered for geriatric patients, patients with concurrent disease, and patients receiving multiple concomitant drug therapies.

Pediatric Dosage. For the management of major depressive disorder in children and adolescents 8–18 years of age, the recommended initial dosage of fluoxetine is 10 or 20 mg daily. If therapy is initiated at 10 mg daily, it can be increased after 1 week to 20 mg daily. Because higher plasma fluoxetine concentrations occur in lower weight children, the manufacturer states that both the initial and target dose in lower weight children may be 10 mg daily. An increase in dosage to 20 mg daily may be considered after several weeks in lower weight children if insufficient clinical improvement is observed. Because a rare but serious drug interaction may occur in depressed children and adolescents with comorbid attention-deficit hyperactivity disorder (ADHD) who receive stimulants and selective serotonin-reuptake inhibitors concomitantly, some experts recommend a maximum fluoxetine dosage of 20 mg daily in such patients. (See Other Drugs under Drug Interactions: Drugs Associated with Serotonin Syndrome.)

Duration of Therapy. The optimum duration of fluoxetine therapy required to prevent recurrence of depressive symptoms has not been established to date. However, many experts state that acute depressive episodes require several months or longer of sustained antidepressant therapy. Systematic evaluation of fluoxetine has shown that its antidepressant efficacy is maintained for periods of up to approximately 9 months following 3 months of open-label acute treatment (12 months total) in adults receiving 20 mg daily as conventional fluoxetine capsules or for periods of up to approximately 6 months with once-weekly dosing of the 90 mg delayed-release fluoxetine capsules following 3 months of open-label treatment with 20 mg once daily as conventional fluoxetine capsules. However, the therapeutic equivalence of once-weekly administration of the 90-mg delayed-release capsules with that of once-daily administration of the 20-mg conventional preparations for delaying time to relapse has not been established. In addition, it has not been determined to date whether the dosage of the antidepressant necessary to treat acute symptoms of depression is the same as the dosage necessary to prevent recurrence of such symptoms. If therapy with the drug is prolonged, the lowest possible dosage should be employed and the need for continued therapy reassessed periodically.

Switching To or From Other Antidepressants. Because concurrent use of fluoxetine and a tricyclic antidepressant may result in greater than two- to 10-fold elevations in plasma tricyclic antidepressant concentrations, dosage of the tricyclic antidepressant may need to be reduced and plasma tricyclic concentrations may need to be monitored temporarily when fluoxetine is administered concurrently or has been recently discontinued. (See Drug Interactions: Tricyclic and Other Antidepressants.)

Because of the potential risk of serotonin syndrome, the manufacturer recommends that an interval of at least 2 weeks elapse when switching a patient from a monoamine oxidase (MAO) inhibitor to fluoxetine. Because both fluoxetine and its principal metabolite have relatively long half-lives, the manufacturer and some clinicians recommend that at least 5 weeks elapse between discontinuance of fluoxetine therapy and initiation of MAO inhibitor therapy. (See Drug Interactions: Drugs Associated with Serotonin Syndrome.)

Obsessive-Compulsive Disorder **Adult Dosage.** For the management of obsessive-compulsive disorder, the recommended initial dosage of fluoxetine in adults is 20 mg once daily. Because a possible dose-response relationship for effectiveness was suggested in one clinical study, an increase in dosage may be considered following several weeks of therapy if insufficient clinical improvement is observed. The manufacturer recommends fluoxetine dosages of 20–60 mg daily for the treatment of obsessive-compulsive disorder; dosages up to 80 mg daily have been well tolerated in clinical studies evaluating the drug in adults with obsessive-compulsive disorder. The manufacturer states that fluoxetine dosage should not exceed 80 mg daily. Like fluoxetine's antidepressant effect, the full therapeutic effect of the drug in patients with obsessive-compulsive disorder may be delayed until 5 weeks of fluoxetine therapy or longer.

Pediatric Dosage. For the management of obsessive-compulsive disorder, the recommended initial dosage of fluoxetine in children and adolescents 7–17 years of age is 10 mg once daily. In adolescents and higher weight children, the dosage should be increased to 20 mg daily after 2 weeks; additional dosage increases may be considered after several more weeks if insufficient clinical improvement is observed. In lower weight children, dosage increases may be considered after several weeks if insufficient clinical improvement is observed. The manufacturer recommends fluoxetine dosages of 20–60 mg daily for adolescents and higher weight children and fluoxetine dosages of 20–30 mg daily for lower weight children for the treatment of obsessive-compulsive disorder. In lower weight children, the manufacturer states that clinical experience with fluoxetine dosages exceeding 20 mg daily is minimal and that there is no experience with dosages exceeding 60 mg daily in such patients.

Duration of Therapy. Although the efficacy of fluoxetine for long-term use (i.e., longer than 13 weeks) has not been demonstrated in controlled studies, patients have been continued on the drug under double-blind conditions for up to an additional 6 months without loss of benefit. The manufacturer and many experts state that obsessive-compulsive disorder is chronic and requires several months or longer of sustained therapy. Therefore, it is reasonable to continue therapy in responding patients. If fluoxetine is used for extended periods, dosage should be adjusted so that the patient is maintained on the lowest effective dosage, and the need for continued therapy with the drug should be reassessed periodically.

Premenstrual Dysphoric Disorder For the management of premenstrual dysphoric disorder (previously late luteal phase dysphoric disorder), the recommended dosage of fluoxetine is 20 mg once daily given continuously throughout the menstrual cycle or intermittently (i.e., only during the luteal phase, starting 14 days prior to the anticipated onset of menstruation and continuing through the first full day of menses). The intermittent dosing regimen is then repeated with each new menstrual cycle. Decisions regarding which dosing regimen to use should be individualized. In a clinical study evaluating continuous dosing of fluoxetine dosages of 20 or 60 mg once daily for the treatment of premenstrual dysphoric disorder (PMDD), both dosages were effective but there was no evidence that the higher dosage provided any additional benefit. The manufacturer states that dosages exceeding 60 mg daily have not been systematically studied in patients with PMDD and that 80 mg daily is the maximum dosage of fluoxetine for the management of PMDD.

Clinical studies using fluoxetine dosages of 20 mg daily given intermittently or continuously have shown that the efficacy of the drug in the treatment of PMDD is maintained for up to 3 or 6 months, respectively. Patients should be periodically reassessed to determine the need for continued treatment. Discontinuance of the drug (even after more than 1 year of therapy) has resulted in relapse of PMDD within approximately 2 menstrual cycles.

Eating Disorders **Bulimia Nervosa.** For the management of bulimia nervosa in adults, the recommended dosage of fluoxetine is 60 mg daily, administered as a single dose in the morning. The manufacturer states that in some patients, oral dosage of the drug may be carefully titrated up to the recommended initial dosage over a period of several days. However, since 60-mg doses of fluoxetine were found to be well tolerated, the APA states that many clinicians initiate treatment for bulimia nervosa at the higher dosage, titrating downward as necessary to minimize adverse effects. Fluoxetine dosages exceeding 60 mg daily have not been evaluated in patients with bulimia.

Systematic evaluation of fluoxetine has demonstrated that its efficacy in the treatment of bulimia nervosa is maintained for periods of up to 12 months following 2 months of acute treatment in patients receiving 60 mg daily as conventional fluoxetine capsules. Pending further accumulation of data, most clinicians recommend that antidepressant therapy, including fluoxetine, be continued for at least 6–12 months in patients with bulimia nervosa before attempting to discontinue therapy. If fluoxetine is used for extended periods, the manufacturer states that the need for continued therapy should be reassessed periodically.

Anorexia Nervosa. Although safety and efficacy of fluoxetine for the management of anorexia nervosa† and optimal dosage of the drug for this disorder have not been established, fluoxetine has been given in a dosage of 40 mg daily in weight-restored patients with anorexia nervosa.

Panic Disorder For the management of panic disorder, the recommended initial dosage of fluoxetine in adults is 10 mg daily. After 1 week, the dosage should be increased to 20 mg once daily. If no clinical improvement is apparent after several weeks of fluoxetine therapy at 20 mg daily, an increase in dosage may be considered. Efficacy of the drug was demonstrated in clinical trials employing 10–60 mg daily. However, the most frequently administered dosage in flexible-dose clinical studies was 20 mg daily. As with the use of fluoxetine for other indications, lower dosages or less frequent dosing regimens should be considered for geriatric patients and patients with concurrent disease or those receiving multiple concomitant drug therapies. The manufacturer states that fluoxetine dosages exceeding 60 mg daily have not been systematically evaluated in patients with panic disorder.

The optimum duration of fluoxetine therapy required to prevent recurrence of panic disorder has not been established to date. The manufacturer states that

the efficacy of fluoxetine beyond 12 weeks of therapy has not been demonstrated in controlled studies. However, the manufacturer and some clinicians state that panic disorder is chronic and requires several months or longer of sustained therapy. Therefore, it is reasonable to continue therapy in responding patients. The manufacturer recommends, however, that patients be reassessed periodically to determine the need for continued therapy.

Bipolar Disorder **Monotherapy.** For the short-term treatment of acute depressive episodes in patients with bipolar disorder†, fluoxetine has been given in a dosage of 20–60 mg daily. Because of the risk of developing manic episodes associated with antidepressant therapy in patients with bipolar disorder, many clinicians recommend using the lowest effective dosage of fluoxetine for the shortest time necessary using the antidepressant in conjunction with a mood-stabilizing agent (e.g., lithium).

Combination Therapy. When used in fixed combination with olanzapine for acute depressive episodes in patients with bipolar disorder, fluoxetine is administered once daily in the evening, usually initiating therapy with a dose of 6 mg of olanzapine and 25 mg of fluoxetine (Symbyax® 6/25). This dosage generally should be used as initial and maintenance therapy in patients with a predisposition to hypotensive reactions, patients with hepatic impairment, or those with factors that may slow metabolism of the drugs(s) (e.g., female gender, geriatric age, nonsmoking status); when indicated, dosage should be escalated with caution. In other patients, dosage can be increased according to patient response and tolerance as indicated. In clinical trials, antidepressive efficacy was demonstrated at olanzapine dosages ranging from 6–12 mg daily and fluoxetine dosages ranging from 25–50 mg daily. Dosages exceeding 18 mg of olanzapine and 75 mg of fluoxetine have not been evaluated in clinical studies.

Cataplexy For the management of cataplexy†, fluoxetine has been given in a dosage of 20 mg once or twice daily in conjunction with CNS stimulant therapy (e.g., methylphenidate, dextroamphetamine).

Alcohol Dependence For the management of alcohol dependence†, fluoxetine has been given in a dosage of 60 mg daily. Studies have shown that reductions in alcohol intake occur only with dosages of selective serotonin-reuptake inhibitors that are higher than the average therapeutic dosages used in depression. Alcohol intake in patients receiving lower dosages of fluoxetine (40 mg daily) was comparable to that of patients receiving placebo.

■ **Dosage in Renal and Hepatic Impairment** The need for modification of fluoxetine dosage in patients with renal impairment has not been fully determined to date, and the drug should be used with caution in such patients. Although the elimination of fluoxetine and norfluoxetine following single-dose administration does not appear to be altered substantially in patients with renal impairment, multiple-dose studies are needed to determine whether accumulation of the parent drug and/or its metabolites occurs during long-term fluoxetine therapy in patients with severe renal impairment. (See Pharmacokinetics.) The manufacturer and some clinicians state that a reduction in dose and/or frequency of administration of fluoxetine should be considered in patients with renal impairment, particularly those with severe renal impairment. Supplemental doses of fluoxetine during hemodialysis do not appear to be necessary since the drug and its active metabolite norfluoxetine are not removed substantially by hemodialysis.

Since fluoxetine is extensively metabolized in the liver, elimination may be prolonged in patients with hepatic impairment. Therefore, the manufacturer and some clinicians recommend a reduction in dose and/or frequency of administration of fluoxetine in patients with hepatic impairment. Some clinicians recommend a 50% reduction in initial fluoxetine dosage for patients with well-compensated cirrhosis; however, patients with more substantial hepatic impairment, particularly those with severe disease, will require careful individualization of dosage. Subsequent dosage adjustment based on the tolerance and therapeutic response of the patient has been recommended in patients with hepatic impairment.

■ **Treatment of Pregnant Women during the Third Trimester** Because some neonates exposed to fluoxetine and other SSRIs or selective serotonin- and norepinephrine-reuptake inhibitors (SNRIs) late in the third trimester of pregnancy have developed severe complications, consideration may be given to cautiously tapering fluoxetine therapy in the third trimester prior to delivery if the drug is administered during pregnancy. (See Pregnancy under Cautions: Pregnancy, Fertility, and Lactation.)

Cautions

The adverse effect profile of fluoxetine is similar to that of other selective serotonin-reuptake inhibitors (e.g., citalopram, escitalopram, fluvoxamine, paroxetine, sertraline). Because fluoxetine is a highly selective serotonin-reuptake inhibitor with little or no effect on other neurotransmitters, the incidence of some adverse effects commonly associated with tricyclic antidepressants, such as anticholinergic effects (dry mouth, dizziness, constipation), adverse cardiovascular effects, drowsiness, and weight gain, is lower in patients receiving fluoxetine. However, certain adverse GI (e.g., nausea) and nervous system (e.g., anxiety, nervousness, insomnia) effects appear to occur more frequently during fluoxetine therapy than during therapy with tricyclic antidepressants.

In controlled studies, the most common adverse reactions occurring more frequently in adults receiving fluoxetine than in those receiving placebo included nervous system effects such as anxiety, nervousness, insomnia, drowsiness, fatigue or asthenia, tremor, and dizziness or lightheadedness; GI effects such as anorexia, nausea, and diarrhea; vasodilation; dry mouth; abnormal vision; decreased libido; abnormal ejaculation; rash; and sweating. Discontinuance of fluoxetine therapy was required in about 15% of adults, principally because of adverse psychiatric (e.g., nervousness, anxiety, insomnia), other nervous system (e.g., dizziness, asthenia, headache), GI (e.g., nausea), and dermatologic (e.g., rash, pruritus) effects. Because of the relatively long elimination half-lives of fluoxetine and its principal metabolite norfluoxetine, the possibility that some adverse effects may resolve slowly following discontinuance of the drug should be considered.

In controlled clinical trials, adverse effects reported in adults with weekly administration of fluoxetine delayed-release capsules were similar to those reported with daily administration of conventional capsules. Diarrhea and cognitive problems occurred more frequently with the delayed-release formulation compared with the conventional capsules.

Common adverse effects associated with fluoxetine therapy for major depressive disorder or obsessive-compulsive disorder in children and adolescents 7 years of age and older are generally similar to those observed in adults and include nausea, tiredness, nervousness, dizziness, and difficulty concentrating. However, manic reactions, including mania and hypomania, were the most common adverse events associated with discontinuance of the drug in 3 pivotal, pediatric, placebo-controlled studies. These reactions occurred in 2.6% of pediatric patients receiving fluoxetine compared with 0% of those receiving placebo and resulted in the discontinuance of fluoxetine in 1.8% of the patients during the acute phases of the studies combined. Consequently, regular monitoring for the occurrence of mania and hypomania is recommended by the manufacturer.

The usual cautions and precautions of olanzapine should be observed when fluoxetine is used in fixed combination with the antipsychotic.

■ **Nervous System Effects** Headache has occurred in approximately 20% of patients receiving fluoxetine and has required discontinuance of therapy in less than 1.5% of patients. Nervousness and anxiety have occurred in about 15 and 9% of patients, respectively, and insomnia has occurred in about 14% of patients receiving the drug; such effects appear to be dose-related and have required discontinuance of therapy in approximately 5% of fluoxetine-treated patients. However, because insomnia is a symptom also associated with depression, relief of insomnia and improvement in sleep patterns may occur when clinical improvement in depression becomes apparent during antidepressant therapy. The manufacturer and some clinicians state that a sedative (e.g., a short-acting benzodiazepine, chloral hydrate) may be administered to patients who experience insomnia or nervousness early in therapy; however, the possibility that fluoxetine may interact with some benzodiazepines (e.g., diazepam) should be considered. (See Drug Interactions: Benzodiazepines.)

Drowsiness and fatigue or asthenia reportedly occur in about 12 and 4%, respectively, of patients receiving fluoxetine therapy. Tremor and dizziness have occurred in about 8 and 6% of patients, respectively; the incidence of dizziness may be dose-related. Adverse nervous system effects reportedly occurring in approximately 1–2% of patients include sedation, sensation disturbance, lightheadedness, confusion, myoclonus, agitation, amnesia, and decreased concentration. Abnormal dreams and agitation have been reported in more than 1% of patients receiving fluoxetine therapy.

Hypomania, mania, and manic reaction have been reported in 1% or less of patients receiving fluoxetine, including those with depression or obsessive-compulsive disorder. In addition, mania reportedly occurred following administration of a higher than recommended dosage (140 mg daily) in a patient with major depression refractory to conventional antidepressant therapy; this patient subsequently responded to a fluoxetine dosage of 60 mg daily without apparent adverse effects. Such reactions have occurred in patients receiving other antidepressant agents and may be caused by antidepressant-induced functional increases in catecholamine activity within the CNS, resulting in a "switch" from depressive to manic behavior. There is some evidence that patients with bipolar disorder may be more likely to experience antidepressant-induced hypomanic or manic reactions than patients without evidence of this disorder. In addition, limited evidence suggests that such reactions may occur more frequently in bipolar depressed patients receiving tricyclics and tetracyclics (e.g., maprotiline, mianserin [not commercially available in the US]) than in those receiving selective serotonin-reuptake inhibitors (e.g., citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline). However, further studies are needed to confirm these findings.

Extrapyramidal reactions, including acute dystonic reactions, torticollis, buccolingual syndrome, and akathisia, have occurred rarely in patients receiving fluoxetine. An extrapyramidal reaction consisting of torticollis, jaw rigidity, cogwheel rigidity, and loss of fluid motion in gait reportedly occurred in one patient several days after initiation of fluoxetine therapy, but responded rapidly to an anticholinergic antiparkinsonian agent (i.e., trihexyphenidyl) and did not recur despite continued fluoxetine therapy. Neuroleptic malignant syndrome also has been reported. Serum prolactin concentrations were increased and CSF 3-methoxy-4-hydroxyphenylacetic acid (homovanillic acid, HVA) concentrations were decreased in this patient, suggesting that a decrease in dopaminergic activity (possibly as a result of enhanced serotonergic neurotransmission) may have contributed to the reaction.

The incidence of seizures during fluoxetine therapy appears to be similar to that observed during therapy with most other currently available antidepressants. Seizures or events that were described as possible seizures have been reported in approximately 0.2% of patients receiving fluoxetine therapy to date. (See Cautions: Precautions and Contraindications.) In addition, seizures have

occurred following acute overdosage of the drug (see Acute Toxicity) and in at least one patient undergoing electroconvulsive therapy (ECT) concomitantly.

Adverse nervous system effects occurring in less than 1% of fluoxetine-treated patients include ataxia, abnormal gait, incoordination, hyperkinesia, hypoesthesia, neuropathy, neuralgia, and hydrocephalus; however, a causal relationship to the drug has not been established. Migraine, acute brain syndrome, amnesia, CNS stimulation, vertigo, emotional lability, hostility, depersonalization, apathy, malaise, hangover effect, and euphoria also have been reported in less than 1% of patients receiving the drug. Psychosis, paranoid reaction, delusions, and hallucinations have been reported in less than 1% of patients, although these adverse effects have not been definitely attributed to fluoxetine. Rarely reported adverse nervous system effects for which a causal relationship has not been established include antisocial reaction, violent behavior, chronic brain syndrome, confusion, circumoral paresthesia, precipitation or worsening of depression, stupor, coma, EEG abnormalities, dysarthria, hypertonia, hysteria, myoclonus, dyskinesia, nystagmus, paralysis, exacerbation of multiple sclerosis, and decreased reflexes. Interference with facial nerve conduction, manifesting as ocular tics and impaired hearing, also has been reported. In some patients developing movement disorders with fluoxetine, there were underlying risk factors such as predisposing drug therapy and/or the disorder was an exacerbation of a preexisting disorder.

Suicidality The US Food and Drug Administration (FDA) has determined that antidepressants increase the risk of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults (18–24 years of age) with major depressive disorder and other psychiatric disorders. Suicidal ideation, which can manifest as persistent, obsessive, and violent suicidal thoughts, has emerged occasionally in adults receiving fluoxetine. In a report of several fluoxetine-associated cases, severe suicidal ideation developed within 2–7 weeks after initiation of fluoxetine therapy and resolved within several days to months after discontinuance of the drug; however, the patients were unresponsive to fluoxetine and had received monoamine oxidase inhibitor therapy previously, and most had a history of suicidal ideation, were receiving relatively high dosages (60–80 mg daily) of fluoxetine, and were receiving other psychotropic therapy concomitantly. Suicidal ideation also has been reported in patients who reportedly had no history of such ideation, but the drug also has been used without recurrence of suicidal ideation in a few patients in whom such ideation emerged during tricyclic antidepressant therapy. Because of the possibility of suicidality, patients should be appropriately monitored and closely observed for clinical worsening, suicidality, and unusual changes in behavior, particularly during initiation of fluoxetine therapy (i.e., the first few months) and during periods of dosage adjustments. (See Cautions: Precautions and Contraindications and see Cautions: Pediatric Precautions and see Acute Toxicity.)

■ **GI Effects** The most frequent adverse effect associated with fluoxetine therapy is nausea, which occurs in about 21% of patients. Nausea generally is mild, occurs early in therapy, and usually subsides after a few weeks of continued therapy with the drug. Limited evidence suggests that the incidence of nausea may be dose-related, but additional experience with the drug is necessary to confirm this finding. Adverse GI effects, principally nausea, have required discontinuance of fluoxetine therapy in about 3% of patients receiving the drug. Although the incidence of vomiting appears to be similar in patients receiving fluoxetine or tricyclic antidepressants (e.g., imipramine), the incidence of nausea appears to be higher with fluoxetine. While the mechanism(s) of fluoxetine-induced GI effects has not been fully elucidated, serotonin has been shown to have complex effects on the GI tract (e.g., stimulation of small intestine motility, inhibition of gastric and large intestine motility).

Diarrhea occurs in about 12%, anorexia in about 9%, and dyspepsia in about 6% of patients receiving the drug; limited evidence suggests that the incidence of anorexia may be dose-related. Other adverse GI effects associated with fluoxetine therapy include abdominal pain and change in taste perception, which occur in approximately 3 and 2% of patients, respectively; taste loss has been reported rarely. Vomiting, melena, and flatulence reportedly occur in about 2% and gastroenteritis in about 1% of patients receiving the drug.

Increased appetite has been reported in more than 1% of patients receiving fluoxetine, but has not been definitely attributed to the drug. Other adverse GI effects, including aphthous stomatitis, dysphagia, eructation, esophagitis, gastritis, gingivitis, glossitis, melena, stomatitis, and thirst, have been reported in less than 1% of fluoxetine-treated patients; however, a causal relationship to the drug has not been established. Bloody diarrhea, GI hemorrhage, colitis, duodenal or gastric ulcer, enteritis, pancreatitis, fecal incontinence, hematemesis, hyperchlorhydria, increased salivation, mouth ulceration, salivary gland enlargement, tongue discoloration, and tongue edema have occurred rarely, but have not been definitely attributed to fluoxetine.

Epidemiologic case-control and cohort design studies have suggested that selective serotonin-reuptake inhibitors may increase the risk of upper GI bleeding. Although the precise mechanism for this increased risk remains to be clearly established, serotonin release by platelets is known to play an important role in hemostasis, and selective serotonin-reuptake inhibitors decrease serotonin uptake from the blood by platelets thereby decreasing the amount of serotonin in platelets. In addition, concurrent use of aspirin or other nonsteroidal anti-inflammatory agents was found to substantially increase the risk of GI bleeding in patients receiving selective serotonin-reuptake inhibitors in 2 of these studies. Although these studies focused on upper GI bleeding, there is some evidence suggesting that bleeding at other sites may be similarly potentiated. Further clinical studies are needed to determine the clinical importance of these findings. (See Cautions: Hematologic Effects and see also Drug Interactions: Drugs Affecting Hemostasis.)

■ **Dermatologic and Sensitivity Reactions** Rash (including maculopapular, purpuric, pustular, and vesiculobullous rash; erythema multiforme) and/or urticaria occurs in about 4% and pruritus occurs in about 2% of patients receiving fluoxetine. Adverse dermatologic effects, principally rash and pruritus, generally occur during the first few weeks of therapy and have required discontinuance of the drug in approximately 1% of patients.

Fluoxetine-induced rash and/or urticaria have been associated with systemic signs or symptoms such as fever, leukocytosis, arthralgia, edema, carpal tunnel syndrome, respiratory distress, lymphadenopathy, proteinuria, and mild elevation in serum aminotransferase (transaminase) concentrations in some patients. Serious systemic illnesses have developed rarely in patients with fluoxetine-induced dermatologic reactions to date. Although the diagnosis was equivocal in at least 2 of these patients, one patient was diagnosed as having a leukocytoclastic vasculitis and the other patient exhibited a severe desquamating syndrome that was variably diagnosed as either vasculitis or erythema multiforme. In addition, serum sickness reactions have developed in several other patients who experienced adverse dermatologic effects in association with fluoxetine therapy. Additional cases of systemic reactions possibly related to vasculitis have been reported in patients with rash. Although systemic reactions appear to occur rarely in patients receiving fluoxetine, such reactions may be serious and potentially may involve the lung, kidney, or liver; death reportedly has occurred in association with such reactions. Anaphylactoid reactions (including bronchospasm, angioedema, and/or urticaria) have been reported, and adverse pulmonary effects (including inflammatory processes of varying histopathology and/or fibrosis), which usually occurred with dyspnea as the only preceding symptom, have been reported rarely. It has not been established whether the systemic reactions and associated skin rash in fluoxetine-treated patients share a common underlying cause and represent a true syndrome induced by the drug or whether the temporal association between the rash and other systemic signs and symptoms occurred only by chance; in addition, a specific, underlying immunologic basis for these effects has not been identified. However, such systemic reactions are of potential concern since zimeldine (another selective serotonin-reuptake inhibitor that previously was commercially available outside the US) reportedly was associated with the development of Guillain-Barré syndrome following flu-like, hypersensitivity reactions to the drug; because of such reactions, zimeldine no longer is commercially available. Most patients with fluoxetine-induced rash and/or urticaria improve soon after discontinuance of therapy and/or administration of an antihistamine or corticosteroid, and most patients with such reactions to date have recovered completely without serious adverse sequelae. In addition, several patients who developed hypersensitivity reactions while receiving zimeldine subsequently received fluoxetine with no recurrence of a similar reaction. However, because of associated severe adverse systemic effects with fluoxetine and pharmacologically similar antidepressants (e.g., zimeldine), it is recommended that fluoxetine be discontinued if rash, urticaria, and/or other manifestations of hypersensitivity (e.g., fever, flu-like symptoms), for which alternative etiologies cannot be identified, occur during therapy with the drug.

Excessive sweating occurs in about 8% of patients receiving fluoxetine. Acne and allergic reactions have occurred in approximately 2 and 1% of patients, respectively. Adverse dermatologic and hypersensitivity reactions occurring in less than 1% of patients receiving fluoxetine include acne, cyst formation, dry skin, contact dermatitis, facial edema, alopecia, and herpes simplex; however, these effects have not been definitely attributed to the drug. Although a causal relationship has not been established, eczema, erythema nodosum, epidermal necrolysis, exfoliative dermatitis, Stevens-Johnson syndrome, seborrhea, psoriasis, fungal dermatitis, cellulitis, hirsutism, herpes zoster, skin discoloration, skin hypertrophy, subcutaneous nodules, and ecchymoses have been reported rarely.

■ **Metabolic Effects** Unlike tricyclic antidepressants, which commonly cause weight gain, weight gain occurs in less than 1% of patients receiving fluoxetine. Weight loss, however, frequently occurs during therapy with the drug. Normal-weight and overweight (i.e., body mass index exceeding 25 kg/m^2) depressed patients lost an average of 0.9–1.8 kg and 1.8 kg, respectively, following 6 weeks of therapy with the drug. In addition, weight loss exceeding 5% of body weight has been reported in approximately 13% of fluoxetine-treated patients. Weight loss associated with fluoxetine therapy appears to be reversible, with a gradual increase in body weight occurring following discontinuance of therapy with the drug. Such weight loss appears to result from decreased food consumption rather than adverse GI effects associated with the drug; there is some evidence that fluoxetine-induced weight loss may be dose-related. (See Pharmacology: Effects on Appetite and Body Weight.) In addition, weight loss appears to occur independent of the antidepressant effect of the drug. Although weight loss is commonly associated with fluoxetine therapy, less than 1% of patients discontinue the drug because of this effect. In some cases, however, substantial weight loss may be an undesirable effect of therapy with the drug, particularly in underweight depressed patients.

Fluoxetine potentially may alter blood glucose concentrations. Hypoglycemia has occurred in less than 1% of patients receiving fluoxetine and hypoglycemic reaction has occurred rarely. In addition, hyperglycemia has developed following discontinuance of the drug. Therefore, the possibility that insulin and/or oral sulfonylurea antidiabetic agent dosage adjustments may be

necessary when fluoxetine therapy is initiated or discontinued in patients with diabetes mellitus should be considered.

Hypercholesterolemia, hyperlipidemia, and hypokalemia have been reported rarely in fluoxetine-treated patients; these adverse effects have not been definitely attributed to the drug.

■ **Ocular Effects** Visual disturbances, including blurred vision, occur in approximately 3% of patients receiving fluoxetine. Adverse ocular effects reported in less than 1% of fluoxetine-treated patients include amblyopia, conjunctivitis, eye pain, mydriasis, and photophobia. Blepharitis, cataract formation, corneal lesion, diplopia, ocular hemorrhage, glaucoma, iritis, ptosis, and strabismus have been reported rarely.

■ **Cardiovascular Effects** Current evidence suggests that fluoxetine is less cardiotoxic than most antidepressant agents (e.g., tricyclic antidepressants, monoamine oxidase inhibitors). Unlike tricyclic antidepressants, which may cause characteristic ECG changes such as prolongation of PR, QRS, and QT intervals and ST-segment and T-wave abnormalities, clinically important ECG changes (such as conduction abnormalities) have not been reported during controlled studies in fluoxetine-treated patients without preexisting cardiac disease. In addition, while tricyclic antidepressants commonly cause an increase in heart rate, heart rate reportedly is reduced by an average of approximately 3 beats/minute in patients receiving fluoxetine. (See Pharmacology: Cardiovascular Effects.)

Palpitations and hot flushes have been reported in approximately 1 and 2% of patients receiving fluoxetine, respectively. Chest pain occurs in about 1% of patients. Unlike tricyclic antidepressants, fluoxetine has been associated with hypotension (including orthostatic hypotension) relatively infrequently; in controlled studies, orthostatic hypotension was reported in less than 1% of patients receiving the drug. Angina pectoris, cardiac arrhythmia, tachycardia, hemorrhage, hypertension, and syncope have occurred infrequently in fluoxetine-treated patients, although a causal relationship to the drug has not been established. First-degree AV block, bundle-branch block, bradycardia, ventricular arrhythmia, ventricular tachycardia (including torsades de pointes-type arrhythmias), myocardial infarction, thrombophlebitis, cerebral ischemia, vascular headache, and cerebrovascular accident have occurred rarely, but these adverse effects have not been definitely attributed to fluoxetine.

■ **Musculoskeletal Effects** Back, joint, muscle, and limb pain reportedly occur in approximately 1–2% of patients receiving fluoxetine. Arthritis, bursitis, tenosynovitis, muscle twitching, jaw pain, and neck pain or rigidity have occurred in less than 1% of fluoxetine-treated patients, but these adverse effects have not been directly attributed to the drug. Bone necrosis, osteoporosis, pathological fracture, chondrodystrophy, myositis, muscle hemorrhage, and rheumatoid arthritis have been reported rarely, although a causal relationship to fluoxetine has not been established.

■ **Hematologic Effects** Lymphadenopathy or anemia has been reported in 2% or less than 1% of patients receiving fluoxetine, respectively. Blood dyscrasia, leukopenia, thrombocythemia, pancytopenia, aplastic anemia, immune-related hemolytic anemia, lymphocytosis, increased sedimentation rate, increased bleeding time, petechiae, purpura, and iron deficiency anemia have occurred rarely, although a causal relationship to the drug has not been established. Thrombocytopenia also has been reported.

Abnormal bleeding has been reported in several patients receiving selective serotonin-reuptake inhibitors. Bleeding complications (e.g., ecchymosis, purpura, menorrhagia, rectal bleeding) have been reported infrequently in patients receiving selective serotonin-reuptake inhibitors. Although the precise mechanism for these reactions has not been established, it has been suggested that impaired platelet aggregation and prolonged bleeding time may be due at least in part to inhibition of serotonin reuptake into platelets and/or that increased capillary fragility and vascular tone may contribute to these cases. (See Cautions: GI Effects and see also Drug Interactions: Drugs Affecting Hemostasis.)

■ **Respiratory Effects** Upper respiratory infection has been reported in approximately 8% of fluoxetine-treated patients. Flu-like syndrome (see Cautions: Dermatologic and Sensitivity Reactions), pharyngitis, nasal congestion, sinusitis, sinus headache, cough, and dyspnea have occurred in approximately 1–3% of patients receiving the drug. Adverse respiratory effects reportedly occurring in at least 1% of patients but not directly attributable to fluoxetine therapy include bronchitis, rhinitis, and yawning, and those occurring in less than 1% of patients but not attributed to the drug include asthma, hyperventilation, pneumonia, and hiccups. Apnea, hypoxia, pulmonary edema, laryngeal edema, pulmonary fibrosis/alveolitis, eosinophilic pneumonia, pleural effusion, and hemoptysis have occurred rarely in patients receiving fluoxetine; however, these adverse effects have not been definitely attributed to the drug.

■ **Renal, Electrolyte, and Genitourinary Effects** ***Sexual Dysfunction*** Like other selective serotonin-reuptake inhibitors, adverse effects on sexual function have been reported in both men and women receiving fluoxetine. Although changes in sexual desire, sexual performance, and sexual satisfaction often occur as manifestations of a psychiatric disorder, they also may occur as the result of pharmacologic therapy. It is difficult to determine the true incidence and severity of adverse effects on sexual function during fluoxetine therapy, in part because patients and clinicians may be reluctant to discuss these effects. Therefore, incidence data reported in product labeling and earlier studies are most likely underestimates of the true incidence of adverse sexual effects. Recent reports indicate that up to 50% of patients receiving selective serotonin-reuptake inhibitors describe some form of sexual dysfunction during treatment and the actual incidence may be even higher.

Ejaculatory disturbances (principally ejaculatory delay) are the most common adverse urogenital effects associated with fluoxetine in men, occurring in about 7% of men receiving the drug compared with less than 1% of those receiving placebo in controlled clinical studies for the treatment of obsessive-compulsive disorder or bulimia. In some cases, the adverse effect of ejaculatory delay has been used for therapeutic benefit in the treatment of premature ejaculation. (See Uses: Premature Ejaculation.) Other genital disorders reported in patients receiving the drug include impotence, penile (of the glans) anesthesia, and anorgasmy (in both males and females). Decreased or increased libido also reportedly occurs in up to 2% of patients. In addition, clitoral engorgement, sexual arousal, and orgasm reportedly occurred in at least one female patient receiving fluoxetine.

Management of sexual dysfunction caused by selective serotonin-reuptake inhibitor therapy includes waiting for tolerance to develop; using a lower dosage of the drug; using drug holidays; delaying administration of the drug until after coitus; or changing to another antidepressant. Although further study is needed, there is some evidence that adverse sexual effects of the selective serotonin-reuptake inhibitors may be reversed by concomitant use of certain drugs, including buspirone, 5-hydroxytryptamine-2 (5-HT_2) receptor antagonists (e.g., nefazodone), 5-HT_3 receptor inhibitors (e.g., granisetron), or α_2-adrenergic receptor antagonists (e.g., yohimbine), selective phosphodiesterase (PDE) inhibitors (e.g., sildenafil), or dopamine receptor agonists (e.g., amantadine, dextroamphetamine, pemoline [no longer commercially available in the US], methylphenidate). In most patients, sexual dysfunction is fully reversed 1–3 days after discontinuance of the antidepressant. Ejaculatory dysfunction associated with fluoxetine therapy also has responded to concomitant cyproheptadine therapy in a few patients.

Other Renal, Electrolyte, and Genitourinary Effects Hyponatremia has occurred in several patients receiving fluoxetine therapy; in some cases, serum sodium values of less than 110 mEq/L were reported. Decreased serum and urine osmolarity may be present. Most cases of hyponatremia reported to date have occurred in older patients and/or patients concurrently receiving diuretics or those who were otherwise volume depleted. Although the cause(s) of the hyponatremia has not been fully established and various factors may have contributed to the condition, it has been suggested that some cases may have been associated with the syndrome of inappropriate secretion of antidiuretic hormone (SIADH). Hyponatremia associated with fluoxetine therapy appears to be reversible following discontinuance of the drug.

Painful menstruation, sexual dysfunction, frequent micturition, and urinary tract infection have occurred in approximately 1–2% of patients receiving fluoxetine. Decreased or increased libido reportedly occur in 1–2% or less than 1% of patients, respectively. Abnormal ejaculation, impotence, penile (of the glans) anesthesia, amenorrhea, leukorrhea, menorrhagia, ovarian disorder, vaginitis, pelvic pain, menopause, urinary incontinence, urinary urgency, impaired urination, cystitis, and dysuria have been reported in less than 1% of fluoxetine-treated patients, although these adverse effects have not been definitely attributed to the drug. Dyspareunia, abortion, hypomenorrhea, metrorrhagia, uterine spasm, uterine hemorrhage, salpingitis, vaginal hemorrhage, and vaginal bleeding (which occurred following discontinuance of therapy) have occurred rarely, although a causal relationship to the drug has not been established. Albuminuria, hematuria, polyuria, pyuria, urinary tract disorder, pyelonephritis, urethritis, epididymitis, orchitis, urethral pain, and urolithiasis (including renal calculus formation) also have been reported rarely in patients receiving fluoxetine therapy, although such effects have not been directly attributed to the drug.

■ **Endocrine Effects** Hypothyroidism has been reported in less than 1% of patients receiving fluoxetine, and goiter and hyperthyroidism have occurred rarely; however, a causal relationship to the drug has not been established.

■ **Anticholinergic Effects** Although bothersome anticholinergic effects occur commonly in patients receiving tricyclic antidepressant agents, such effects occur less frequently with fluoxetine. Dry mouth, dizziness, and constipation have been reported in about 10, 6, and 5% of patients receiving the drug. Urinary retention has occurred in less that 1% of fluoxetine-treated patients; blurred vision also has been reported.

■ **Other Adverse Effects** Viral infection and influenza have been reported in approximately 3 and 1% of patients receiving fluoxetine, respectively. Fever or chills alone have occurred in more than 1% of patients receiving fluoxetine; however, fever with accompanying chills has been reported in less than 1% of patients. (See Cautions: Dermatologic and Sensitivity Reactions.) Hypothermia has occurred rarely; however, a causal relationship to the drug has not been definitely established.

Abnormal liver function test results, lymphadenopathy, and epistaxis have been reported in less than 1% of fluoxetine-treated patients, although such effects have not been definitely attributed to the drug. Adverse effects occurring rarely in patients receiving fluoxetine include hepatitis, hepatomegaly, liver tenderness, jaundice, cholecystitis, cholelithiasis, acute abdominal syndrome, moniliasis, serum sickness, and lupus erythematosus syndrome.

Ear pain and tinnitus have occurred in less than 1% of patients, and deafness has been reported rarely. Although not directly attributed to the drug, generalized and peripheral edema have been reported in less than 1% of fluoxetine-treated patients; dehydration and gout have occurred rarely.

Breast pain and fibrocystic breast disease have occurred in less than 1% of

patients, and breast enlargement and female lactation have been reported rarely. Hyperprolactinemia also has occurred in patients receiving the drug. Although a causal relationship to fluoxetine has not been established for these effects, serotonin has been implicated as a possible physiologic factor in the release of prolactin. (See Pharmacology: Neuroendocrine Effects.)

■ **Precautions and Contraindications** Worsening of depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior may occur in both adult and pediatric (see Cautions: Pediatric Precautions) patients with major depressive disorder or other psychiatric disorders, whether or not they are taking antidepressants. This risk may persist until clinically important remission occurs. Suicide is a known risk of depression and certain other psychiatric disorders, and these disorders themselves are the strongest predictors of suicide. However, there has been a long-standing concern that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients during the early phases of treatment. Pooled analyses of short-term, placebo-controlled studies of antidepressants (i.e., selective serotonin-reuptake inhibitors and other antidepressants) have shown an increased risk of suicidality in children, adolescents, and young adults (18–24 years of age) with major depressive disorder and other psychiatric disorders. An increased suicidality risk was not demonstrated with antidepressants compared with placebo in adults older than 24 years of age, and a reduced risk was observed in adults 65 years of age or older. It currently is unknown whether the suicidality risk extends to longer-term use (i.e., beyond several months); however, there is substantial evidence from placebo-controlled maintenance trials in adults with major depressive disorder that antidepressants can delay the recurrence of depression.

The US Food and Drug Administration (FDA) recommends that all patients being treated with antidepressants for any indication be appropriately monitored and closely observed for clinical worsening, suicidality, and unusual changes in behavior, particularly during initiation of therapy (i.e., the first few months) and during periods of dosage adjustments. Families and caregivers of patients being treated with antidepressants for major depressive disorder or other indications, both psychiatric and nonpsychiatric, also should be advised to monitor patients on a daily basis for the emergence of agitation, irritability, or unusual changes in behavior, as well as the emergence of suicidality, and to report such symptoms immediately to a health care provider.

Although a causal relationship between the emergence of symptoms such as anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia, hypomania, and/or mania and either the worsening of depression and/or the emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality. Consequently, consideration should be given to changing the therapeutic regimen or discontinuing therapy in patients whose depression is persistently worse or in patients experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidality, particularly if such manifestations are severe, abrupt in onset, or were not part of the patient's presenting symptoms. FDA also recommends that the drugs be prescribed in the smallest quantity consistent with good patient management, in order to reduce the risk of overdosage.

It is generally believed (though not established in controlled trials) that treating a major depressive episode with an antidepressant alone may increase the likelihood of precipitating a mixed or manic episode in patients at risk for bipolar disorder. Therefore, patients should be adequately screened for bipolar disorder prior to initiating treatment with an antidepressant; such screening should include a detailed psychiatric history (e.g., family history of suicide, bipolar disorder, and depression).

Because clinical experience with fluoxetine in patients with concurrent systemic disease, including cardiovascular disease, hepatic impairment, and renal impairment, is limited, caution should be exercised when fluoxetine is administered to patients with any systemic disease or condition that may alter metabolism of the drug or adversely affect hemodynamic function. (See Dosage and Administration: Dosage.) Fluoxetine should be used with caution in patients with hepatic impairment, since prolonged elimination of the drug and its principal metabolite has been reported to occur in patients with liver cirrhosis. Because the safety of long-term fluoxetine therapy in patients with severe renal impairment has not been adequately evaluated to date, fluoxetine also should be used with caution in patients with severe renal impairment. (See Dosage and Administration: Dosage in Renal and Hepatic Impairment.) Although current evidence suggests that fluoxetine is less cardiotoxic than most older antidepressant agents (see Cautions: Cardiovascular Effects), the safety of fluoxetine in patients with a recent history of myocardial infarction or unstable cardiovascular disease has not been adequately evaluated to date.

Patients receiving fluoxetine should be advised to notify their physician if they are taking or plan to take nonprescription (over-the-counter) or prescription medications or alcohol-containing beverages or products. (See Drug Interactions.)

Patients receiving fluoxetine should be cautioned about the concurrent use of nonsteroidal anti-inflammatory agents (including aspirin) or other drugs that affect coagulation since combined use of selective serotonin-reuptake inhibitors and these drugs has been associated with an increased risk of bleeding. (See Cautions: GI Effects and see also Drug Interactions: Drugs Affecting Hemostasis.)

Fluoxetine generally is less sedating than many other currently available antidepressants and does not appear to produce substantial impairment of cognitive or psychomotor function. However, patients should be cautioned that fluoxetine may impair their ability to perform activities requiring mental alertness or physical coordination (e.g., operating machinery, driving a motor vehicle) and to avoid such activities until they experience how the drug affects them.

Patients receiving fluoxetine should be advised to notify their physician if they develop rash or hives during therapy with the drug. Pending further accumulation of data, monitoring for such effects is particularly important since these effects have been associated with the development of potentially serious systemic reactions in patients receiving fluoxetine or pharmacologically similar antidepressants (e.g., zimeldine). (See Cautions: Dermatologic and Sensitivity Reactions.)

Seizures have been reported in patients receiving therapeutic dosages and following acute overdosage of fluoxetine. Because of limited experience with fluoxetine in patients with a history of seizures, therapy with the drug should be initiated with caution in such patients.

Because fluoxetine may alter blood glucose concentrations in patients with diabetes mellitus (see Cautions: Metabolic Effects), the possibility that insulin and/or oral sulfonylurea antidiabetic agent dosage adjustments may be necessary when fluoxetine therapy is initiated or discontinued should be considered.

Because fluoxetine therapy has been commonly associated with anorexia and weight loss, the drug should be used with caution in patients who may be adversely affected by these effects (e.g., underweight patients).

Potentially life-threatening serotonin syndrome may occur with selective serotonin-reuptake inhibitors (SSRIs), including fluoxetine, or selective serotonin- and norepinephrine-reuptake inhibitors (SNRIs), particularly with concurrent administration of other serotonergic drugs (e.g., serotonin [5-hydroxytryptamine; 5-HT] type 1 agonists ["triptans"]) or drugs that impair serotonin metabolism (e.g., monoamine oxidase [MAO] inhibitors). Symptoms of serotonin syndrome may include mental status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g., hyperreflexia, incoordination), and/or GI symptoms (e.g., nausea, vomiting, diarrhea). Patients should be cautioned about the risk of serotonin syndrome with the concomitant use of fluoxetine and 5-HT_1 receptor agonists (triptans), tramadol, or other serotonergic agents. Because of the risk of serotonin syndrome, caution is also advised when fluoxetine is concurrently administered with other drugs affecting serotonergic neurotransmission, including linezolid, lithium, tramadol, and St. John's wort. If concurrent therapy with fluoxetine and a 5-HT_1 receptor agonist is clinically warranted, the patient should be observed carefully, particularly during initiation of therapy, when dosage is increased, or when another serotonergic agent is initiated. Concomitant use of fluoxetine and serotonin precursors (e.g., tryptophan) is not recommended. Fluoxetine is contraindicated in patients receiving MAO inhibitor therapy; at least 2 weeks should elapse between discontinuance of MAO inhibitor therapy and initiation of fluoxetine and vice versa. (See Drug Interactions: Drugs Associated with Serotonin Syndrome.)

Fluoxetine therapy also is contraindicated in patients currently receiving, or having recently received, thioridazine therapy. In addition, concurrent use of fluoxetine in patients receiving pimozide is contraindicated. (See Thioridazine and also see Pimozide under Drug Interactions: Antipsychotic Agents.)

Fluoxetine is contraindicated in patients with known hypersensitivity to the drug.

■ **Pediatric Precautions** Safety and efficacy of fluoxetine in pediatric patients have not been established in children younger than 8 years of age for the management of major depressive disorder (see Pediatric Considerations under Uses: Major Depressive Disorder) or in children younger than 7 years of age for the management of obsessive-compulsive disorder.

FDA warns that antidepressants increase the risk of suicidal thinking and behavior (suicidality) in children and adolescents with major depressive disorder and other psychiatric disorders. The risk of suicidality for these drugs was identified in a pooled analysis of data from a total of 24 short-term (4–16 weeks), placebo-controlled studies of 9 antidepressants (i.e., fluoxetine, bupropion, citalopram, fluvoxamine, mirtazapine, nefazodone, paroxetine, sertraline, venlafaxine) in over 4400 children and adolescents with major depressive disorder, obsessive-compulsive disorder (OCD), or other psychiatric disorders. The analysis revealed a greater risk of adverse events representing suicidal behavior or thinking (suicidality) during the first few months of treatment in pediatric patients receiving antidepressants than in those receiving placebo. The average risk of such events was 4% among children and adolescents receiving these drugs, twice the risk (2%) that was observed among those receiving placebo. However, a more recent meta-analysis of 27 placebo-controlled trials of 9 antidepressants (SSRIs and others) in patients younger than 19 years of age with major depressive disorder, OCD, or non-OCD anxiety disorders suggests that the benefits of antidepressant therapy in treating these conditions may outweigh the risks of suicidal behavior or suicidal ideation. No suicides occurred in these pediatric trials.

The risk of suicidality in FDA's pooled analysis differed across the different psychiatric indications, with the highest incidence observed in the major depressive disorder studies. In addition, although there was considerable variation in risk among the antidepressants, a tendency toward an increase in suicidality risk in younger patients was found for almost all drugs studied. It is currently unknown whether the suicidality risk in pediatric patients extends to longer-term use (i.e., beyond several months).

As a result of this analysis and public discussion of the issue, FDA has directed manufacturers of all antidepressants to add a boxed warning to the labeling of their products to alert clinicians of this suicidality risk in children

and adolescents and to recommend appropriate monitoring and close observation of patients receiving these agents. (See Cautions: Precautions and Contraindications.) The drugs that are the focus of the revised labeling are all drugs included in the general class of antidepressants, including those that have not been studied in controlled clinical trials in pediatric patients, since the available data are not adequate to exclude any single antidepressant from an increased risk. In addition to the boxed warning and other information in professional labeling on antidepressants, FDA currently recommends that a patient medication guide explaining the risks associated with the drugs be provided to the patient each time the drugs are dispensed. Caregivers of pediatric patients whose depression is persistently worse or who are experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidality during antidepressant therapy should consult their clinician regarding the best course of action (e.g., whether the therapeutic regimen should be changed or the drug discontinued). *Patients should not discontinue use of selective serotonin-reuptake inhibitors without first consulting their clinician. (See Dosage and Administration: Dosage.)*

Anyone considering the use of fluoxetine in a child or adolescent for any clinical use must balance the potential risks of therapy with the clinical need.

Important toxicity, including myotoxicity, long-term neurobehavioral and reproductive toxicity, and impaired bone development, has been observed following exposure of juvenile animals to fluoxetine; some of these effects occurred at clinically relevant exposures to the drug. In a study in which fluoxetine (3, 10, or 30 mg/kg) was orally administered to young rats from weaning (postnatal day 21) through adulthood (day 90), male and female sexual development was delayed at all dosages, and growth (body weight gain, femur length) was decreased during the dosing period in animals receiving the highest dosage. At the end of the treatment period, serum levels of creatine kinase (a marker of muscle damage) were increased in animals receiving the intermediate and highest dosage, and abnormal muscle and reproductive organ histopathology (skeletal muscle degeneration and necrosis, testicular degeneration and necrosis, epididymal vacuolation and hypospermia) was observed at the highest dosage. When animals were evaluated after a recovery period (up to 11 weeks after drug cessation), neurobehavioral abnormalities (decreased reactivity at all dosages and learning deficit at the highest dosage) and reproductive functional impairment (decreased mating at all dosages and impaired fertility at the highest dosage) were noted; testicular and epididymal microscopic lesions and decreased sperm concentrations were observed in the high-dosage group indicating that the reproductive organ effects seen at the end of treatment were irreversible. Reversibility of fluoxetine-induced muscle damage was not assessed in this study. Adverse effects similar to those observed in rats treated with fluoxetine during the juvenile period have not been reported after administration of fluoxetine to adult animals. Plasma exposures (AUC) to fluoxetine in juvenile rats receiving the low, intermediate, and high dosages in this study were approximately 0.1–0.2, 1–2, and 5–10 times, respectively, the average exposure in pediatric patients receiving the maximum recommended dosage of 20 mg daily. Exposures to norfluoxetine, the principal active metabolite of fluoxetine, in rats were approximately 0.3–0.8, 1–8, and 3–20 times the pediatric exposure at the maximum recommended dosage, respectively.

A specific effect of fluoxetine on bone development has been reported in mice treated with fluoxetine during the juvenile period. In mice treated with fluoxetine (5 or 20 mg/kg given intraperitoneally) for 4 weeks beginning at 4 weeks of age, bone formation was reduced resulting in decreased bone mineral content and density. These dosages did not affect overall growth (e.g., body weight gain or femoral length). The dosages given to juvenile mice in this study were approximately 0.5 and 2 times the maximum recommended dose for pediatric patients on a mg/m^2 basis.

In a study conducted in mice, fluoxetine administration (10 mg/kg intraperitoneally) during early postnatal development (postnatal days 4 to 21) produced abnormal emotional behaviors (decreased exploratory behavior in elevated plus-maze, increased shock avoidance latency) in adulthood (12 weeks of age). The dosage used in this study was approximately equal to the pediatric maximum recommended dosage on a mg/m^2 basis. Because of the early dosing period in this study, the clinical importance of these findings for the labeled pediatric use in humans is unknown.

As with other selective serotonin-reuptake inhibitors, decreased weight gain has been observed in association with the use of fluoxetine in children and adolescents. In one clinical trial in pediatric patients 8–17 years of age, height gain averaged about 1.1 cm less and weight gain averaged about 1 kg less after 19 weeks of fluoxetine therapy relative to placebo-treated patients. In addition, fluoxetine therapy was associated with a decrease in plasma alkaline phosphatase concentrations. Because the safety of fluoxetine in pediatric patients has not been systematically assessed for chronic therapy longer than several months in duration and studies that directly evaluate the long-term effects of fluoxetine on the growth, development, and maturation of children and adolescents are lacking, height and weight should be monitored periodically in pediatric patients receiving fluoxetine. The clinical importance of these findings on long-term growth currently is not known, but the manufacturer will conduct a phase IV study to evaluate any potential impact of fluoxetine therapy on long-term pediatric growth. For further information on adverse effects associated with the use of fluoxetine in pediatric patients, see the opening discussion in Cautions.

■ **Geriatric Precautions** The efficacy of fluoxetine has been established in clinical studies in geriatric patients. Although no overall differences in efficacy or safety were observed between geriatric and younger patients, the possibility that some older patients particularly those with systemic disease or those who are receiving other drugs concomitantly (see Pharmacokinetics: Elimination and also see Uses: Major Depressive Disorder) may exhibit increased sensitivity to the drug cannot be ruled out.

In pooled data analyses, a *reduced* risk of suicidality was observed in adults 65 years of age or older with antidepressant therapy compared with placebo. (See Cautions: Precautions and Contraindications.)

■ **Mutagenicity and Carcinogenicity** Fluoxetine and norfluoxetine did not exhibit mutagenic activity in vitro in mammalian cell (e.g., mouse lymphoma, rat hepatocyte DNA repair) or microbial (the *Salmonella* microbial mutagen [Ames]) test systems, or with the in vivo sister chromatid-exchange assay in Chinese hamster bone marrow cells. No evidence of carcinogenesis was seen in rats or mice receiving oral fluoxetine dosages of about 7.5 or 9 times the maximum recommended human dosage of the drug, respectively, for 24 months.

■ **Pregnancy, Fertility, and Lactation** ***Pregnancy*** Some neonates exposed to fluoxetine and other selective serotonin-reuptake inhibitors (SSRIs) or selective serotonin- and norepinephrine-reuptake inhibitors (SNRIs) late in the third trimester of pregnancy have developed complications that have sometimes been severe and required prolonged hospitalization, respiratory support, enteral nutrition, and other forms of supportive care in special care nurseries. Such complications can arise immediately upon delivery and usually last several days or up to 2–4 weeks. Clinical findings reported to date in the neonates have included respiratory distress, cyanosis, apnea, seizures, temperature instability or fever, feeding difficulty, dehydration, excessive weight loss, vomiting, hypoglycemia, hypotonia, hyperreflexia, tremor, jitteriness, irritability, lethargy, reduced or lack of reaction to pain stimuli, and constant crying. These clinical features appear to be consistent with either a direct toxic effect of the SSRI or SNRI or, possibly, a drug withdrawal syndrome. It should be noted that, in some cases, the clinical picture was consistent with serotonin syndrome (see Drug Interactions: Drugs Associated with Serotonin Syndrome). When treating a pregnant woman with fluoxetine during the third trimester of pregnancy, the clinician should carefully consider the potential risks and benefits of such therapy. Consideration may be given to cautiously tapering fluoxetine therapy in the third trimester prior to delivery if the drug is administered during pregnancy. (See Dosage and Administration: Treatment of Pregnant Women during the Third Trimester.)

FDA states that decisions about management of depression in pregnant women are challenging and that the patient and her clinician must carefully consider and discuss the potential benefits and risks of SSRI therapy during pregnancy for the individual woman. Two recent studies provide important information on risks associated with discontinuing or continuing antidepressant therapy during pregnancy.

The first study, which was prospective, naturalistic, and longitudinal in design, evaluated the potential risk of relapsed depression in pregnant women with a history of major depressive disorder who discontinued or attempted to discontinue antidepressant (SSRIs, tricyclic antidepressants, or others) therapy during pregnancy compared with that in women who continued antidepressant therapy throughout their pregnancy; all women were euthymic while receiving antidepressant therapy at the beginning of pregnancy. In this study, women who discontinued antidepressant therapy were found to be 5 times more likely to have a relapse of depression during their pregnancy than were women who continued to receive their antidepressant while pregnant, suggesting that pregnancy does not protect against a relapse of depression.

The second study suggests that infants exposed to SSRIs in late pregnancy may have an increased risk of persistent pulmonary hypertension of the newborn (PPHN), which is associated with substantial neonatal morbidity and mortality. PPHN occurs at a rate of 1–2 neonates per 1000 live births in the general population in the US. In this retrospective case-control study of 377 women whose infants were born with PPHN and 836 women whose infants were born healthy, the risk for developing PPHN was approximately sixfold higher for infants exposed to SSRIs after the twentieth week of gestation compared with infants who had not been exposed to SSRIs during this period. The study was too small to compare the risk of PPHN associated with individual SSRIs, and the findings have not been confirmed. Although the risk of PPHN identified in this study still is low (6–12 cases per 1000) and further study is needed, the findings add to concerns from previous reports that infants exposed to SSRIs late in pregnancy may experience adverse serotonergic effects.

Fluoxetine and its principal metabolite norfluoxetine have been shown to cross the placenta in animals. There are no adequate and controlled studies to date using fluoxetine in pregnant women, and the drug should be used during pregnancy only when clearly needed. Women should be advised to notify their clinician if they are or plan to become pregnant. FDA states that women who are pregnant or thinking about becoming pregnant should not discontinue any antidepressant, including fluoxetine, without first consulting their clinician. The decision whether or not to continue antidepressant therapy should be made only after careful consideration of the potential benefits and risks of antidepressant therapy for each individual pregnant patient. If a decision is made to discontinue treatment with fluoxetine or other SSRIs before or during pregnancy, discontinuance of therapy should be done in consultation with the clinician in accordance with the prescribing information for the antidepressant, and the patient should be closely monitored for possible relapse of depression. In addition, the prolonged elimination of the drug and its active metabolite from the body after discontinuance of therapy should be considered when a woman of childbearing potential receiving fluoxetine plans to become pregnant.

Most epidemiologic studies of pregnancy outcome following first trimester exposure to SSRIs, including fluoxetine, conducted to date have not revealed evidence of an increased risk of major congenital malformations. In a prospective, controlled, multicenter study, maternal use of several SSRIs (sertraline, fluvoxamine, paroxetine) in a limited number of pregnant women did not appear to increase the risk of congenital malformation, miscarriage, stillbirth, or premature delivery when used during pregnancy at recommended dosages. Birth weight and gestational age in neonates exposed to the drugs were similar to those in the control group. In another small study based on medical records review, the incidence of congenital anomalies reported in infants born to women who were treated with fluoxetine and other SSRIs during pregnancy was comparable to that observed in the general population. However, the results of epidemiologic studies indicate that exposure to paroxetine during the first trimester of pregnancy may increase the risk for congenital malformations, particularly cardiovascular malformations. (See Pregnancy, under Cautions: Pregnancy, Fertility, and Lactation in Paroxetine 28:16.04.20.) Additional epidemiologic studies are needed to more thoroughly evaluate the relative safety of fluoxetine and other SSRIs during pregnancy, including their potential teratogenic risks and possible effects on neurobehavioral development.

The effect of fluoxetine on labor and delivery is not known.

Fertility Reproduction studies in rats using fluoxetine dosages 5–9 times the maximum recommended human daily dosage have not revealed evidence of impaired fertility. However, a slight decrease in neonatal survival that probably was related to reduced maternal food consumption and suppressed weight gain was reported in the offspring. Like some other SSRIs, pretreatment with fluoxetine inhibits methoxydimethyltryptamine-induced ejaculation in rats; this effect is blocked by metergoline, a serotonin antagonist. Alterations in sexual function also have been reported in patients receiving the drug. (See Sexual Dysfunction under Cautions: Renal, Electrolyte, and Genitourinary Effects and see also Cautions: Pediatric Precautions.)

Lactation Fluoxetine and its metabolites distribute into human milk. Limited data indicate that fluoxetine and norfluoxetine concentrations are 20–30% of concurrent maternal plasma drug concentrations. Crying, sleep disturbance, vomiting, and watery stools developed in an infant who nursed from a woman receiving fluoxetine; plasma fluoxetine and norfluoxetine concentrations in the infant on the second day of feeding were 340 and 208 ng/mL, respectively. Therefore, fluoxetine should not be used in nursing women, and women should be advised to notify their physician if they plan to breast-feed. In addition, the slow elimination of fluoxetine and norfluoxetine from the body after discontinuance of the drug should be considered.

Drug Interactions

As with other drugs, the possibility that fluoxetine may interact with any concomitantly administered drug by a variety of mechanisms, including pharmacodynamic and pharmacokinetic interactions, should be considered. The potential for interactions exists not only with concomitantly administered drugs but also with drugs administered for several weeks after discontinuance of fluoxetine therapy due to the prolonged elimination of fluoxetine and its principal metabolite, norfluoxetine. (See Pharmacokinetics: Elimination.)

■ **Drugs Associated with Serotonin Syndrome** Serotonin syndrome may occur in patients who receive selective serotonin-reuptake inhibitors (SSRIs) such as fluoxetine concurrently or in close succession with other serotonergic drugs. Symptoms of serotonin syndrome may include mental status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g., hyperreflexia, incoordination), and/or GI symptoms (e.g., nausea, vomiting, diarrhea). Although the syndrome appears to be relatively uncommon and usually mild in severity, serious and potentially life-threatening complications, including seizures, disseminated intravascular coagulation, respiratory failure, and severe hyperthermia, as well as death occasionally have been reported. The precise mechanism of the syndrome is not fully understood; however, it appears to result from excessive serotonergic activity in the CNS, probably mediated by activation of serotonin 5-HT_{1A} receptors. The possible involvement of dopamine and 5-HT_2 receptors also has been suggested, although their roles remain unclear.

Serotonin syndrome most commonly occurs when 2 or more serotonergic agents with different mechanisms of action are administered either concurrently or in close succession. Serotonergic agents include those that increase serotonin synthesis (e.g., the serotonin precursor tryptophan), stimulate synaptic serotonin release (e.g., some amphetamines, dexfenfluramine [no longer commercially available in the US], fenfluramine [no longer commercially available in the US]), inhibit the reuptake of serotonin after release (e.g., SSRIs, selective serotonin- and norepinephrine-reuptake inhibitors [SNRIs], tricyclic antidepressants, trazodone, dextromethorphan, meperidine, tramadol), decrease the metabolism of serotonin (e.g., MAO inhibitors), have direct serotonin postsynaptic receptor activity (e.g., buspirone), or nonspecifically induce increases in serotonergic neuronal activity (e.g., lithium salts). Selective agonists of serotonin (5-hydroxytryptamine; 5-HT) type 1 receptors ("triptans") and dihydroergotamine, agents with serotonergic activity used in the management of migraine headache, and St. John's wort *(Hypericum perforatum)* also have been implicated in serotonin syndrome.

The combination of SSRIs and MAO inhibitors appears to be responsible for many of the reported cases of serotonin syndrome. The syndrome also has been reported when SSRIs have been used concurrently with tryptophan, lithium, dextromethorphan, sumatriptan, or dihydroergotamine. In rare cases, the serotonin syndrome reportedly has occurred in patients receiving the recommended dosage of a single serotonergic agent (e.g., clomipramine) or during accidental overdosage (e.g., sertraline intoxication in a child). Some other drugs that have been implicated in certain circumstances include buspirone, bromocriptine, dextropropoxyphene, methylenedioxymethamphetamine (MDMA; "ecstasy"), selegiline (a selective MAO-B inhibitor), and sibutramine (an SNRI used for the management of obesity). Other drugs that have been associated with the syndrome but for which less convincing data are available include carbamazepine, fentanyl, and pentazocine.

Clinicians should be aware of the potential for serious, possibly fatal reactions associated with serotonin syndrome in patients receiving 2 or more drugs that increase the availability of serotonin in the CNS, even if no such interactions with the specific drugs have been reported to date in the medical literature. Pending further accumulation of data, drugs with serotonergic activity should be used cautiously in combination and such combinations should be avoided whenever clinically possible. Serotonin syndrome may be more likely to occur when initiating therapy with a serotonergic agent, increasing the dosage, or following the addition of another serotonergic drug. Some clinicians state that patients who have experienced serotonin syndrome may be at higher risk for recurrence of the syndrome upon reinitiation of serotonergic drugs. Pending further experience in such cases, some clinicians recommend that therapy with serotonergic agents be limited following recovery. In cases in which the potential benefit of the drug is thought to outweigh the risk of serotonin syndrome, lower potency agents and reduced dosages should be used, combination serotonergic therapy should be avoided, and patients should be monitored carefully for manifestations of serotonin syndrome.

Serotonin Syndrome **Manifestations.** Serotonin syndrome is characterized by mental status and behavioral changes, altered muscle tone or neuromuscular activity, autonomic instability with rapid fluctuations of vital signs, hyperthermia, and diarrhea. Some clinicians have stated that the diagnosis of serotonin syndrome can be made based on the presence of at least 3 of the following manifestations: mental status changes (e.g., confusion, hypomania), agitation, myoclonus, hyperreflexia, fever, shivering, tremor, diaphoresis, ataxia, and diarrhea in the setting of a recent addition or an increase in dosage of a serotonergic agent; the absence of other obvious causes of mental status changes and fever (e.g., infection, metabolic disorders, substance abuse or withdrawal); and no recent initiation or increase in dosage of an antipsychotic agent prior to the onset of the signs and symptoms (in order to rule out neuroleptic malignant syndrome [NMS]). In some cases, features of the serotonin syndrome have resembled those associated with NMS, which may occur in patients receiving phenothiazines or other antipsychotic agents. (See Extrapyramidal Reactions in Cautions: Nervous System Effects in the Phenothiazines General Statement 28:16.08.24.)

Other signs and symptoms associated with serotonin syndrome have included restlessness, irritability, insomnia, aggressive behavior, headache, drowsiness, dizziness, disorientation, loss of coordination, anxiety, euphoria, hallucinations, dilated pupils, nystagmus, paresthesias, rigidity, clonus, seizures, and coma. Nausea, vomiting, abdominal cramping, flushing, hypertension, hypotension, tachycardia, tachypnea, and hyperventilation also have occurred.

The onset of the serotonin syndrome can range from minutes after initiating therapy with a second serotonergic agent to several weeks after receiving a stable dosage. Preliminary evidence to date suggests that neither the occurrence nor the severity of serotonin syndrome is related to the dose or duration of serotonergic drug therapy.

The incidence of serotonin syndrome is unknown, but it is likely that the syndrome is underreported because it is not recognized or appears in various degrees of severity (mild, moderate, or severe). In addition, serotonin syndrome may be confused with NMS in some cases.

Treatment. Mild cases of serotonin syndrome generally respond within 12–24 hours to the immediate discontinuance of serotonergic agents and general supportive therapy. Symptoms rarely last more than 72–96 hours in the absence of complications. Supportive therapy in such cases may include hospitalization, adequate hydration, control of myoclonus and hyperreflexia with benzodiazepines such as clonazepam (and possibly propranolol), and control of fever with acetaminophen and external cooling, if necessary. Other possible causes of altered mental status and fever also should be considered and treated accordingly.

Patients with severe hyperthermia (i.e., a temperature of more than 40.5°C) are considered to have more severe cases of serotonin syndrome which are associated with more serious complications and mortality. Muscular rigidity often accompanies hyperthermia and may respond to benzodiazepine therapy. Such patients should be managed with aggressive cooling measures, including external cooling, the institution of muscular paralysis (to decrease body temperature, help prevent rhabdomyolysis and disseminated intravascular coagulation from muscular rigidity refractory to benzodiazepines, and facilitate intubation), and maintenance of a patent airway with endotracheal intubation. Seizures may be treated with benzodiazepines and, if necessary, other anticonvulsants (e.g., barbiturates). Patients who develop hypertension, cardiac arrhythmias, and other serious complications such as disseminated intravascular coagulation or rhabdomyolysis associated with serotonin syndrome should receive appropriate therapy for these conditions.

Although there is no specific therapy for serotonin syndrome, nonspecific serotonin (5-HT_1 and 5-HT_2) receptor antagonists such as cyproheptadine and

methysergide and drugs with 5-HT_{1A} receptor affinity such as propranolol have been used with some success in a limited number of patients whose symptoms persisted or were unusually severe. Dantrolene, bromocriptine, and chlorpromazine (for sedation, to help reduce fever, and because of its 5-HT-receptor blocking activity) also have been used in a limited number of patients with serotonin syndrome but with inconsistent results; the possibility that chlorpromazine may lower the seizure threshold in this setting should be considered.

Monoamine Oxidase Inhibitors Concurrent use of selective serotonin-reuptake inhibitors and MAO inhibitors potentially is hazardous and may result in the serotonin syndrome.

Probably because of its extensive clinical use and the prolonged elimination half-life of both fluoxetine and norfluoxetine, fluoxetine has been the selective serotonin-reuptake inhibitor most commonly implicated in serotonin syndrome. In at least 2 cases, serotonin syndrome developed when MAO inhibitor therapy was initiated after the discontinuance of fluoxetine therapy. Shivering, diplopia, nausea, confusion, and anxiety reportedly occurred in one patient 6 days after discontinuance of fluoxetine therapy and 4 days after initiation of tranylcypromine therapy; signs and symptoms resolved without apparent sequelae within 24 hours following discontinuance of the MAO inhibitor in this patient. In another case, the initiation of tranylcypromine therapy more than 5 weeks after discontinuance of fluoxetine reportedly resulted in serotonin syndrome.

The manufacturer and some clinicians state that concurrent administration of fluoxetine and MAO inhibitors is contraindicated. Because both fluoxetine and its principal metabolite have relatively long half-lives, the manufacturer and some clinicians recommend that at least 5 weeks elapse between discontinuance of fluoxetine therapy and initiation of MAO inhibitor therapy, since administration of an MAO inhibitor prior to elapse of this time may increase the risk of serious adverse effects. Based on clinical experience with concurrent administration of tricyclic antidepressants and MAO inhibitors, the manufacturer of fluoxetine recommends that at least 2 weeks elapse following discontinuance of an MAO inhibitor prior to initiation of fluoxetine therapy.

Several other selective serotonin-reuptake inhibitors, including sertraline and citalopram, have been associated with serotonin syndrome when given in combination with MAO inhibitors. Because of the potential risk of serotonin syndrome when serotonin-reuptake inhibitors are combined with MAO inhibitor therapy, citalopram, escitalopram, fluvoxamine, paroxetine, and sertraline should not be used concomitantly with MAO inhibitors and it is recommended that at least 2 weeks elapse between discontinuance of MAO inhibitor therapy and initiation of therapy with these selective serotonin-reuptake inhibitors and vice versa.

Moclobemide. Moclobemide, a selective and reversible MAO-A inhibitor (not commercially available in the US), also has been associated with serotonin syndrome and such reactions have been fatal in several cases in which the drug was given in combination with the selective serotonin-reuptake inhibitor citalopram or with clomipramine. Pending further experience with such combinations, some clinicians recommend that concurrent therapy with moclobemide and selective serotonin-reuptake inhibitors be used only with extreme caution and serotonin-reuptake inhibitors should have been discontinued for some time (depending on the elimination half-lives of the drug and its active metabolites) before initiating moclobemide therapy.

Selegiline. Selegiline, a selective MAO-B inhibitor used in the management of parkinsonian syndrome, also has been reported to cause serotonin syndrome when given concurrently with selective serotonin-reuptake inhibitors (fluoxetine, paroxetine, sertraline). Although selegiline is a selective MAO-B inhibitor at therapeutic dosages, the drug appears to lose its selectivity for the MAO-B enzyme at higher dosages (e.g., those exceeding 10 mg/kg), thereby increasing the risk of serotonin syndrome in patients receiving higher dosages of the drug either alone or in combination with other serotonergic agents. The manufacturer of selegiline recommends avoiding concurrent selegiline and selective serotonin-reuptake inhibitor therapy. In addition, the manufacturer of selegiline recommends that a drug-free interval of at least 2 weeks elapse between discontinuance of selegiline and initiation of selective serotonin-reuptake inhibitor therapy. Because of the long half-lives of fluoxetine and its principal metabolite, at least 5 weeks should elapse or even longer (particularly if fluoxetine has been prescribed chronically and/or at higher dosages) between discontinuance of fluoxetine and initiation of selegiline therapy.

Isoniazid. Isoniazid, an antituberculosis agent, appears to have some MAO-inhibiting activity. In addition, iproniazid (not commercially available in the US), another antituberculosis agent structurally related to isoniazid that also possesses MAO-inhibiting activity, reportedly has resulted in serotonin syndrome in at least 2 patients when given in combination with meperidine. Pending further experience, clinicians should be aware of the potential for serotonin syndrome when isoniazid is given in combination with selective serotonin-reuptake inhibitor therapy or other serotonergic agents.

Linezolid. Linezolid, an anti-infective agent that is a nonselective and reversible MAO inhibitor, has been associated with drug interactions resulting in serotonin syndrome and should therefore be used with caution in patients receiving fluoxetine.

Tramadol Because tramadol affects the serotonergic neurotransmitter system, the drug should be used with caution in patients receiving fluoxetine.

Tryptophan and Other Serotonin Precursors Adverse nervous system effects (e.g., agitation, restlessness, aggressive behavior, insomnia, poor concentration, headache, paresthesia, incoordination, worsening of symptoms of obsessive-compulsive disorder), adverse GI effects (e.g., nausea, abdominal cramps, diarrhea), palpitation, and/or chills reportedly have occurred in a limited number of patients receiving fluoxetine concurrently with tryptophan, a serotonin precursor. Such symptoms generally resolved within several weeks following discontinuance of tryptophan despite continued fluoxetine therapy. Although the mechanism for this interaction has not been fully elucidated, it has been suggested that these adverse effects resemble the serotonin syndrome observed in animals and therefore may result from a marked increase in serotonin availability when tryptophan and potent serotonin-reuptake inhibitors such as fluoxetine are administered concurrently. Because of the potential risk of serotonin syndrome, concurrent use of tryptophan or other serotonin precursors should be avoided in patients receiving fluoxetine.

5-HT_1 Receptor Agonists ("Triptans") Weakness, hyperreflexia, and incoordination have been reported rarely during postmarketing surveillance in patients receiving sumatriptan concomitantly with an SSRI (e.g., fluoxetine, citalopram, escitalopram, fluvoxamine, paroxetine, sertraline). Oral or subcutaneous sumatriptan and SSRIs were used concomitantly in some clinical studies without unusual adverse effects. However, an increase in the frequency of migraine attacks and a decrease in the effectiveness of sumatriptan in relieving migraine headache have been reported in a patient receiving subcutaneous injections of sumatriptan intermittently while undergoing fluoxetine therapy.

Because of the risk of potentially life-threatening serotonin syndrome, clinicians prescribing 5-HT_1 receptor agonists (triptans; e.g., almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan, zolmitriptan), SSRIs, and selective serotonin- and norepinephrine-reuptake inhibitors (SNRIs) should consider that triptans often are used intermittently and that either the triptan, SSRI, or SNRI may be prescribed by a different clinician. Clinicians also should weigh the potential risk of serotonin syndrome with the expected benefit of using a triptan concurrently with SSRI or SNRI therapy. If concomitant treatment with fluoxetine and a triptan is clinically warranted, the patient should be observed carefully, particularly during treatment initiation, dosage increases, and following the addition of other serotonergic agents. Patients receiving concomitant triptan and fluoxetine therapy should be informed of the possibility of serotonin syndrome and advised to immediately seek medical attention if they experience symptoms of this syndrome.

Other Drugs Pentazocine, an opiate partial agonist analgesic, has been reported to cause transient symptoms of diaphoresis, ataxia, flushing, and tremor suggestive of the serotonin syndrome when used concurrently with fluoxetine. In addition, serotonin syndrome rarely may occur following concomitant use of fluoxetine and stimulants because stimulants can release serotonin, and amphetamine is metabolized by the cytochrome P-450 (CYP) 2D6 isoenzyme, which is inhibited by some selective serotonin-reuptake inhibitors (e.g., fluoxetine, paroxetine).

■ **Drugs Undergoing Metabolism by Hepatic Microsomal Enzymes** ***Drugs Metabolized by Cytochrome P-450 (CYP) 2D6*** Fluoxetine, like many other antidepressants (e.g., other selective serotonin-reuptake inhibitors, many tricyclic antidepressants), is metabolized by the drug-metabolizing cytochrome P-450 (CYP) 2D6 isoenzyme (debrisoquine hydroxylase). In addition, like many other drugs metabolized by CYP2D6, fluoxetine inhibits the activity of CYP2D6 and potentially may increase plasma concentrations of concomitantly administered drugs that also are metabolized by this enzyme. Fluoxetine may make normal CYP2D6 metabolizers resemble "poor metabolizers". Although similar interactions are possible with other selective serotonin-reuptake inhibitors, there is considerable variability among the drugs in the extent to which they inhibit CYP2D6; fluoxetine and paroxetine appear to be more potent in this regard than sertraline.

Concomitant use of fluoxetine with other drugs metabolized by CYP2D6 has not been systematically studied. The extent to which this potential interaction may become clinically important depends on the extent of inhibition of CYP2D6 by the antidepressant and the therapeutic index of the concomitantly administered drug. The drugs for which this potential interaction is of greatest concern are those that are metabolized principally by CYP2D6 and have a narrow therapeutic index, such as tricyclic antidepressants, class IC antiarrhythmics (e.g., propafenone, flecainide, encainide), vinblastine, and some phenothiazines (e.g., thioridazine).

Caution should be exercised whenever concurrent therapy with fluoxetine and other drugs metabolized by CYP2D6 is considered. If fluoxetine therapy is initiated in a patient already receiving a drug metabolized by CYP2D6, the need for decreased dosage of that drug should be considered. In addition, a low initial dosage should be used whenever a drug that is predominantly metabolized by CYP2D6 and has a relatively narrow therapeutic margin (e.g., tricyclic antidepressants, class IC antiarrhythmics) is initiated in a patients who is receiving or has received fluoxetine during the previous 5 weeks. Because of the risk of serious ventricular arrhythmias and sudden death potentially associated with increased plasma concentrations of thioridazine, thioridazine is contraindicated in any patient who is receiving or has received fluoxetine during the previous 5 weeks. (See Thioridazine under Drug Interactions: Antipsychotic Agents.)

Drugs Metabolized by Cytochrome P-450 (CYP) 3A4 Although fluoxetine can inhibit the cytochrome P-450 (CYP) 3A4 isoenzyme, results of in vitro and in vivo studies indicate that the drug is a much less potent inhibitor of this enzyme than many other drugs. In one in vivo drug interaction study, concomitant administration of single doses of the CYP3A4 substrate terfenadine (no longer commercially available in the US) and fluoxetine did not in-

crease plasma concentrations of terfenadine. In addition, in vitro studies have shown that ketoconazole, a potent inhibitor of CYP3A4 activity, is at least 100 times more potent than fluoxetine or norfluoxetine as an inhibitor of several substrates of this enzyme (e.g., astemizole [no longer commercially available in the US], cisapride, midazolam). Some clinicians state that concomitant use of fluoxetine with astemizole or terfenadine is not recommended since substantially increased plasma concentrations of unchanged astemizole or terfenadine could occur, resulting in an increased risk of serious adverse cardiac effects. However, the manufacturer of fluoxetine states that the extent of fluoxetine's inhibition of CYP3A4 activity is unlikely to be of clinical importance.

■ **Tricyclic and Other Antidepressants** Concurrent administration of fluoxetine and a tricyclic antidepressant (e.g., nortriptyline, desipramine, imipramine) reportedly has resulted in adverse effects associated with tricyclic toxicity (including sedation, decreased energy, lightheadedness, psychomotor retardation, dry mouth, constipation, memory impairment). In patients receiving imipramine or desipramine, initiation of fluoxetine therapy reportedly resulted in plasma concentrations of these tricyclic antidepressants that were at least 2–10 times higher; this effect persisted for 3 weeks or longer after fluoxetine was discontinued. Elevated plasma trazodone concentrations and adverse effects possibly associated with trazodone toxicity (e.g., sedation, unstable gait) also have been reported during concomitant fluoxetine and trazodone therapy. Although the mechanism for this possible interaction has not been established, it has been suggested that fluoxetine may inhibit the hepatic metabolism of tricyclic antidepressants. (See Drugs Metabolized by Cytochrome P-450 (CYP) 2D6 under Drug Interactions: Drugs Undergoing Metabolism by Hepatic Microsomal Enzymes.) Further study of this potential interaction is needed, but current evidence suggests that patients receiving fluoxetine and a tricyclic antidepressant or trazodone concomitantly should be closely observed for adverse effects; monitoring of plasma tricyclic or trazodone concentrations also should be considered and their dosage reduced as necessary. Because fluoxetine may increase plasma concentrations and prolong elimination half-life of tricyclic antidepressants, the need for more prolonged monitoring following combined tricyclic and fluoxetine overdose should be considered. In addition, because of the prolonged elimination of fluoxetine and norfluoxetine, the possibility that the drug may interact with tricyclic antidepressants after recent discontinuance of fluoxetine also should be considered.

■ **Antipsychotic Agents** Some clinical data suggest a possible pharmacodynamic and/or pharmacokinetic interaction between selective serotonin-reuptake inhibitors, including fluoxetine, and some antipsychotic agents.

Clozapine Concomitant use of fluoxetine and clozapine can increase plasma concentrations of clozapine and enhance clozapine's pharmacologic effects secondary to suspected inhibition of clozapine metabolism by fluoxetine. Increased plasma clozapine concentrations also have been reported in patients receiving other selective serotonin-reuptake inhibitors (e.g., fluvoxamine, paroxetine). There has been at least one fatality related to clozapine toxicity following ingestion of clozapine, fluoxetine, and alcohol. The manufacturer of clozapine states that caution should be used and patients closely monitored if clozapine is used in patients receiving selective serotonin-reuptake inhibitors, and a reduction in clozapine dosage should be considered.

Haloperidol Elevated plasma concentrations of haloperidol have been observed in patients receiving concomitant fluoxetine therapy. Severe extrapyramidal symptoms (e.g., tongue stiffness, parkinsonian symptoms, akathisia), which required hospitalization and were refractory to conventional therapy (including anticholinergic antiparkinsonian agents, diphenhydramine, and diazepam), reportedly occurred in a patient receiving fluoxetine and haloperidol concurrently; this patient previously had experienced only mild adverse extrapyramidal effects with haloperidol therapy alone. The extrapyramidal symptoms gradually abated following discontinuance of both drugs, and the patient subsequently tolerated haloperidol therapy with evidence of only a slight parkinsonian gait. The clinical importance of this possible interaction has not been established, and additional study is required to determine the safety of combined fluoxetine and antipsychotic therapy.

Pimozide Clinical studies evaluating pimozide in combination with and other antidepressants have demonstrated an increase in adverse drug interactions or QT_c prolongation during combined therapy. In addition, rare case reports have suggested possible additive cardiovascular effects of fluoxetine and pimozide, resulting in bradycardia. Marked changes in mental status (e.g., stupor, inability to think clearly) and hypersalivation also were reported in one woman who received both drugs concurrently. Although a specific study evaluating concurrent fluoxetine and pimozide therapy has not been performed to date, concurrent use of these drugs is contraindicated because of the potential for adverse drug interactions or QT_c prolongation.

Risperidone Extrapyramidal symptoms followed by persistent tardive dyskinesia (dyskinetic tongue movements) have occurred in one 18-year old who received risperidone concomitantly with fluoxetine; however, a causal relationship has not been established. The AUC of risperidone increased during concomitant fluoxetine therapy in one study in psychotic patients, and the AUC of active drug (risperidone plus 9-hydroxyrisperidone) increased in poor and extensive metabolizers (determined by CYP2D6 genotyping): there was no evidence of increased severity or incidence of extrapyramidal symptoms in this 30-day study.

Thioridazine Although specific drug interaction studies evaluating concomitant use of fluoxetine and thioridazine are not available, concomitant use of other selective serotonin-reuptake inhibitors (e.g., fluvoxamine) has resulted in increased plasma concentrations of the antipsychotic agent. Because of the risk of serious ventricular arrhythmia and sudden death associated with elevated plasma concentrations of thioridazine, thioridazine is contraindicated in any patients who is receiving or has received fluoxetine during the previous 5 weeks. (See Drugs Metabolized by Cytochrome P-450 (CYP) 2D6 under Drug Interactions: Drugs Undergoing Hepatic Microsomal Metabolism.)

■ **Benzodiazepines** Fluoxetine appears to inhibit the metabolism of diazepam, as evidenced by increases in the elimination half-life and plasma concentration of diazepam and decreases in diazepam clearance and the rate of formation of desmethyldiazepam (an active metabolite of diazepam) during concomitant use of the drugs. Although clinically important increase in psychomotor impairment has not been noted when fluoxetine and diazepam were administered concomitantly as compared with administration of diazepam alone, concomitant administration of alprazolam and fluoxetine have resulted in increased plasma concentrations of alprazolam and further psychomotor performance impairments. Pending further accumulation of data, the possibility that a clinically important interaction could occur in geriatric or other susceptible patients should be considered.

■ **Buspirone** Buspirone has serotonergic activity and may have been partially responsible for a case of serotonin syndrome that resulted in the death of a patient receiving fluoxetine, buspirone, and an MAO inhibitor (tranylcypromine) concomitantly. (See Drug Interactions: Drugs Associated with Serotonin Syndrome.)

In a patient with depression, generalized anxiety disorder, and panic attacks who was receiving concomitant buspirone and trazodone therapy, an increase in anxiety symptoms to a level comparable to that observed prior to buspirone therapy occurred when fluoxetine was added to the regimen. Although the mechanism of this possible interaction has not been established, it was suggested that fluoxetine may have either directly antagonized the therapeutic activity of buspirone or may have precipitated the anxiety symptoms through a separate mechanism. However, combined use of the drugs also has been reported to potentiate therapeutic efficacy in patients with obsessive-compulsive disorder.

■ **Lithium** Fluoxetine and lithium have been used concurrently in a limited number of patients without apparent adverse effects. However, both increased and decreased serum lithium concentrations and adverse neuromuscular effects possibly associated with lithium toxicity and/or serotonin syndrome (e.g., ataxia, dizziness, dysarthria, stiffness of the extremities) have been reported during combined therapy with the drugs. Lithium appears to have some serotonergic activity and serotonin syndrome has been reported following the initiation of lithium therapy in at least one patient receiving fluoxetine. (See Drug Interactions: Drugs Associated with Serotonin Syndrome.) The clinical importance of this potential interaction remains to be determined and further substantiation is required; however, caution should be exercised when fluoxetine and lithium are administered concurrently. It is recommended that serum lithium concentrations be monitored closely during concomitant fluoxetine therapy.

■ **Anticonvulsants** ***Carbamazepine*** Fluoxetine can increase plasma carbamazepine and carbamazepine 10,11-epoxide (CBZ-E, an active metabolite) concentrations, and carbamazepine toxicity (e.g., ocular changes, vertigo, tremor) has been reported in some patients maintained on carbamazepine following initiation of fluoxetine. It has been suggested that fluoxetine-induced inhibition of hepatic metabolism (e.g., inhibition of epoxide hydrolase) of carbamazepine and/or CBZ-E may be principally responsible for such increases; alteration in protein binding does not appear to be principally responsible for this interaction. The patient and plasma concentrations of carbamazepine and its metabolite should be monitored closely whenever fluoxetine therapy is initiated or discontinued; carbamazepine dosage should be adjusted accordingly.

Phenytoin Initiation of fluoxetine in patients stabilized on phenytoin has resulted in increased plasma phenytoin concentrations and clinical manifestations of phenytoin toxicity.

■ **β-Adrenergic Blocking Agents** Concomitant use of fluoxetine and a β-adrenergic blocking agent has resulted in increased plasma concentrations that have enhanced the β-adrenergic blocking effects of the drug, possibly resulting in cardiac toxicity. Metoprolol is metabolized by the CYP2D6 isoenzyme and fluoxetine is known to potently inhibit this enzyme. Although specific data are lacking, β-adrenergic blocking agents that are renally eliminated (e.g., atenolol) may be a safer choice. Patients who were previously stabilized on propranolol or metoprolol should be monitored for toxicity (e.g., bradycardia, conduction defects, hypotension, heart failure, central nervous system disturbances) following initiation of fluoxetine therapy.

■ **Protein-bound Drugs** Because fluoxetine is highly protein bound, the drug theoretically could be displaced from binding sites by, or it could displace from binding sites, other protein-bound drugs such as oral anticoagulants and digitoxin (no longer commercially available in the US). Pending further accumulation of data, patients receiving fluoxetine with any highly protein-bound drug should be observed for potential adverse effects associated with such therapy. (See Drug Interactions: Drugs Affecting Hemostasis.)

■ **Drugs Affecting Hemostasis** ***Anticoagulants*** Concomitant use of fluoxetine and warfarin has resulted in altered anticoagulant effects, includ-

ing increased bleeding. Therefore, patients receiving warfarin should be carefully monitored whenever fluoxetine is initiated or discontinued.

Other Drugs that Interfere with Hemostasis Epidemiologic case-control and cohort design studies that have demonstrated an association between selective serotonin-reuptake inhibitor therapy and an increased risk of upper GI bleeding also have shown that concurrent use of aspirin or other nonsteroidal anti-inflammatory agents substantially increases the risk of GI bleeding. Although these studies focused on upper GI bleeding, there is some evidence suggesting that bleeding at other sites may be similarly potentiated. The precise mechanism for this increased risk remains to be clearly established; however, serotonin release by platelets is known to play an important role in hemostasis, and selective serotonin-reuptake inhibitors decrease serotonin uptake from the blood by platelets, thereby decreasing the amount of serotonin in platelets. Patients receiving fluoxetine should be cautioned about the concomitant use of drugs that interfere with hemostasis, including aspirin and other nonsteroidal anti-inflammatory agents.

■ **Alcohol** Concurrent administration of single or multiple doses of fluoxetine and alcohol does not appear to alter blood or Breathalyzer® alcohol, plasma fluoxetine, or plasma norfluoxetine concentrations in healthy individuals, suggesting that there is no pharmacokinetic interaction between fluoxetine and alcohol. In addition, fluoxetine does not appear to potentiate the psychomotor and cognitive impairment or cardiovascular effects induced by alcohol. However, the drug's ability to reduce alcohol consumption in animals and humans suggests that there may be a serotonergically mediated, pharmacodynamic interaction between fluoxetine and alcohol within the CNS. (See Pharmacology: Effects on Alcohol Intake, and also see Uses: Alcohol Dependence.)

■ **Electroconvulsive Therapy** The effects of fluoxetine in conjunction with electroconvulsive therapy (ECT) for the management of depression have not been evaluated to date in clinical studies. Prolonged seizures reportedly have occurred rarely during concurrent use of fluoxetine and ECT.

■ **Antidiabetic Agents** Fluoxetine potentially may alter blood glucose concentrations in patients with diabetes mellitus. (See Cautions: Metabolic Effects.) Therefore, dosage adjustments of insulin and/or sulfonylurea antidiabetic agents may be necessary when fluoxetine therapy is initiated or discontinued in such patients.

Acute Toxicity

Limited information is available on the acute toxicity of fluoxetine.

■ **Pathogenesis** The acute lethal dose of fluoxetine in humans is not known. The median oral LD_{50} of fluoxetine has been reported to be approximately 452 and 248 mg/kg in rats and mice, respectively. In animals, oral administration of single large doses of the drug has resulted in hyperirritability and seizures. Tonic-clonic seizures occurred in 5 of 6 dogs given a toxic dose of fluoxetine orally; the seizures ceased immediately after IV administration of diazepam. In these dogs, the lowest plasma fluoxetine concentration at which seizures occurred reportedly was only twice the maximum plasma concentration reported in humans receiving 80 mg of the antidepressant daily during long-term therapy. Single large oral doses of fluoxetine reportedly do not cause QT- or PR-interval prolongation or widening of the QRS complex in dogs, although tachycardia and an increase in blood pressure have occurred.

The risk of fluoxetine overdosage may be increased in patients with a genetic deficiency in the cytochrome P-450 (CYP) isoenzyme 2D6.

■ **Manifestations** In general, overdosage of fluoxetine may be expected to produce effects that are extensions of the drug's pharmacologic and adverse effects. Animal studies and case reports in humans indicate that possible effects of overdosage include agitation, restlessness, hypomania, vertigo, insomnia, tremor, and other signs of CNS excitation; nausea and vomiting; and tachycardia and/or increased blood pressure. Seizures have been reported in at least one patient after overdosage of fluoxetine. Acute overdosage of fluoxetine alone reportedly has resulted in nystagmus, drowsiness, coma, urticaria, spontaneous emesis, and ST-segment depression. Nausea and vomiting appear to occur commonly following acute ingestion of relatively large single doses of the drug.

Several fatalities following fluoxetine overdosage have been reported to date. One of the deaths occurred in a patient who reportedly ingested 1.8 g of fluoxetine and an unknown quantity of maprotiline; plasma fluoxetine and maprotiline concentrations in this patient were approximately 4570 and 4180 ng/mL, respectively. Another patient died after concomitantly ingesting fluoxetine, codeine, and temazepam; plasma fluoxetine, norfluoxetine, codeine, and temazepam concentrations in this patient reportedly were 1930, 1110, 1800, and 3800 ng/mL, respectively; a fatal overdose also has been reported in a patient ingesting fluoxetine and alcohol concomitantly. There also are a few reported cases of overdose in which fatality was attributed to fluoxetine alone. In one such case, death was associated with extracted blood fluoxetine and norfluoxetine concentrations of 6000 and 5000 ng/mL, respectively, and biliary concentrations of 13,000 ng/mL each for the drug and metabolite. A patient enrolled in a clinical study of fluoxetine reportedly died following intentional ingestion of an unknown quantity of amitriptyline, clobazam, and pentazocine; however, it is not known whether this patient also ingested fluoxetine with the other drugs.

A patient with a history of seizures who reportedly ingested 3 g of fluoxetine and an unknown quantity of aspirin experienced 2 tonic-clonic seizures, tachycardia, dizziness, blurred vision, unsustained clonus, and ECG changes. The seizures occurred about 9 hours post-ingestion, lasted approximately 2–3 minutes, and remitted spontaneously without anticonvulsant therapy. Although the actual amount of fluoxetine absorbed by this patient may have been less than expected because of vomiting and gastric lavage, the plasma fluoxetine concentration reportedly was 2461 ng/mL when seizures occurred; the patient recovered with no apparent sequelae. Another patient reported that he experienced sleepiness and nausea that lasted for several days following the intentional ingestion of 840 mg of fluoxetine with alcohol; this patient did not seek medical treatment. Drowsiness, lethargy, and nausea occurred in a patient who reportedly ingested 1.4 g of fluoxetine and 15 mg of clonazepam. No ECG abnormalities were reported in 2 patients who intentionally ingested 200 mg and 1 g of fluoxetine.

A child with a genetic deficiency in the CYP2D6 isoenzyme died following prolonged therapy with fluoxetine, methylphenidate, and clonidine. Autopsy findings revealed blood, brain, and other tissue concentrations of fluoxetine and norfluoxetine that were several-fold higher than expected. Poor metabolism of fluoxetine via CYP2D6 was the likely cause of fluoxetine intoxication in this child.

■ **Treatment** Because fatalities and severe toxicity have been reported following overdosage of selective serotonin-reuptake inhibitors, particularly in large overdosage and when taken with other drugs or alcohol, some clinicians recommend that any overdosage involving these drugs be managed aggressively.

Management of fluoxetine overdosage generally involves symptomatic and supportive care. A patent airway should be established and maintained, and adequate oxygenation and ventilation should be assured. ECG and vital sign monitoring is recommended following acute overdosage with the drug, although the value of ECG monitoring in predicting the severity of fluoxetine-induced cardiotoxicity is not known. (See Acute Toxicity: Manifestations, in the Tricyclic Antidepressants General Statement.) There is no specific antidote for fluoxetine intoxication. Because suicidal ingestion often involves more than one medication, clinicians treating fluoxetine overdosage should be alert to possible toxic manifestations caused by medications other than fluoxetine.

Following recent (i.e., within 4 hours) ingestion of a potentially toxic amount of fluoxetine and in the absence of signs and symptoms of cardiac toxicity, the stomach should be emptied immediately by inducing emesis or by gastric lavage. If the patient is comatose, having seizures, or lacks the gag reflex, gastric lavage may be performed if an endotracheal tube with cuff inflated is in place to prevent aspiration of gastric contents. Since administration of activated charcoal (which may be used in conjunction with sorbitol or a saline cathartic) may be as effective or more effective than induction of emesis or gastric lavage, its use has been recommended either in the initial management of fluoxetine overdosage or following induction of emesis or gastric lavage in patients who have ingested a potentially toxic quantity of the drug.

Based on data from animal studies, IV diazepam should be considered for the management of fluoxetine-induced seizures that do not remit spontaneously. If seizures are not controlled or recur following administration of diazepam, administration of phenytoin or phenobarbital has been recommended by some clinicians.

Fluoxetine and norfluoxetine are not substantially removed by hemodialysis. Because of the large volume of distribution and extensive protein binding of the drug and its principal metabolite, peritoneal dialysis, forced diuresis, hemoperfusion, and/or exchange transfusion probably are also ineffective in removing substantial amounts of fluoxetine and norfluoxetine from the body. Clinicians should consider consulting a poison control center for additional information on the management of fluoxetine overdosage.

Chronic Toxicity

Fluoxetine has not been studied systematically in animals or humans to determine whether therapy with the drug is associated with tolerance or psychologic and/or physical dependence. One patient receiving the drug for the management of obesity reportedly experienced nervousness 2 days following discontinuance of fluoxetine therapy. However, it is unclear whether this adverse effect represented a withdrawal reaction since both the parent drug and its principal metabolite have relatively long half-lives, and withdrawal reactions following discontinuance of fluoxetine therapy may therefore be more delayed. Although clinical experience to date has not revealed substantial evidence of drug-seeking behavior or a withdrawal syndrome associated with discontinuance of fluoxetine therapy, it is difficult to predict from the limited data currently available the extent to which a CNS-active drug like fluoxetine may be misused, diverted, and/or abused.

Despite the lack of substantial evidence for abuse potential or dependence liability, clinicians should carefully evaluate patients for a history of substance abuse prior to initiating fluoxetine therapy. If fluoxetine therapy is initiated in patients with a history of substance abuse, such patients should be monitored closely for signs of misuse or abuse of the drug (e.g., development of tolerance, use of increasing doses, drug-seeking behavior).

The potential for misuse of fluoxetine by depressed patients with concurrent eating disorders and/or those who may seek the drug for its appetite-suppressant effects also should be considered. One patient with an undisclosed history of anorexia nervosa and laxative abuse who was given fluoxetine for depression ingested larger-than-prescribed doses (e.g., 90–120 mg/day) and lost 9.1 kg within 2 months; this patient falsely claimed mood improvement in order to continue receiving the drug for its anorectic and weight-reducing effects.

Fluoxetine has produced phospholipidosis following long-term administration in animals; however, no evidence of phospholipidosis has been reported in humans receiving the drug to date. Additional study is needed to determine the clinical importance of these findings in patients receiving long-term fluoxetine therapy. (See Pharmacology: Effects on Phospholipids.)

Pharmacology

The pharmacology of fluoxetine is complex and in many ways resembles that of other antidepressant agents, particularly those agents (e.g., citalopram, clomipramine, escitalopram, fluvoxamine, paroxetine, sertraline, trazodone) that predominantly potentiate the pharmacologic effects of serotonin (5-HT). Like other selective serotonin-reuptake inhibitors (SSRIs), fluoxetine is a potent and highly selective reuptake inhibitor of serotonin and has little or no effect on other neurotransmitters.

■ **Nervous System Effects** The precise mechanism of antidepressant action of fluoxetine is unclear, but the drug has been shown to selectively inhibit the reuptake of serotonin at the presynaptic neuronal membrane. Fluoxetine-induced inhibition of serotonin reuptake causes increased synaptic concentrations of serotonin in the CNS, resulting in numerous functional changes associated with enhanced serotonergic neurotransmission. Like other selective serotonin-reuptake inhibitors (fluvoxamine, paroxetine, sertraline), fluoxetine appears to have minimal or no effect on the reuptake of norepinephrine or dopamine and does not exhibit clinically important anticholinergic, antihistaminic, or α_1-adrenergic blocking activity at usual therapeutic dosages.

Although the mechanism of antidepressant action of antidepressant agents may involve inhibition of the reuptake of various neurotransmitters (i.e., norepinephrine, serotonin) at the presynaptic neuronal membrane, it has been suggested that postsynaptic receptor modification is mainly responsible for the antidepressant action observed during long-term administration of antidepressant agents. During long-term therapy with most antidepressants (e.g., tricyclic antidepressants, monoamine oxidase [MAO] inhibitors), these adaptive changes generally consist of subsensitivity of the noradrenergic adenylate cyclase system in association with a decrease in the number of β-adrenergic receptors; such effects on noradrenergic receptor function commonly are referred to as "down-regulation." In addition, some antidepressants reportedly decrease the number of 5-HT binding sites following chronic administration. Fluoxetine may exert its antidepressant activity by somewhat different mechanisms than those usually associated with tricyclic and some other antidepressants. Although some evidence indicates that long-term administration of fluoxetine does not substantially decrease the number of β-adrenergic binding sites or reduce the sensitivity of β-adrenergic receptors, a decrease in the number of β-adrenergic binding sites in the brain has been reported in at least one study in animals. Data regarding the effects of fluoxetine on the number of serotonin (5-HT_1 and/or 5-HT_2) binding sites have been conflicting, with either no change or a reduction in the number of binding sites being reported during chronic administration of the drug. Increased postsynaptic receptor binding of GABA B also has been reported following prolonged administration of many antidepressants, including fluoxetine. The clinical importance of these findings for fluoxetine has not been fully elucidated to date, and further study is needed to determine the role, if any, of binding site alteration in the antidepressant action of fluoxetine and other antidepressants.

The precise mechanism of action responsible for the efficacy of fluoxetine in the treatment of obsessive-compulsive disorder is unclear. However, based on the efficacy of other selective serotonin-reuptake inhibitors (e.g., fluvoxamine, paroxetine, sertraline) and clomipramine in the treatment of obsessive-compulsive disorder and the potency of these drugs in inhibiting serotonin reuptake, a serotonergic hypothesis has been developed to explain the pathogenesis of the condition. The hypothesis postulates that a dysregulation of serotonin is responsible for obsessive-compulsive disorder and that fluoxetine and these other agents are effective because they correct this imbalance. Although the available evidence supports the serotonergic hypothesis of obsessive-compulsive disorder, additional studies are necessary to confirm this hypothesis.

Serotonergic Effects Fluoxetine is a highly selective inhibitor of serotonin reuptake at the presynaptic neuronal membrane. In addition, the potency and selectivity of serotonin-reuptake inhibition exhibited by fluoxetine's principal metabolite, norfluoxetine, appear to be similar to those of the parent drug. Fluoxetine- and norfluoxetine-induced inhibition of serotonin reuptake causes increased synaptic concentrations of serotonin, resulting in numerous functional changes associated with enhanced serotonergic neurotransmission.

Data from in vitro studies suggest that fluoxetine is approximately equivalent to or less potent than clomipramine as a serotonin-reuptake inhibitor; however, in vivo studies indicate that the serotonin-reuptake inhibiting effect of fluoxetine may be more potent than that of clomipramine on a weight as well as an equimolar basis. This apparent discrepancy may be explained at least in part by the relatively long elimination half-lives of fluoxetine and norfluoxetine. In addition, metabolism via *N*-demethylation decreases the potency and specificity of serotonin-reuptake inhibition of clomipramine but not fluoxetine. Data from both in vivo and in vitro studies indicate that fluoxetine also is a more potent serotonin-reuptake inhibitor than other currently available antidepressant agents, including imipramine and trazodone. Fluoxetine appears to have practically no affinity for serotonin (e.g., 5-HT_1 and 5-HT_2) receptors in vitro, although limited in vivo data suggest that the drug may bind to low-affinity sites on 5-HT receptors.

Fluoxetine appears to decrease the turnover of serotonin in the CNS, probably as a result of a decrease in the rate of serotonin synthesis. The drug reportedly decreases brain concentrations of 5-hydroxyindoleacetic acid (5-HIAA), the principal metabolite of serotonin; reduces the uptake of radiolabeled tryptophan by synaptosomes; and reduces the rate of conversion of tryptophan to serotonin. Fluoxetine also inhibits spontaneous firing of serotonergic neurons in the dorsal raphe nucleus.

Like other serotonin-reuptake inhibitors, administration of fluoxetine alone does not produce the serotonin behavioral syndrome (a characteristic behavioral pattern caused by central stimulation of serotonin activity) in animals. However, the drug potentiates the serotonin behavioral syndrome induced by oxitriptan (l-5-hydroxytryptophan, l-5HTP), MAO inhibitors, and MAO inhibitors combined with tryptophan.

Effects on Other Neurotransmitters Like other selective serotonin-reuptake inhibitors, fluoxetine appears to have little or no effect on the reuptake of other neurotransmitters such as norepinephrine or dopamine. In addition, the drug appears to have a substantially higher selectivity ratio of serotonin-to-norepinephrine reuptake inhibiting activity than tricyclic antidepressant agents, including clomipramine.

Unlike tricyclic and some other antidepressants, fluoxetine does not exhibit clinically important anticholinergic, α_1-adrenergic blocking, or antihistaminic activity at usual therapeutic dosages. As a result, the incidence of adverse effects commonly associated with blockade of muscarinic cholinergic receptors (e.g., dry mouth, blurred vision, urinary retention, constipation, confusion), α_1-adrenergic receptors (e.g., orthostatic hypotension), and histamine H_1- and H_2-receptors (e.g., sedation) is lower in fluoxetine-treated patients. In vitro studies have demonstrated that the drug possesses only weak affinity for α_1- and α_2-adrenergic, β-adrenergic, H_1 and H_2, muscarinic, opiate, GABA-benzodiazepine, and dopamine receptors.

Effects on Sleep Like tricyclic and most other antidepressants, fluoxetine suppresses rapid eye movement (REM) sleep. Although not clearly established, there is some evidence that the REM-suppressing effects of antidepressant agents may contribute to the antidepressant activity of these drugs. In animal studies, fluoxetine produces a dose-related suppression of REM sleep; the drug generally appears to reduce the amount of REM sleep by increasing REM latency (the time to onset of REM sleep) and by decreasing the number rather than the duration of REM episodes. Limited data in animals suggest that REM rebound does not occur following discontinuance of fluoxetine. The precise mechanism has not been fully elucidated, but results of animal studies indicate that fluoxetine's effects on REM sleep are serotonergically mediated. Like other specific serotonin-reuptake inhibitors (e.g., zimeldine [previously zimelidine]), the effects of fluoxetine on non-REM sleep reported to date have been variable and do not appear to be as clearly defined as those of tricyclic antidepressants, which usually increase slow-wave sleep.

Effects on EEG Limited data currently are available regarding the effects of fluoxetine on the EEG. Substantial EEG changes did not occur following oral administration of single 30-mg doses of the drug in healthy individuals. An increase in alpha activity and a decrease in fast beta activity and slow activity were noted following single oral 60-mg doses in this study; such changes are characteristic of desipramine-type antidepressants and appear to indicate increased vigilance. Single 75-mg doses of fluoxetine produced an increase in slow and fast activity and a decrease in alpha activity; such EEG changes are similar to those observed with amitriptyline and imipramine and suggest possible sedative activity.

Effects on Psychomotor Function Fluoxetine does not appear to cause clinically important sedation and does not interfere with psychomotor performance. Controlled studies in healthy young adults 21–45 of years and in adults with major depression did not demonstrate any adverse effects on psychomotor performance in those receiving the drug. No adverse effects on psychomotor performance or cognitive function were observed in men with depression older than 60 years of age who received 20-mg doses of fluoxetine in a controlled study. Results of this study showed that overall cognition, as assessed by the critical flicker fusion thresholds test, generally was better in patients receiving fluoxetine than in those receiving amitriptyline (a tricyclic antidepressant); however, less sedating tricyclic antidepressants (e.g., desipramine) were not included in the study and it is possible that fluoxetine may not have such an advantage over these other agents. In a controlled study evaluating the effects of fluoxetine (20 mg daily for 22 days) on psychomotor performance and car driving in healthy adults, the drug did not affect the highway driving or the car following tests but slightly impaired performance in correctly detecting changes in visual signals was evident in the sustained attention test.

Analgesic Effects Like other serotonin-reuptake inhibitors (e.g., zimeldine), fluoxetine exhibits analgesic activity in some analgesic test systems when administered alone in animals, but the lack of such effects observed in other test systems suggests that demonstration of analgesic activity may be test-dependent. Fluoxetine has potentiated opiate agonist-induced analgesia in most but not all studies, possibly as a result of the drug's ability to enhance serotonergic neurotransmission. The clinical importance of these effects in the management of acute and chronic pain remains to be determined.

Effects on Respiration Usual therapeutic dosages of fluoxetine do not appear to affect respiration substantially in humans; however, the effect of higher dosages of the drug on respiratory function remains to be established. In animals, administration of single 20-mg/kg doses of fluoxetine reportedly

increased blood Po_2 concentrations but did not alter blood P_{CO_2} concentrations. The drug also has been shown to attenuate morphine-induced respiratory depression, although the precise mechanism for this effect has not been established.

Effects on Thermoregulation Data are conflicting regarding the effect of fluoxetine on thermoregulation. In animals, fluoxetine has produced dose-dependent hypothermia in some studies, suggesting that serotonin may play a role in thermoregulation, but the drug has produced only slight or minimal hypothermia in other studies.

The drug has been used safely in at least one patient with established susceptibility to malignant hyperthermia; however, additional experience with the drug is needed to confirm the safety of fluoxetine in patients known to be susceptible to this condition.

■ **Cardiovascular Effects** The cardiovascular effects of fluoxetine have been studied in animals and to a limited extent in humans. Unlike some other antidepressant agents (e.g., tricyclic antidepressants, MAO inhibitors), fluoxetine has been associated with only minimal cardiovascular effects. The absence of substantial anticholinergic activity, α_1-adrenergic blocking activity, catecholamine-potentiating effects, and quinidine-like cardiotoxic effects appears to be the principal reason for the general lack of cardiovascular effects associated with fluoxetine.

Fluoxetine does not exhibit clinically important α_1-adrenergic blocking activity and does not inhibit catecholamine reuptake. Unlike tricyclic antidepressants, fluoxetine does not block the neuronal reuptake of norepinephrine and therefore does not potentiate the pressor response associated with administration of norepinephrine. In addition, the drug does not inhibit the reuptake of and has no effect on the pressor response to tyramine.

Fluoxetine does not appear to have substantial arrhythmogenic activity; however, safety of the drug in patients with a recent history of myocardial infarction or unstable cardiovascular disease has not been adequately evaluated to date. Fluoxetine generally does not appear to affect cardiac conduction, and clinically important ECG changes have not been reported in patients without preexisting heart disease receiving therapeutic dosages of the drug. Unlike tricyclic antidepressants, which commonly cause an increase in heart rate, fluoxetine reportedly reduces heart rate by an average of about 3 beats/minute in patients receiving usual therapeutic dosages of the antidepressant. (See Cautions: Cardiovascular Effects.) Unlike tricyclics, the drug does not appear to exhibit direct quinidine-like cardiotoxic activity, although the cardiovascular effects associated with fluoxetine overdosage have not been fully established to date. (See Acute Toxicity.)

■ **Effects on Appetite and Body Weight** Like some other serotonergic agents (e.g., fenfluramine [no longer commercially available in the US], zimeldine), fluoxetine possesses anorectic activity. Although the precise mechanism has not been clearly established, results of animal studies indicate that the drug's appetite-inhibiting action may result from serotonin-reuptake blockade and the resultant increase in serotonin availability at the neuronal synapse. Following administration of single and multiple doses of fluoxetine in both meal-fed and free-feeding animals, a reduction in food intake usually occurs, particularly at relatively high doses of the drug (i.e., 10 mg/kg). The anorectic effect of fluoxetine appears to be potentiated by oxitriptan. Tolerance to the anorectic effect of fluoxetine has not developed following short-term administration in humans and animals; however, long-term studies in humans are necessary to fully determine whether tolerance develops during chronic therapy with the drug.

In animal studies, fluoxetine has been shown to suppress palatability-induced food consumption (as determined by the volume of sweetened versus plain water ingested). Like fenfluramine, fluoxetine also appears to selectively suppress carbohydrate and overall food intake while maintaining protein intake. Such carbohydrate intake-suppressing and protein-sparing effects may be of potential clinical importance in the management of obesity; however, additional study is necessary. (See Uses: Obesity.) Fluoxetine therapy also has resulted in decreases in body weight in normal-weight and obese animals as well as in depressed, nondepressed, and obese individuals receiving the drug. (See Uses: Obesity and also see Cautions: Metabolic Effects.)

■ **Effects on Alcohol Intake** Like some other serotonergic agents, fluoxetine produces a dose-dependent decrease in voluntary alcohol intake in normal and alcohol-preferring animals. Like some other serotonin-reuptake inhibitors (e.g., citalopram, zimeldine), fluoxetine has been shown to reduce alcohol consumption in a limited number of heavy drinkers receiving 60 mg of the drug daily. Because serotonin appears to be involved in the regulation of alcohol intake, it has been suggested that fluoxetine may attenuate alcohol consumption via enhanced serotonergic neurotransmission. In addition, there is some evidence that such effects may be at least partially mediated by the renin-angiotensin-aldosterone system. (See Uses: Alcohol Dependence and see Drug Interactions: Alcohol.)

■ **Neuroendocrine Effects** Fluoxetine affects the endocrine system. Like other selective inhibitors of serotonin reuptake, the drug has produced a dose-related increase in serum corticosterone concentrations in animals. Fluoxetine also reportedly potentiates oxitriptan-induced elevation in serum corticosterone concentrations. Such effects appear to be serotonergically mediated. Following parenteral administration of fluoxetine in animals, the elevation in serum corticosterone concentration generally lasts only a few hours, although fluoxetine-induced inhibition of serotonin reuptake is known to persist for longer than 24 hours. Therefore, it has been suggested that other compensatory mechanisms, possibly including decreased firing of serotonergic neurons, may contribute to the restoration of normal hypothalamic-pituitary-adrenal (HPA) axis function despite prolonged blockade of serotonin reuptake by the drug. Fluoxetine also has increased corticotropin (ACTH) and vasopressin (antidiuretic hormone, ADH) concentrations in peripheral plasma and has increased corticotropin and corticotropin-releasing factor (CRF, corticoliberin) concentrations in hypophysial portal blood. These effects may represent the initial step in fluoxetine-induced elevation of plasma corticosterone concentrations.

The effects of fluoxetine on serum prolactin concentrations have not been clearly established. In some animal studies, fluoxetine potentiated tryptophan-induced increases in serum prolactin concentrations, although administration of the drug alone in animals and humans usually does not substantially alter prolactin concentrations. However, administration of fluoxetine alone reportedly increased serum prolactin concentrations in young but not old male rats in one study. Fluoxetine-induced effects on prolactin secretion appear to be serotonergically mediated.

■ **Effects on Phospholipids** Like many other cationic, amphiphilic drugs (e.g., amiodarone, fenfluramine, imipramine, ranitidine), fluoxetine reportedly increases tissue phospholipid concentrations following chronic administration in animal studies; however, such effects have not been demonstrated in humans receiving fluoxetine to date. Histologic examination following long-term (i.e., 1–12 months) fluoxetine administration in animals has revealed the presence of characteristic concentric, lamellar inclusion bodies associated with phospholipidosis in alveolar macrophages of the lung, Kupffer cells of the liver, and adrenal cortical cells; an increase in phospholipid content of the lung also has been reported. Fluoxetine-induced phospholipid accumulation in these animals was reversible within 1–2 months following discontinuance of the drug.

Studies in humans receiving fluoxetine have not revealed biochemical or clinical evidence of drug-induced phospholipidosis to date. There was no evidence of increased phospholipid content or changes in lamellar inclusion bodies in peripheral blood lymphocytes of either healthy individuals receiving 1 month of fluoxetine therapy or depressed patients receiving long-term (0.9–2.6 years) therapy with the drug. In addition, ophthalmologic examination and chest radiographs in patients receiving fluoxetine during clinical studies have not revealed evidence of phospholipidosis induced by the drug. Although data from clinical studies suggest that fluoxetine-induced phospholipidosis is unlikely to occur in humans receiving long-term therapy with the drug, further study is needed to fully determine whether the phospholipidosis observed in animal studies is clinically important in humans receiving therapeutic dosages of the drug.

■ **Other Effects** Fluoxetine has demonstrated some antimyoclonic activity in animals and humans when used in combination with oxitriptan. Although the mechanism of fluoxetine's antimyoclonic activity has not been fully elucidated, some forms of myoclonus appear to be related to impaired serotonergic neurotransmission. Therefore, it has been suggested that fluoxetine-induced enhancement of serotonergic neurotransmission via serotonin-reuptake blockade potentially may contribute to oxitriptan-induced increases in CNS serotonin concentrations in the management of this condition. (See Uses: Myoclonus.)

Fluoxetine also has reduced cataplexy in both humans and animals. (See Uses: Cataplexy.)

Fluoxetine reportedly has produced a dose-related elevation in plasma β-endorphin and β-lipotropin concentrations in healthy individuals receiving single oral doses of the drug.

Pharmacokinetics

In all human studies described in the Pharmacokinetics section, fluoxetine was administered as the hydrochloride salt.

■ **Absorption** Fluoxetine hydrochloride appears to be well absorbed from the GI tract following oral administration. The oral bioavailability of fluoxetine in humans has not been fully elucidated to date, but at least 60–80% of an oral dose appears to be absorbed. However, the relative proportion of an oral dose reaching systemic circulation unchanged currently is not known. The oral conventional capsules and tablets, delayed-release capsules, and solution of fluoxetine hydrochloride reportedly are bioequivalent. However, onset of absorption of fluoxetine hydrochloride delayed-release capsules (Prozac® Weekly®) is delayed 1–2 hours relative to the onset of absorption when the drug is administered as a conventional preparation. Limited data from animals suggest that the drug may undergo first-pass metabolism and extraction in the liver and/or lung following oral administration. In these animals (beagles), approximately 72% of an oral dose reached systemic circulation unchanged. Food appears to cause a slight decrease in the rate, but not the extent, of absorption of fluoxetine in humans.

Peak plasma fluoxetine concentrations usually occur within 4–8 hours (range: 1.5–12 hours) after oral administration of conventional preparations. Following oral administration of a single 40-mg dose of the drug in healthy fasting adults, peak plasma concentrations of approximately 15–55 ng/mL are attained. Peak plasma fluoxetine concentrations following administration of single oral doses of 20–80 mg are approximately proportional and are linearly related to dose, although there appears to be considerable interindividual variation in plasma concentrations attained with a given dose. The manufacturer

states that the peak plasma concentrations achieved following weekly administration of fluoxetine 90-mg delayed-release capsules are in the range of the average concentrations achieved following daily administration of 20-mg conventional preparations; however, average trough concentrations are reported to be lower following weekly administration of the delayed-release preparation. Peak-to-trough fluctuations in plasma concentrations of fluoxetine and norfluoxetine (the principal metabolite) reportedly are greater following weekly administration of the delayed-release capsules (164 and 43%, respectively) compared with daily administration of conventional preparations (24 and 17%, respectively).

Preliminary data suggest that fluoxetine may exhibit nonlinear accumulation following multiple dosing. (See Pharmacokinetics: Elimination.) The relatively slow elimination of fluoxetine and its active metabolite, norfluoxetine, leads to clinically important accumulation of these active species in chronic use and delayed attainment of steady state, even when a fixed dose is used. In healthy adults receiving 40 mg of fluoxetine daily for 30 days, plasma concentrations of 91–302 and 72–258 ng/mL of fluoxetine and norfluoxetine, respectively, were attained. These plasma concentrations of fluoxetine were higher than those predicted by single-dose studies because fluoxetine's metabolism is not proportional to dose. In addition, prolonged administration of the drug and/or patient's disease states did not appear to affect steady-state concentrations. In one study, steady-state plasma fluoxetine and norfluoxetine concentrations did not differ substantially among healthy individuals receiving 4 weeks of fluoxetine therapy, depressed patients receiving 5 weeks of fluoxetine therapy, or depressed patients receiving more than a year of fluoxetine therapy.

Average steady-state fluoxetine and norfluoxetine concentrations, however, were affected by patient age. In pediatric patients with major depressive disorder or obsessive-compulsive disorder (OCD) who received fluoxetine 20 mg daily for up to 62 days, average steady-state concentrations of fluoxetine and norfluoxetine in children 6–12 years of age were 2- and 1.5-fold higher, respectively, than in adolescents 13–17 years of age who received the same fluoxetine regimen. These results are consistent with those observed in another study in 94 pediatric patients 8–17 years of age diagnosed with major depressive disorder, and can be almost entirely explained by differences in children's weight. Higher average steady-state fluoxetine and norfluoxetine concentrations also were observed in children relative to adults; however, these concentrations were within the range of concentrations observed in the adult population. As in adults, fluoxetine and norfluoxetine accumulated extensively following multiple oral dosing. Following daily oral administration of the drug, steady-state plasma fluoxetine and norfluoxetine concentrations generally are achieved within about 2–4 weeks.

The manufacturer states that average steady-state plasma fluoxetine concentrations are approximately 50% lower with weekly administration of the 90-mg delayed-release capsules compared with daily administration of a 20-mg conventional preparation. In patients being switched from daily therapy with fluoxetine 20-mg conventional preparations to weekly therapy with fluoxetine 90-mg delayed-release capsules, peak plasma fluoxetine concentrations reportedly were 1.7 times higher with the weekly regimen than with the established daily regimen when there was no transition period (i.e., therapy with delayed-release fluoxetine was initated the day after the last daily dose of fluoxetine 20 mg). When weekly therapy was initiated one week after the last daily dose of fluoxetine 20 mg, peak plasma fluoxetine concentrations for the 2 regimens were similar. (See Dosage and Administration: Dosage.)

The onset of antidepressant activity following oral administration of fluoxetine hydrochloride usually occurs within the first 1–3 weeks of therapy, but optimum therapeutic effect usually requires 4 weeks or more of therapy with the drug. Maximal EEG changes and behavioral changes on psychometric tests reportedly occur about 8–10 hours after single oral doses of the drug; the delay in maximal CNS effects compared with achievement of peak plasma fluoxetine concentrations may relate to formation of an active metabolite or to delayed distribution of the parent drug and its principal metabolite into the CNS.

The relationship between plasma fluoxetine and norfluoxetine concentrations and the therapeutic and/or toxic effects of the drug has not been clearly established. In a group of patients receiving fluoxetine for the management of major depressive disorder, there was no correlation between plasma fluoxetine, norfluoxetine, or total fluoxetine plus norfluoxetine concentrations and either the antidepressant response or the weight-reducing effect of the drug.

■ **Distribution** Distribution of fluoxetine and its metabolites into human body tissues and fluids has not been fully characterized. Limited pharmacokinetic data obtained during long-term administration of fluoxetine to animals suggest that the drug and some of its metabolites, including norfluoxetine, are widely distributed in body tissues, with highest concentrations occurring in the lungs and liver. The drug crosses the blood-brain barrier in humans and animals. In animals, fluoxetine:norfluoxetine ratios reportedly were similar in the cerebral cortex, corpus striatum, hippocampus, hypothalamus, brain stem, and cerebellum 1 hour after administration of a single dose of the drug.

The apparent volumes of distribution of fluoxetine and norfluoxetine in healthy adults each reportedly average 20–45 L/kg. Limited data suggest that the volume of distribution of fluoxetine is not altered substantially following multiple dosing. The apparent volume of distribution of norfluoxetine reportedly is higher in patients with cirrhosis than in healthy individuals, although this difference may reflect decreases in the rates of formation and elimination of the metabolite rather than changes in volume of distribution. The volumes of distribution of fluoxetine and norfluoxetine do not appear to be altered substantially in patients with renal impairment.

At in vitro plasma concentrations of 200–1000 ng/mL, fluoxetine is approximately 94.5% bound to plasma proteins, including albumin and α_1-acid glycoprotein (α_1-AGP); the extent of protein binding appears to be independent of plasma concentration. The extent of fluoxetine protein binding does not appear to be altered substantially in patients with hepatic cirrhosis or renal impairment, including those undergoing hemodialysis.

It is not known whether fluoxetine or its metabolites cross the placenta in humans, but fluoxetine and norfluoxetine reportedly cross the placenta in rats following oral administration. Fluoxetine and norfluoxetine are distributed into milk. Limited data indicate that concentrations of the drug and this metabolite in milk are about 20–30% of concurrent plasma concentrations.

■ **Elimination** Fluoxetine and norfluoxetine, the principal metabolite, are eliminated slowly. Following a single oral dose of fluoxetine in healthy adults, the elimination half-life of fluoxetine reportedly averages approximately 2–3 days (range: 1–9 days) and that of norfluoxetine averages about 7–9 days (range: 3–15 days). The plasma half-life of fluoxetine exhibits considerable interindividual variation, which may be related to genetic differences in the rate of *N*-demethylation of the drug in the liver. The absence of either a bimodal or trimodal distribution of clearance values suggests that the rate of such metabolism may be under polygenic control. The half-life of fluoxetine reportedly is prolonged (to approximately 4–5 days) after administration of multiple versus single doses, suggesting a nonlinear pattern of drug accumulation during long-term administration. Norfluoxetine appears to exhibit dose-proportional pharmacokinetics following multiple dosing, although limited data indicate that the rate of formation of the metabolite is decreased slightly once steady-state plasma concentrations have been achieved.

Following oral administration of single doses of fluoxetine in healthy individuals, total apparent plasma clearances of fluoxetine and norfluoxetine average approximately 346 mL/minute (range: 94–703 mL/minute) and 145 mL/minute (range: 61–284 mL/minute), respectively. Limited data suggest that plasma clearance of fluoxetine decreases by approximately 75% following multiple oral doses of the drug once steady-state plasma fluoxetine concentrations have been achieved. Plasma clearances of fluoxetine and norfluoxetine also reportedly are decreased in patients with chronic liver disease (e.g., cirrhosis). Evidence from single-dose studies indicates that clearances of the drug and its principal metabolite are not altered substantially in patients with renal impairment.

The exact metabolic fate of fluoxetine has not been fully elucidated. The drug appears to be metabolized extensively, probably in the liver, to norfluoxetine and several other metabolites. Norfluoxetine (desmethylfluoxetine), the principal metabolite, is formed by *N*-demethylation of fluoxetine, which may be under polygenic control. The potency and selectivity of norfluoxetine's serotonin-reuptake inhibiting activity appear to be similar to those of the parent drug. Both fluoxetine and norfluoxetine undergo conjugation with glucuronic acid in the liver, and limited evidence from animals suggests that both the parent drug and its principal metabolite also undergo *O*-dealkylation to form *p*-trifluoromethylphenol, which subsequently appears to be metabolized to hippuric acid.

Following oral administration, fluoxetine and its metabolites are excreted principally in urine. In healthy individuals, approximately 60% of an orally administered, radiolabeled dose of fluoxetine is excreted in urine within 35 days, with approximately 72.8% of excreted drug as unidentified metabolites, 10% as norfluoxetine, 9.5% as norfluoxetine glucuronide, 5.2% as fluoxetine glucuronide, and 2.5% as unchanged drug. Approximately 12% of the dose was eliminated in feces within 28 days following oral administration, but the relative proportion of unabsorbed versus absorbed drug that is excreted in feces (e.g., via biliary elimination) is not known.

The effect of age on the elimination of fluoxetine has not been fully elucidated. Single-dose studies suggest that the pharmacokinetics of fluoxetine in healthy geriatric individuals do not differ substantially from those in younger adults. However, because the drug has a relatively long half-life and nonlinear disposition following multiple-dose administration, single-dose studies are not sufficient to exclude the possibility of altered pharmacokinetics in geriatric individuals, particularly those with systemic disease and/or in those receiving multiple medications concomitantly. The elimination half-lives of fluoxetine and norfluoxetine may be prolonged in patients with hepatic impairment. Following a single oral dose of the drug in patients with hepatic cirrhosis, the elimination half-lives of fluoxetine and norfluoxetine reportedly average approximately 7 and 12 days, respectively.

The elimination half-lives of fluoxetine and norfluoxetine do not appear to be altered substantially in patients with renal impairment following oral administration of single doses of the drug, although multiple-dose studies are needed to determine whether accumulation of the parent drug and/or its metabolites occurs during long-term therapy in such patients.

Fluoxetine and norfluoxetine are not removed substantially by hemodialysis. Because of the large volume of distribution and extensive protein binding of the drug and its principal metabolite, peritoneal dialysis, forced diuresis, hemoperfusion, and/or exchange transfusion also are likely to be ineffective in removing substantial amounts of fluoxetine and norfluoxetine from the body.

Chemistry and Stability

■ **Chemistry** Fluoxetine, a selective serotonin-reuptake inhibitor (SSRI) antidepressant, is a phenylpropylamine-derivative. The drug differs structurally from other selective serotonin-reuptake inhibitor antidepressants (e.g., citalo-

pram, paroxetine, sertraline) and also differs structurally and pharmacologically from other currently available antidepressant agents (e.g., tricyclic antidepressants, monoamine oxidase inhibitors).

Fluoxetine contains a *p*-trifluoromethyl substituent that appears to contribute to the drug's high selectivity and potency for inhibiting serotonin reuptake, possibly as a result of its electron-withdrawing effect and lipophilicity. The commercially available drug is a racemic mixture of 2 optical isomers. Limited in vivo and in vitro data suggest that the pharmacologic activities of the optical isomers do not differ substantially, although the dextrorotatory isomer appears to have slightly greater serotonin-reuptake inhibiting activity and a longer duration of action than the levorotatory isomer.

Fluoxetine is commercially available as the hydrochloride salt, which occurs as a white to off-white crystalline solid and has a solubility of 14 mg/mL in water.

■ **Stability** Fluoxetine hydrochloride capsules and the oral solution should be stored in tight, light-resistant containers, both at 15–30°C. Fluoxetine tablets and delayed-release capsules should be stored at 15–30°C.

Preparations

Excipients in commercially available drug preparations may have clinically important effects in some individuals; consult specific product labeling for details.

Fluoxetine Hydrochloride

Oral		
Capsules	10 mg (of fluoxetine)*	**Fluoxetine Hydrochloride Capsules**
		Prozac® Pulvules®, Dista
		Sarafem® Pulvules®, Lilly
	20 mg (of fluoxetine)*	**Fluoxetine Hydrochloride Capsules**
		Prozac® Pulvules®, Dista
		Sarafem® Pulvules®, Lilly
	40 mg (of fluoxetine)*	**Fluoxetine Hydrochloride Capsules**
		Prozac® Pulvules®, Dista
Capsules, delayed-release (containing enteric-coated pellets)	90 mg (of fluoxetine)	**Prozac® Weekly**, Dista
Solution	20 mg (of fluoxetine) per 5 mL*	**Fluoxetine Hydrochloride Oral Solution**
		Prozac®, Dista
Tablets	10 mg (of fluoxetine)*	**Fluoxetine Hydrochloride Tablets** (scored)
	20 mg (of fluoxetine)*	**Fluoxetine Hydrochloride Tablets**

*available from one or more manufacturer, distributor, and/or repackager by generic (nonproprietary) name

Fluoxetine Hydrochloride Combinations

Oral		
Capsules	25 mg (of fluoxetine) with Olanzapine 6 mg	**Symbyax®**, Lilly
	25 mg (of fluoxetine) with Olanzapine 12 mg	**Symbyax®**, Lilly
	50 mg (of fluoxetine) with Olanzapine 6 mg	**Symbyax®**, Lilly
	50 mg (of fluoxetine) with Olanzapine 12 mg	**Symbyax®**, Lilly

†Use is not currently included in the labeling approved by the US Food and Drug Administration

Fluvoxamine Maleate

■ Fluvoxamine maleate, a selective serotonin-reuptake inhibitor (SSRI), is an antidepressant.

Uses

■ **Obsessive-Compulsive Disorder** Fluvoxamine is used in the treatment of obsessive-compulsive disorder when obsessions or compulsions cause marked distress, are time-consuming, or interfere substantially with social or occupational functioning. Efficacy of fluvoxamine for the management of obsessive-compulsive disorder has been established by controlled studies of 10 weeks' duration principally in outpatient settings. In a limited number of clinical studies in patients with moderate to severe obsessive-compulsive disorder, fluvoxamine was more effective than placebo in reducing the severity of symptoms associated with this disorder. In the studies used to establish efficacy, a positive clinical response (much or very much improved on the Clinical Global Impressions scale) occurred in 43 or 12% of patients receiving fluvoxamine or placebo, respectively. In these studies, no age- or gender-related differences in efficacy were noted. Results from a limited number of comparative studies suggest that fluvoxamine is as effective as clomipramine in the management of obsessive-compulsive disorder. Like fluoxetine and clomipramine, fluvoxamine reduces but does not eliminate obsessions and compulsions. Therapeutic response to fluvoxamine in patients with obsessive-compulsive disorder generally is evident within 2–3 weeks, but may not be maximal until several months after beginning therapy with the drug. The efficacy of fluvoxamine for long-term use (i.e., longer than 10 weeks) has not been established in placebo-controlled studies, but the drug has been used in some patients for prolonged periods (e.g., reportedly up to 8 years) without apparent loss of clinical effect. If fluvoxamine is used for extended periods, the need for continued therapy should be reassessed periodically.

As with other antidepressants, the possibility that fluvoxamine may precipitate hypomanic or manic attacks in patients with bipolar or other major affective disorders should be considered.

■ **Bulimia Nervosa** Fluvoxamine has been used in the treatment of bulimia nervosa†. In one double-blind placebo-controlled study in patients with bulimia nervosa, maintenance therapy with fluvoxamine following an inpatient treatment program resulted in an attenuated relapse rate compared with treatment with placebo. For further information on use of antidepressants in the treatment of bulimia nervosa, see Bulimia Nervosa under Uses: Eating Disorders, in Fluoxetine Hydrochloride 28:16.04.20.

Dosage and Administration

■ **Administration** Fluvoxamine maleate is administered orally. Dosages of 100 mg daily or less in adults or 50 mg or less in pediatric patients generally are given as a single daily dose at bedtime; higher dosages generally are given as 2 divided doses, either as equally divided doses or as unequal doses with the larger dose given at bedtime. Since food does not appear to affect GI absorption of fluvoxamine maleate, the drug generally can be administered without regard to meals.

Patients receiving fluvoxamine should be monitored for possible worsening of depression, suicidality, or unusual changes in behavior, especially at the beginning of therapy or during periods of dosage adjustment. (See Suicidality Precautions under Dosage and Administration: Dosage.)

Fluvoxamine should *not* be used concomitantly with thioridazine. In addition, fluvoxamine should *not* be used concurrently with alosetron, astemizole (no longer commercially available in the US), cisapride, pimozide, terfenadine (no longer commercially available in the US), or tizanidine. For additional information on potentially serious drug interactions that may occur between selective serotonin-reuptake inhibitors such as fluvoxamine and these agents, see Drug Interactions in Fluoxetine Hydrochloride 28:16.04.20.

Risk of Serotonin Syndrome The development of potentially life-threatening serotonin syndrome may occur with fluvoxamine therapy, particularly during concomitant administration of other serotonergic drugs such as other selective serotonin-reuptake inhibitors (SSRIs), selective serotonin- and norepinephrine-reuptake inhibitors (SNRIs), selective serotonin (5-hydroxytryptamine; 5-HT) type 1 agonists used as antimigraine agents (also called triptans), drugs that impair the metabolism of serotonin (e.g., monoamine oxidase [MAO] inhibitors), tramadol, or tryptophan (a serotonin precursor) supplements. Therefore, patients should be cautioned about the potential risk of serotonin syndrome when fluvoxamine is given concurrently with other serotonergic agents. Symptoms of serotonin syndrome may include mental status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g., hyperreflexia, incoordination), and/or GI symptoms (e.g., nausea, vomiting, diarrhea).

Serious (sometimes fatal) adverse reactions, possibly related to serotonin syndrome, have been reported in patients who received an MAO inhibitor during or after SSRI therapy. Therefore, concomitant use of fluvoxamine and MAO inhibitors is contraindicated, and it is recommended that at least 2 weeks elapse between discontinuance of an MAO inhibitor and initiation of fluvoxamine and vice versa.

If concurrent therapy with fluvoxamine and an SSRI, SNRI, or 5-HT_1 receptors agonist ("triptan") is clinically warranted, careful observation of the patient is recommended, particularly during treatment initiation, increases in dosage, or following the addition of another serotonergic drug. In addition, clinicians should assess the potential risks and benefits of concurrent therapy with fluvoxamine and triptans prior to prescribing these drugs concurrently. Concurrent use of SSRIs with serotonin precursors (such as tryptophan supplements) is not recommended. For additional information on serotonin syndrome, see Drug Interactions: Drugs Associated with Serotonin Syndrome, in the Monoamine Oxidase Inhibitors General Statement 28:16.04.12 and see Drug Interactions: Drugs Associated with Serotonin Syndrome, in Fluoxetine Hydrochloride 28:16.04.20.

■ **Dosage** ***Obsessive-Compulsive Disorder*** **Adult Dosage.** For the management of obsessive-compulsive disorder in adults, the recommended initial dosage of fluvoxamine maleate is 50 mg at bedtime. Based on the tolerance

Fluoxetine Hydrochloride

Dosing & Indications

- **Adult Dose**

  - dose change: clinical effect may not be evident for several weeks due to the long elimination half-life of fluoxetine and its major active metabolite, affecting dose titration and withdrawal from therapy
  - discontinuing treatment: gradually reduce dose to avoid withdrawal symptoms; if intolerable symptoms develop, consider resuming therapy at the previously prescribed dose and taper at a slower rate
  - MAOI use: discontinue MAOIs intended to treat psychiatric disorders at least 14 days prior to initiation of fluoxetine; at least 5 weeks should elapse after fluoxetine discontinuation before an MAOI is initiated; if urgent treatment with linezolid or IV methylene blue is required, immediately stop fluoxetine and closely monitor the patient for 5 weeks or until 24 hours after the last dose, whichever comes first; fluoxetine may be resumed 24 hours after the last dose of linezolid or IV methylene blue
  - Bulimia nervosa: (delayed-release capsule, Pulvule(R), solution) 60 mg ORALLY once daily in the morning; may initiate at a lower dose and titrate up; doses greater than 60 mg/day have not been evaluated
  - Depressed bipolar I disorder, In combination with olanzapine: (delayed-release capsule, Pulvule(R)) initial, 20 mg ORALLY once daily in the evening in combination with olanzapine 5 mg
  - Depressed bipolar I disorder, In combination with olanzapine: (delayed-release capsule, Pulvule(R)) titrate to clinical effect and tolerability within the dose range, fluoxetine 20 to 50 mg/olanzapine 5 to 12.5 mg ORALLY once daily each evening; safety of doses greater than fluoxetine 75 mg/olanzapine 18 mg has not been established
  - Major depressive disorder: (delayed-release capsule, Pulvule(R), solution) initial, 20 mg ORALLY once daily in the morning
  - Major depressive disorder: (delayed-release capsule, Pulvule(R), solution) maintenance, may increase daily dose after several weeks if inadequate response (MAX 80 mg/day) OR 90 mg ORALLY once a week (Weekly(TM) capsule), starting 7 days after the last daily dose of 20 mg
  - Major depressive disorder, Treatment resistant, in combination with olanzapine: (delayed-release capsule, Pulvule(R)) initial, 20 mg ORALLY once daily in the evening in combination with olanzapine 5 mg
  - Major depressive disorder, Treatment resistant, in combination with olanzapine: (delayed-release capsule, Pulvule(R)) titrate to clinical effect and tolerability within the dose range, fluoxetine 20 to 50 mg/olanzapine 5 to 20 mg ORALLY once daily each evening; safety of doses greater than fluoxetine 75 mg/olanzapine 18 mg has not been established
  - Obsessive-compulsive disorder: (delayed-release capsule, Pulvule(R), solution) initial, 20 mg ORALLY once daily in the morning
  - Obsessive-compulsive disorder: (delayed-release capsule, Pulvule(R), solution) maintenance, 20 to 60 mg ORALLY once daily (single dose in morning, or 2 divided doses morning and noon); after several weeks if inadequate response may increase to MAX 80 mg/day
  - Panic disorder: (delayed-release capsule, Pulvule(R), solution) initial, 10 mg ORALLY once daily for 1 week, should increase to 20 mg/day; further dosage increases may be considered after several weeks if inadequate clinical response; doses greater than 60 mg/day have not been evaluated
  - Premenstrual dysphoric disorder: (Sarafem(R) tablets) 20 mg ORALLY once daily continuously OR 20 mg ORALLY once daily intermittently (start 14 days prior to the anticipated onset of menstruation and continue daily through the first full day of menses); maximum dosage 80 mg daily

- **Pediatric Dose**

  - dose change: clinical effect may not be evident for several weeks due to the long elimination half-life of fluoxetine and its major active metabolite, affecting dose titration and withdrawal from therapy
  - discontinuing treatment: gradually reduce dose to avoid withdrawal symptoms; if intolerable

symptoms develop, consider resuming therapy at the previously prescribed dose and taper at a slower rate
- MAOI use: discontinue MAOIs intended to treat psychiatric disorders at least 14 days prior to initiation of fluoxetine; at least 5 weeks should elapse after fluoxetine discontinuation before an MAOI is initiated; if urgent treatment with linezolid or IV methylene blue is required, immediately stop fluoxetine and closely monitor the patient; fluoxetine may be resumed 24 hours after the last dose of linezolid or IV methylene blue
- safety and effectiveness not established in pediatric patients younger than 8 years (major depressive disorder) and younger than 7 years (obsessive-compulsive disorder); when used concomitantly with olanzapine, safety and efficacy in children younger than 10 years for depressive episodes associated with bipolar I disorder not established; safety and effectiveness not established for other indications in pediatric patients
- Depressed bipolar I disorder, In combination with olanzapine: (10 to 17 years; delayed-release capsule, Pulvule(R)) initial, 20 mg ORALLY once daily in the evening in combination with olanzapine 2.5 mg
- Depressed bipolar I disorder, In combination with olanzapine: (10 to 17 years; delayed-release capsule, Pulvule(R)) titrate to clinical effect and tolerability; safety of doses greater than fluoxetine 50 mg/olanzapine 12 mg has not been established
- Major depressive disorder: adolescents and children 8 years or older (delayed-release capsule, Pulvule(R), solution), 10 or 20 mg ORALLY once daily; may initiate with 10 mg/day for 1 week, should increase to 20 mg/day
- Major depressive disorder: lower-weight children 8 years or older (delayed-release capsule, Pulvule(R), solution), initial, 10 mg ORALLY once daily, if insufficient clinical response after several weeks, consider increasing to 20 mg/day
- Obsessive-compulsive disorder: adolescents and children 7 years or older (delayed-release capsule, Pulvule(R), solution), initial, 10 mg ORALLY once daily for 2 weeks; should increase dose to 20 mg ORALLY once daily; recommended dose range, 20 to 60 mg daily
- Obsessive-compulsive disorder: lower-weight children 7 years or older (delayed-release capsule, Pulvule(R), solution), initiate at 10 mg ORALLY once daily; may increase dose after several weeks if inadequate response; recommended dose range, 20 to 30 mg daily; no experience with doses greater than 60 mg/day

- **Dose Adjustments**

  - renal impairment: dosage adjustments are not routinely necessary
  - renal dialysis: dosage adjustments are not routinely necessary
  - hepatic impairment: a lower dose or less frequent dosage schedule is recommended
  - geriatric: a lower dose or less frequent dosage schedule is recommended
  - concomitant olanzapine: initial dose, olanzapine 2.5 to 5 mg/fluoxetine 20 mg; increase dose cautiously if predisposition to hypotensive reaction, hepatic impairment, slow metabolizers of either drug in combination (female gender, geriatric, nonsmoking status), or those who are pharmacodynamically sensitive to olanzapine; dose escalate with caution

- **FDA Labeled Indications**

  - Bulimia nervosa

    ◇ FDA Approval:
    Adult, yes delayed-release capsule, Pulvule(R), solution only
    Pediatric, no

    ◇ Efficacy:
    Adult, Effective
    Pediatric, Evidence is inconclusive

    ◇ Strength of Recommendation:
    Adult, Class IIa
    Pediatric, Class IIb

- Strength of Evidence:
  Adult, Category B
  Pediatric, Category B

- Depressed bipolar I disorder, In combination with olanzapine

  - FDA Approval:
    Adult, yes delayed-release capsule, Pulvule(R) only
    Pediatric, yes 10 to 17 years of age; delayed-release capsule, Pulvule(R) only

  - Efficacy:
    Adult, Effective
    Pediatric, Evidence favors efficacy

  - Strength of Recommendation:
    Adult, Class IIa
    Pediatric, Class IIb

  - Strength of Evidence:
    Adult, Category B
    Pediatric, Category B

- Major depressive disorder

  - FDA Approval:
    Adult, yes delayed-release capsule, Pulvule(R), solution, Weekly(TM) capsule only
    Pediatric, yes 8 years or older; delayed-release capsule, Pulvule(R), solution only

  - Efficacy:
    Adult, Effective
    Pediatric, Effective

  - Strength of Recommendation:
    Adult, Class IIa
    Pediatric, Class IIb

  - Strength of Evidence:
    Adult, Category B
    Pediatric, Category B

- Major depressive disorder, Treatment resistant, in combination with olanzapine

  - FDA Approval:
    Adult, yes delayed-release capsule, Pulvule(R) only
    Pediatric, no

  - Efficacy:
    Adult, Evidence favors efficacy

  - Strength of Recommendation:
    Adult, Class IIb

  - Strength of Evidence:
    Adult, Category B

- Obsessive-compulsive disorder
  - FDA Approval:
    Adult, yes delayed-release capsule, Pulvule(R), solution only
    Pediatric, yes 7 years or older; delayed-release capsule, Pulvule(R), solution only
  - Efficacy:
    Adult, Effective
    Pediatric, Effective
  - Strength of Recommendation:
    Adult, Class IIa
    Pediatric, Class IIa
  - Strength of Evidence:
    Adult, Category B
    Pediatric, Category B
- Panic disorder
  - FDA Approval:
    Adult, yes delayed-release capsule, Pulvule(R), solution only
    Pediatric, no
  - Efficacy:
    Adult, Effective
  - Strength of Recommendation:
    Adult, Class IIa
  - Strength of Evidence:
    Adult, Category B
- Premenstrual dysphoric disorder
  - FDA Approval:
    Adult, yes Sarafem(R) tablets only
    Pediatric, no
  - Efficacy:
    Adult, Effective
  - Strength of Recommendation:
    Adult, Class IIa
  - Strength of Evidence:
    Adult, Category B

- **Non-FDA Labeled Indications**
  - Body dysmorphic disorder
    - FDA Approval:
      Adult, no
      Pediatric, no

- Efficacy:
  Adult, Evidence favors efficacy
- Strength of Recommendation:
  Adult, Class IIb
- Strength of Evidence:
  Adult, Category B

- Cancer - Depression
  - FDA Approval:
    Adult, no
    Pediatric, no
  - Efficacy:
    Adult, Evidence favors efficacy
  - Strength of Recommendation:
    Adult, Class IIb
  - Strength of Evidence:
    Adult, Category B
- Depression - Diabetes mellitus
  - FDA Approval:
    Adult, no
    Pediatric, no
  - Efficacy:
    Adult, Evidence favors efficacy
  - Strength of Recommendation:
    Adult, Class IIb
  - Strength of Evidence:
    Adult, Category B
- Dysthymia
  - FDA Approval:
    Adult, no
    Pediatric, no
  - Efficacy:
    Adult, Evidence favors efficacy
  - Strength of Recommendation:
    Adult, Class IIb
  - Strength of Evidence:
    Adult, Category B
- Fibromyalgia

- FDA Approval:
  Adult, no
  Pediatric, no

- Efficacy:
  Adult, Evidence favors efficacy

- Strength of Recommendation:
  Adult, Class IIb

- Strength of Evidence:
  Adult, Category B

- Hot sweats

  - FDA Approval:
    Adult, no
    Pediatric, no

  - Efficacy:
    Adult, Evidence favors efficacy

  - Strength of Recommendation:
    Adult, Class IIb

  - Strength of Evidence:
    Adult, Category B

- Posttraumatic stress disorder

  - FDA Approval:
    Adult, no
    Pediatric, no

  - Efficacy:
    Adult, Evidence favors efficacy

  - Strength of Recommendation:
    Adult, Class IIb

  - Strength of Evidence:
    Adult, Category B

- Raynaud's phenomenon

  - FDA Approval:
    Adult, no
    Pediatric, no

  - Efficacy:
    Adult, Evidence favors efficacy

  - Strength of Recommendation:
    Adult, Class IIb

  - Strength of Evidence:

Adult, Category B

Black Box WARNING

Antidepressants increased the risk of suicidal thoughts and behavior in children, adolescents, and young adults. Monitor patients of all ages for clinical worsening and emergence of suicidal thoughts and behaviors. Prozac(R) is not approved for use in children less than 7 years of age. When using Prozac and olanzapine in combination, also refer to the Boxed Warning section of the package insert for Symbyax(R) .Antidepressants increased the risk of suicidal thinking and behavior in children, adolescents, and young adults in short-term studies with major depressive disorder (MDD) and other psychiatric disorders. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared with placebo in adults older than 24 years, and there was a reduction in risk with antidepressants compared with placebo in adults aged 65 or older. This risk must be balanced with the clinical need. Monitor patients closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. PROZAC(R) is approved for use in pediatric patients with MDD and obsessive compulsive disorder (OCD) .Antidepressants increased the risk of suicidal thinking and behavior in children, adolescents, and young adults in short-term studies with major depressive disorder (MDD) and other psychiatric disorders. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared with placebo in adults older than 24 years, and there was a reduction in risk with antidepressants compared with placebo in adults aged 65 or older. This risk must be balanced with the clinical need. Monitor patients closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. SARAFEM(R) is not approved for use in pediatric patients.

Contraindications/Warnings

- **Contraindications**

  - concomitant use with an MAOI, including linezolid or IV methylene blue, or within 14 days of discontinuing an MAOI; at least 5 weeks should elapse after fluoxetine hydrochloride discontinuation before MAOI initiation; increased risk of serotonin syndrome
  - concomitant use of pimozide or thioridazine; risk of QT prolongation

- **Precautions**

  - suicidal ideation and behavior or worsening depression may occur; increased risk in children, adolescents, and young adults with major depressive and other psychiatric disorders during the first few months of therapy or following changes in dosage
  - abrupt withdrawal; serious discontinuation symptoms have been reported; gradual reduction in dose recommended
  - acute narrow-angle glaucoma or increased intraocular pressure; mydriasis has been reported
  - allergic reactions, including anaphylaxis, angioedema, and urticaria have been reported; in the case of rash, or other possibly allergic symptoms for which an alternative etiology cannot be identified, discontinue therapy
  - bipolar disorder; increased risk of precipitation of a mixed/manic episode with antidepressant treatment only
  - cirrhosis; dosage adjustment may be necessary
  - concomitant use with antipsychotics, antibiotics, antiarrhythmic drugs, and other drugs known to prolong the QT interval should be avoided
  - concomitant serotonergic drug use (serotonin precursors (tryptophan), SSRIs, serotonin-norepinephrine reuptake inhibitors); risk of serotonin syndrome, use is not recommended
  - concurrent illness; dosage adjustment may be necessary
  - diabetes, history of; increased risk of hypoglycemia
  - elderly; consider dosage adjustment
  - hepatic impairment; dosage adjustment recommended

- pregnancy; fetal harm has occurred with maternal use of SSRIs and serotonin norepinephrine reuptake inhibitors in the third trimester; consider risks versus benefits
- pulmonary events, including fibrosis, have been rarely reported
- QT prolongation, torsades de pointes, and ventricular arrhythmia, have been reported; monitoring recommended for patients at risk; discontinue use if signs or symptoms occur
- seizures, history of
- serotonin syndrome has been reported, including cases that are life-threatening, often with concurrent use with other serotonergic drugs (eg, triptans, tricyclic antidepressants, fentanyl, lithium, tramadol, buspirone, tryptophan, St John's wort), MAOIs (including methylene blue IV and linezolid), and other drugs that impair serotonin metabolism; monitoring recommended; discontinue use if suspected
- skin reactions, including serious cutaneous systemic illnesses (eg leukocytoclastic vasculitis, erythema multiforme, and lupuslike syndrome) with fatalities have been reported rarely; in the case of rash, or other possibly allergic symptoms for which an alternative etiology cannot be identified, discontinue therapy
- volume-depleted, elderly, or concurrent diuretic therapy; hyponatremia and syndrome of inappropriate antidiuretic hormone secretion (SIADH) has occurred with fluoxetine

- **Pregnancy Category**

  - Fluoxetine: C (FDA)
  - Fluoxetine: C (AUS)

- **Breast Feeding**

  - Fluoxetine: AAP: Drugs for which the effect on nursing infants is unknown but may be of concern.
  - Fluoxetine: Micromedex: Infant risk cannot be ruled out.

Drug Interactions

- **Contraindicated**

  - ◇ Bepridil (theoretical)
  - ◇ Cisapride (theoretical)
  - ◇ Clorgyline (theoretical)
  - ◇ Dronedarone (theoretical)
  - ◇ Furazolidone (theoretical)
  - ◇ Iproniazid (theoretical)
  - ◇ Isocarboxazid (theoretical)
  - ◇ Levomethadyl (theoretical)
  - ◇ Linezolid (probable)
  - ◇ Mesoridazine (theoretical)
  - ◇ Methylene Blue (theoretical)
  - ◇ Metoclopramide (theoretical)
  - ◇ Moclobemide (theoretical)
  - ◇ Nialamide (probable)
  - ◇ Pargyline (theoretical)
  - ◇ Phenelzine (theoretical)
  - ◇ Pimozide (probable)
  - ◇ Procarbazine (theoretical)
  - ◇ Rasagiline (theoretical)
  - ◇ Saquinavir (theoretical)
  - ◇ Selegiline (theoretical)
  - ◇ Sparfloxacin (theoretical)
  - ◇ Terfenadine (probable)
  - ◇ Thioridazine (probable)
  - ◇ Toloxatone (probable)

- ◇ Tranylcypromine (theoretical)
- ◇ Ziprasidone (theoretical)

- **Major**

  - ◇ Abciximab (probable)
  - ◇ Abiraterone Acetate (theoretical)
  - ◇ Acecainide (theoretical)
  - ◇ Aceclofenac (probable)
  - ◇ Acemetacin (probable)
  - ◇ Acenocoumarol (probable)
  - ◇ Ajmaline (theoretical)
  - ◇ Alfuzosin (theoretical)
  - ◇ Almotriptan (theoretical)
  - ◇ Amineptine (theoretical)
  - ◇ Amiodarone (theoretical)
  - ◇ Amisulpride (theoretical)
  - ◇ Amitriptyline (theoretical)
  - ◇ Amitriptylinoxide (theoretical)
  - ◇ Amoxapine (theoretical)
  - ◇ Amphetamine (theoretical)
  - ◇ Amtolmetin Guacil (probable)
  - ◇ Anagrelide Hydrochloride (theoretical)
  - ◇ Ancrod (probable)
  - ◇ Anisindione (probable)
  - ◇ Antithrombin III Human (probable)
  - ◇ Apixaban (theoretical)
  - ◇ Aprindine (theoretical)
  - ◇ Ardeparin (probable)
  - ◇ Argatroban (theoretical)
  - ◇ Arsenic Trioxide (theoretical)
  - ◇ Asenapine (theoretical)
  - ◇ Aspirin (probable)
  - ◇ Astemizole (theoretical)
  - ◇ Azimilide (theoretical)
  - ◇ Bedaquiline (theoretical)
  - ◇ Bivalirudin (probable)
  - ◇ Bretylium (theoretical)
  - ◇ Bromfenac (probable)
  - ◇ Brompheniramine (theoretical)
  - ◇ Bufexamac (probable)
  - ◇ Carbamazepine (probable)
  - ◇ Carvedilol (theoretical)
  - ◇ Celecoxib (probable)
  - ◇ Certoparin (probable)
  - ◇ Chloral Hydrate (theoretical)
  - ◇ Chloroquine (theoretical)
  - ◇ Chlorpheniramine (theoretical)
  - ◇ Chlorpromazine (theoretical)
  - ◇ Choline Salicylate (probable)
  - ◇ Cilostazol (probable)
  - ◇ Cinacalcet (theoretical)
  - ◇ Ciprofloxacin (theoretical)
  - ◇ Citalopram (theoretical)
  - ◇ Clarithromycin (theoretical)
  - ◇ Clomipramine (theoretical)
  - ◇ Clonixin (probable)
  - ◇ Clopidogrel (theoretical)

- Clozapine (established)
- Cobicistat (theoretical)
- Cocaine (theoretical)
- Codeine (theoretical)
- Crizotinib (theoretical)
- Cyclobenzaprine (probable)
- Dabigatran Etexilate Mesylate (theoretical)
- Dalteparin (probable)
- Danaparoid (probable)
- Defibrotide (probable)
- Dermatan Sulfate (probable)
- Desipramine (theoretical)
- Desirudin (probable)
- Desvenlafaxine (theoretical)
- Dexfenfluramine (theoretical)
- Dexibuprofen (probable)
- Dexketoprofen (probable)
- Dextroamphetamine (theoretical)
- Dextromethorphan (theoretical)
- Dibenzepin (theoretical)
- Diclofenac (probable)
- Dicumarol (probable)
- Diflunisal (probable)
- Dipyridamole (probable)
- Dipyrone (probable)
- Disopyramide (theoretical)
- Dofetilide (theoretical)
- Dolasetron (theoretical)
- Domperidone (theoretical)
- Donepezil (theoretical)
- Doxepin (theoretical)
- Droperidol (theoretical)
- Drotrecogin Alfa (theoretical)
- Duloxetine (probable)
- Ebastine (theoretical)
- Eletriptan (theoretical)
- Enflurane (theoretical)
- Enoxaparin (probable)
- Eptifibatide (probable)
- Erythromycin (theoretical)
- Escitalopram (theoretical)
- Etodolac (probable)
- Etofenamate (probable)
- Etoricoxib (probable)
- Felbinac (probable)
- Fenfluramine (theoretical)
- Fenoprofen (probable)
- Fentanyl (theoretical)
- Fepradinol (probable)
- Feprazone (probable)
- Flecainide (theoretical)
- Floctafenine (probable)
- Fluconazole (theoretical)
- Flufenamic Acid (probable)
- Fluphenazine (probable)
- Flurbiprofen (probable)
- Fluvoxamine (theoretical)
- Fondaparinux (probable)

- Foscarnet (theoretical)
- Frovatriptan (probable)
- Gatifloxacin (theoretical)
- Gemifloxacin (probable)
- Halofantrine (theoretical)
- Haloperidol (probable)
- Halothane (theoretical)
- Heparin (probable)
- Hydroquinidine (theoretical)
- Ibuprofen (probable)
- Ibuprofen Lysine (probable)
- Ibutilide (theoretical)
- Iloperidone (established)
- Imipramine (theoretical)
- Indomethacin (probable)
- Iobenguane I 123 (theoretical)
- Isoflurane (theoretical)
- Isradipine (theoretical)
- Ketoprofen (probable)
- Ketorolac (probable)
- Lapatinib (theoretical)
- Lepirudin (theoretical)
- Levofloxacin (theoretical)
- Levomilnacipran (theoretical)
- Lidoflazine (theoretical)
- Lofepramine (theoretical)
- Lorcaserin (theoretical)
- Lornoxicam (probable)
- Loxoprofen (probable)
- Lumefantrine (theoretical)
- Lumiracoxib (probable)
- Meclofenamate (probable)
- Mefenamic Acid (probable)
- Mefloquine (theoretical)
- Melitracen (theoretical)
- Meloxicam (probable)
- Meperidine (probable)
- Methadone (theoretical)
- Mexiletine (theoretical)
- Milnacipran (theoretical)
- Mirtazapine (probable)
- Mizolastine (theoretical)
- Morniflumate (probable)
- Moxifloxacin (theoretical)
- Nabumetone (probable)
- Nadroparin (probable)
- Naproxen (probable)
- Naratriptan (probable)
- Nefazodone (theoretical)
- Nepafenac (probable)
- Niflumic Acid (probable)
- Nilotinib (theoretical)
- Nimesulide (probable)
- Nortriptyline (theoretical)
- Octreotide (theoretical)
- Ondansetron (theoretical)
- Opipramol (theoretical)
- Oxaprozin (probable)

- Oxyphenbutazone (probable)
- Paliperidone (theoretical)
- Parecoxib (probable)
- Parnaparin (probable)
- Paroxetine (theoretical)
- Pazopanib (theoretical)
- Pentamidine (theoretical)
- Pentazocine (theoretical)
- Pentosan Polysulfate Sodium (probable)
- Perphenazine (theoretical)
- Phenindione (probable)
- Phenprocoumon (probable)
- Phenylbutazone (probable)
- Piketoprofen (probable)
- Pirmenol (theoretical)
- Piroxicam (probable)
- Posaconazole (theoretical)
- Prajmaline (theoretical)
- Pranoprofen (probable)
- Prasugrel (probable)
- Probucol (theoretical)
- Procainamide (theoretical)
- Prochlorperazine (theoretical)
- Proglumetacin (probable)
- Propafenone (probable)
- Propranolol (probable)
- Propyphenazone (probable)
- Proquazone (probable)
- Protein C, Human (theoretical)
- Protriptyline Hydrochloride (theoretical)
- Quetiapine (theoretical)
- Quinine (theoretical)
- Ranolazine (theoretical)
- Reviparin (probable)
- Rivaroxaban (theoretical)
- Rizatriptan (probable)
- Rofecoxib (probable)
- Salicylic Acid (probable)
- Salsalate (probable)
- Sematilide (theoretical)
- Sertindole (theoretical)
- Sertraline (theoretical)
- Sibutramine (probable)
- Sodium Phosphate (theoretical)
- Sodium Phosphate, Dibasic (theoretical)
- Sodium Phosphate, Monobasic (theoretical)
- Sodium Salicylate (probable)
- Sotalol (theoretical)
- Spiramycin (theoretical)
- St John's Wort (probable)
- Sulfamethoxazole (theoretical)
- Sulfinpyrazone (theoretical)
- Sulindac (probable)
- Sultopride (theoretical)
- Sumatriptan (probable)
- Sunitinib (theoretical)
- Tacrolimus (theoretical)
- Tamoxifen (theoretical)

- Tapentadol (theoretical)
- Tedisamil (theoretical)
- Telithromycin (theoretical)
- Tenoxicam (probable)
- Terbinafine (theoretical)
- Tetrabenazine (probable)
- Tianeptine (theoretical)
- Tiaprofenic Acid (probable)
- Ticagrelor (theoretical)
- Ticlopidine (probable)
- Timolol (theoretical)
- Tinzaparin (probable)
- Tirofiban (probable)
- Tolfenamic Acid (probable)
- Tolmetin (probable)
- Tramadol (probable)
- Trazodone (probable)
- Treprostinil Sodium (theoretical)
- Trifluoperazine (theoretical)
- Trimethoprim (theoretical)
- Trimipramine (theoretical)
- Tryptophan (probable)
- Valdecoxib (probable)
- Valproic Acid (theoretical)
- Vandetanib (theoretical)
- Vasopressin (theoretical)
- Vemurafenib (theoretical)
- Venlafaxine (theoretical)
- Vilazodone (theoretical)
- Voriconazole (theoretical)
- Warfarin (probable)
- Zolmitriptan (theoretical)
- Zotepine (theoretical)

- **Moderate**

  - Alprazolam (probable)
  - Bupropion (probable)
  - Buspirone (probable)
  - Cyproheptadine (probable)
  - Delavirdine (probable)
  - Digoxin (probable)
  - Fosphenytoin (probable)
  - Galantamine (probable)
  - Ginkgo (probable)
  - Lithium (established)
  - Nebivolol (established)
  - Phenytoin (probable)
  - Risperidone (probable)
  - Ritonavir (established)

Adverse Effects

- **COMMON**

  - Gastrointestinal: Diarrhea (8% to 18%), Indigestion (6% to 10%), Loss of appetite (3.8% to 17%), Nausea (12% to 29%), Xerostomia (4% to 12%)

- ◇ Neurologic: Asthenia (7% to 21%), Dizziness (2% to 11%), Insomnia (9% to 33%), Somnolence (5% to 17%), Tremor (3% to 13%)
- ◇ Psychiatric: Anxiety (3% to 15%), Feeling nervous (3% to 14%)
- ◇ Respiratory: Pharyngitis (3% to 11%), Rhinitis (16% to 23%)
- ◇ Other: Influenza-like symptoms (3% to 12%)

- **SERIOUS**

  - ◇ Cardiovascular: Prolonged QT interval
  - ◇ Dermatologic: Erythema multiforme
  - ◇ Endocrine metabolic: Hyponatremia
  - ◇ Hematologic: Bleeding
  - ◇ Immunologic: Anaphylactoid reaction
  - ◇ Neurologic: Seizure (0.2%)
  - ◇ Psychiatric: Depression, worsening, Mania, Suicidal thoughts, Suicide
  - ◇ Other: Serotonin syndrome

Name Info

- **US Trade Names**
  - Prozac
  - Prozac Weekly
  - Sarafem
  - Rapiflux
  - Selfemra
- **Class**
  - Antidepressant
  - Serotonin Reuptake Inhibitor
- **Regulatory Status**
  - RX
- **Generic Availability**
  - Yes

Mechanism of Action/Pharmacokinetics

- **Mechanism of Action**
  - Fluoxetine HCl is a psychotropic agent whose antidepressive, antiobsessive-compulsive, and antibulimic properties are attributed to its inhibition of serotonin uptake in neurons of the central nervous system. Binding to muscarinic, histaminergic, alpha(1)-adrenergic and other receptors in the brain is much less compared to classical tricyclic antidepressants.
- **Pharmacokinetics**
  - **Absorption**
    - ◇ Oral: time to peak concentration, 6 h to 8 h
    - ◇ Effect of food: not significant

- **Distribution**
  - ◇ Protein binding: approximately 94.5%
- **Metabolism**
  - ◇ Hepatic; extensive P450 CYP2D6, demethylation
  - ◇ Active metabolite: norfluoxetine
- **Excretion**
  - ◇ Renal: as inactive metabolites
  - ◇ Dialyzable: no
- **Elimination Half Life**
  - ◇ 4 days to 6 days
  - ◇ liver cirrhosis: 7.6 days mean
  - ◇ Norfluoxetine: 9.3 days
  - ◇ Norfluoxetine, liver cirrhosis: 12 days mean

Administration/Monitoring

- **Administration**
- Oral
  - ◇ Oral: give with or without food
- **Monitoring**
- reduction or resolution of signs and symptoms of bulimia nervosa, major depressive disorder, panic disorder, or obsessive-compulsive disorder is indicative of efficacy
- clinical worsening of depression, suicidality, or unusual changes in behavior; particularly during the initial few months of therapy or at times of dose changes, either increases or decreases
- signs and symptoms of serotonin syndrome
- bipolar disorder risk factor (ie, personal and family history of suicide, bipolar disorder, and depression) screening; before therapy initiation
- occurrence of mania or hypomania; during treatment
- weight changes; during therapy
- ECG in patients with risk factors for QT prolongation and ventricular arrhythmia; at baseline and periodically during treatment
- height and weight in pediatric patients; periodically during therapy

How Supplied

- Generic
  - ◇ Oral Capsule: 10 MG, 20 MG, 40 MG
  - ◇ Oral Capsule, Delayed Release: 90 MG
  - ◇ Oral Solution: 20 MG/5 ML
  - ◇ Oral Syrup: 20 MG/5 ML
  - ◇ Oral Tablet: 10 MG, 20 MG
- Fluoxetine
  - ◇ Oral Tablet: 60 MG
- Prozac

- Oral Capsule: 10 MG, 20 MG, 40 MG

- Prozac Weekly
  - Oral Capsule, Delayed Release: 90 MG

- Sarafem
  - Oral Capsule: 10 MG
  - Oral Tablet: 10 MG, 20 MG

Toxicology

- **Clinical Effects**

  - FLUOXETINE
    - USES: Fluoxetine is a selective serotonin reuptake inhibitor (SSRI) and is used for depressive disorder, obsessive-compulsive disorder, panic attack, and bulimia nervosa. PHARMACOLOGY: Fluoxetine and its active metabolite norfluoxetine inhibit reuptake of serotonin from the synaptic cleft, therefore increasing serotonergic neurotransmission. TOXICOLOGY: Severe toxicity is not common, but may develop from excessive serotonergic effects, particularly when fluoxetine is ingested with another agent that increases CNS serotonin. EPIDEMIOLOGY: Poisoning with fluoxetine and other SSRIs are common. Life threatening toxicity is rare, and patients usually recover without sequelae. MILD TO MODERATE POISONING: Somnolence, dizziness, nausea, and vomiting are common; QTc prolongation may occur even in therapeutic or mild overdose. SEVERE POISONING: Significant CNS depression, seizures, and QTc prolongation. Ventricular dysrhythmias have rarely been reported. Serotonin toxicity (autonomic instability, altered mental status, seizures, muscle rigidity, hyperreflexia, and hyperthermia) may occur; however most reported cases involve patients using multiple serotonergic agents. ADVERSE EFFECTS: Somnolence, dizziness, insomnia, nervousness, headache, nausea, vomiting, and diarrhea are often reported. Hyponatremia, due to inappropriate secretion of antidiuretic hormone (SIADH), may be observed.

- **Treatment of Exposure**

  - FLUOXETINE

    - Support: MANAGEMENT OF MILD TO MODERATE TOXICITY: Primarily supportive care; a single dose of activated charcoal may be helpful in patients presenting shortly after ingestion. MANAGEMENT OF SEVERE TOXICITY: Consider a single dose of activated charcoal if patients present early after ingestion. In case of significant CNS depression, perform orotracheal intubation for airway protection prior to giving charcoal. Use primarily benzodiazepines for serotonin toxicity. In case of autonomic instability, severe muscle rigidity, and significant hyperthermia consider intubation and muscle paralysis.
    - Decontamination: PREHOSPITAL: GI decontamination is not recommended because of potential for somnolence and seizures. HOSPITAL: Single dose activated charcoal if recent, substantial ingestion, and patient is able to protect airway.
    - Airway management: Early orotracheal intubation in patients with signs of severe intoxication (CNS depression, seizures, severe serotonin toxicity).
    - Antidote: None.
    - Seizure: Use IV benzodiazepines or barbiturates as needed.
    - Serotonin syndrome: Treat with benzodiazepines. In severe cases cyproheptadine is sometimes used. Cyproheptadine, Adult: 12 mg orally initially followed by 2 mg every 2 hours if symptoms persist, maximum 32 mg/day, maintenance dose 8 mg every 6 hours. Pediatric: 0.25 mg/kg/day divided every 6 hours, maximum 12 mg/day.
    - Monitoring of patient: Monitor vital signs and mental status. Obtain an ECG and institute continuous cardiac monitoring in patients with moderate to severe toxicity (CNS depression, seizures, serotonin toxicity). Monitor serum electrolytes and creatinine phosphokinase

concentrations in patients with seizures or prolonged CNS depression. Fluoxetine plasma levels are not clinically useful or widely available. No specific lab work is needed in most patients.
- ◇ Enhanced elimination procedure: There is no role for repeat-dose activated charcoal, hemodialysis or hemoperfusion.
- ◇ Patient disposition: HOME CRITERIA: Children and adults with mild symptoms (eg, vomiting, mydriasis, diaphoresis, mild somnolence) with inadvertent ingestions of up to 100 mg fluoxetine can be managed at home. A patient on chronic fluoxetine therapy may be managed at home if there are only mild symptoms, the ingestion is inadvertent and less than 5 times that patient's single therapeutic dose. OBSERVATION CRITERIA: Any patient who overdoses in suicidal attempt or who develops more than mild symptoms should be sent to a healthcare facility for evaluation and treatment. For fluoxetine naive patients with ingestion more than 100 mg and for patients on chronic fluoxetine therapy with an ingestion of more than five times that patient's single therapeutic dose, prompt referral to a healthcare facility is necessary for evaluation and treatment. Patients should be observed for 6 hours. ADMISSION CRITERIA: Patients with persistent mental status changes, seizures or dysrhythmias should be admitted. CONSULT CRITERIA: Consult a poison center or medical toxicologist for assistance in decision making whether or not admission is advisable, managing patients with severe toxicity (CNS depression, seizures, serotonin toxicity), or in whom the diagnosis is not clear.

- **Range of Toxicity**

- FLUOXETINE
  - ◇ TOXICITY: Acute ingestion of up to 100 mg is not expected to cause toxicity. Expect mild toxicity in fluoxetine naive patients after ingestion of more than 100 mg. Adding fluoxetine to an established therapy with serotonergic agents may lead to serotonin toxicity. There have been rare reports of fatalities to fluoxetine alone. THERAPEUTIC DOSE: ADULTS: Bulimia nervosa: 20 to 60 mg orally once daily. Depression: 20 to 80 mg orally once daily. Begin with 20 mg and titrate dose slowly within weeks. CHILDREN (more than 7 years): Depression: 10 to 40 mg once daily. Begin with 10 mg and titrate dose within weeks.

Clinical Teaching

- Instruct patient to report anxiety, panic attacks, worsening depression, suicidal ideation, or unusual changes in behavior, especially at initiation of therapy or with dose changes.
- Counsel patient to report symptoms of QT prolongation and ventricular arrhythmias (Torsade de pointes) .
- Advise patient to avoid activities requiring mental alertness or coordination until drug effects are realized.
- Drug may cause sweating, weight loss, dyspepsia, anorexia, nausea, asthenia, insomnia, tremor, abnormal ejaculation, or impotence.
- Counsel patient to report symptoms of serotonin syndrome (agitation, confusion, diaphoresis, hallucinations, hyperreflexia) .
- Advise patient to report abnormal bruising or bleeding.
- Tell patient to report a skin rash, with or without systemic symptoms (fever, edema, pulmonary effects), as drug may cause a serious cutaneous systemic illness.
- Instruct diabetic patients to monitor for symptoms of hypoglycemia and report any changes in glycemic control.
- Advise patient against sudden discontinuation of drug.
- Warn patient to limit alcohol use with this drug.

Last Modified: September 04, 2013

Images & Imprints

Ingredients: Fluoxetine Hydrochloride (90 MG)
Color: Dark Green; Clear
Shape: Capsule-shape

Pattern: Two-toned
Imprint: Lilly; 3004 90mg
NDC: 00002-3004-75, 52959-0638-04

Ingredients: Fluoxetine Hydrochloride (10 MG)
Color: Purple
Shape: Capsule-shape
Pattern: Solid
Imprint: LILLY 3210/10MG
NDC: 00002-3210-45, 00430-0435-14

Ingredients: Fluoxetine Hydrochloride (20 MG)
Color: Pink; Purple
Shape: Capsule-shape
Imprint: LILLY 3220/20 MG
NDC: 00002-3220-45, 00430-0436-14

Ingredients: Fluoxetine Hydrochloride (10 MG)
Color: Green
Shape: Oval
Pattern: Solid
Imprint: PROZAC 10
NDC: 00002-4006-02, 00002-4006-30

Ingredients: Fluoxetine Hydrochloride (10 MG)
Color: Purple
Shape: Capsule-shape
Pattern: Solid
Imprint: 93 7225
NDC: 00093-7225-28

Ingredients: Fluoxetine Hydrochloride (20 MG)
Color: Off-White; Purple
Shape: Capsule-shape
Pattern: Two-toned
Imprint: 93 7226
NDC: 00093-7226-28

Ingredients: Fluoxetine Hydrochloride (40 MG)
Color: Light Blue
Shape: Capsule-shape
Pattern: Solid
Imprint: LOGO 4346(Logo resembles an hourglass.); 40mg
NDC: 00172-4346-10, 00172-4346-46, 00172-4346-60, 00172-4346-70

Ingredients: Fluoxetine Hydrochloride (10 MG)
Color: Light Blue; White
Shape: Capsule-shape
Pattern: Two-toned
Imprint: LOGO(Ivax LOGO is modified hourglass); 4363 10 mg(4363 on cap and 10 mg on body in black ink)
NDC: 00172-4363-10, 00172-4363-60, 00172-4363-70, 00172-4363-80, 49999-0362-90

Ingredients: Fluoxetine Hydrochloride (20 MG)
Color: White
Shape: Capsule-shape
Pattern: Banded
Imprint: PLIVA 648(The capsule is printed PLIVA 648 in green band on cap only.)
NDC: 00555-0877-04, 00555-0877-05, 42254-0235-30, 42254-0235-60, 42254-0235-90, 50111-0648-01, 50111-0648-02, 50111-0648-03, 50111-0648-44, 54569-5291-01, 55048-0230-30, 55048-0230-60, 55048-0230-90

Ingredients: Fluoxetine Hydrochloride (10 MG)
Color: Green
Shape: Capsule-shape
Pattern: Solid
Imprint: DISTA 3104 PROZAC 10 MG
NDC: 00777-3104-02, 00777-3104-07, 00777-3104-82, 54868-3033-02

Ingredients: Fluoxetine Hydrochloride (20 MG)
Color: Green; Off-White
Shape: Capsule-shape
Pattern: Two-toned
Imprint: Prozac 20mg; DISTA 3105
NDC: 00777-3105-02, 00777-3105-07, 00777-3105-30, 00777-3105-33, 00777-3105-82, 16590-0843-90, 68115-0719-00, 68115-0719-30

Ingredients: Fluoxetine Hydrochloride (40 MG)
Color: Green; Orange
Shape: Capsule-shape
Pattern: Two-toned
Imprint: PROZAC 40mg; DISTA 3107
NDC: 00777-3107-30, 54868-4394-00

Ingredients: Fluoxetine Hydrochloride (20 MG/5 ML)

Flavor: Mint
NDC: 00777-5120-58

Ingredients: Fluoxetine Hydrochloride (20 MG)
Color: White
Shape: Capsule-shape
Pattern: Banded
Imprint: PLIVA 648
NDC: 00904-5785-61

Ingredients: Fluoxetine Hydrochloride (10 MG)
Shape: Capsule-shape
Pattern: Banded
Imprint: PLIVA 647
NDC: 16590-0099-30, 50111-0647-02, 55045-2907-06, 55045-2907-08, 63629-1609-03, 63629-1609-04, 65162-0176-10, 65162-0176-11, 66336-0844-90, 67046-0210-30

Ingredients: Fluoxetine Hydrochloride (10 MG)
Color: White
Shape: Oval
Pattern: Solid
Imprint: G; FL;10
NDC: 21695-0320-60, 35356-0649-30, 45865-0378-30, 45865-0378-51, 45865-0378-60, 45865-0378-90, 49884-0734-01, 49884-0734-10, 49884-0734-11, 49884-0734-82, 49999-0362-14, 49999-0362-30, 52959-0991-30, 54868-4560-00, 54868-4560-02, 66267-0576-30

Ingredients: Fluoxetine Hydrochloride (20 MG)
Color: White
Shape: Oval
Pattern: Solid
Imprint: G; FL;20
NDC: 33261-0803-30, 33261-0803-60, 33261-0803-90, 45865-0535-30, 45865-0535-51, 45865-0535-60, 45865-0535-90, 49884-0735-01, 49884-0735-10, 49884-0735-11, 49884-0735-82

Ingredients: Fluoxetine Hydrochloride (40 MG)
Color: Light Green; Light Orange
Shape: Capsule-shape
Pattern: Two-toned
Imprint: RX632
NDC: 35356-0729-30, 45865-0359-30, 45865-0359-51, 45865-0359-60, 45865-0359-90, 50436-0923-01, 63304-0632-01, 63304-0632-30, 68258-7003-03, 68258-7003-06, 68258-7003-09

Ingredients: Fluoxetine Hydrochloride (10 MG)
Color: Purple; Green
Shape: Capsule-shape
Pattern: Two-toned
Imprint: G; FL 10
NDC: 49884-0732-01, 49884-0732-10

Ingredients: Fluoxetine Hydrochloride (20 MG)
Color: Light Purple; Light Green
Shape: Capsule-shape
Pattern: Two-toned
Imprint: G FL20
NDC: 49884-0733-01, 49884-0733-10, 49884-0733-82, 49884-0751-01, 49884-0751-10, 68115-0144-60

Ingredients: Fluoxetine Hydrochloride (40 MG)
Color: Blue; White
Shape: Capsule-shape
Pattern: Two-toned
Imprint: R149; FLUOXETINE 40mg
NDC: 49884-0743-01, 49884-0743-05, 49884-0743-11, 52959-0717-30, 54868-4562-00, 58016-0704-00, 58016-0704-02, 58016-0704-03, 58016-0704-30, 58016-0704-60, 58016-0704-73, 58016-0704-89, 58016-0704-90, 63629-3312-01, 63629-3312-02, 63874-1080-03, 63874-1080-06, 68115-0145-30

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pression, or unusual changes in behavior, especially during the first few months of therapy or during periods of dosage adjustment. FDA recommends providing written patient information (medication guide) explaining risks of suicidality each time the drug is dispensed.

Risk of orthostatic hypotension, especially during initial dosage titration and at times of reinitiation of therapy or increases in dosage.

Risk of somnolence and impairment of judgment, thinking, or motor skills; avoid driving, operating machinery, or performing hazardous tasks until effects on the individual are known.

Importance of avoiding alcohol during quetiapine therapy.

Importance of informing clinicians of existing or contemplated concomitant therapy, including prescription and OTC drugs, as well as any concomitant illnesses (e.g., diabetes mellitus).

Importance of women informing clinicians if they are or plan to become pregnant or plan to breast-feed.

Importance of avoiding overheating or dehydration.

Importance of informing patients of other important precautionary information. (See Cautions.)

Overview* (see Users Guide). For additional information on this drug until a more detailed monograph is developed and published, the manufacturer's labeling should be consulted. It is *essential* that the manufacturer's labeling be consulted for more detailed information on usual cautions, precautions, contraindications, potential drug interactions, laboratory test interferences, and acute toxicity.

Preparations

Excipients in commercially available drug preparations may have clinically important effects in some individuals; consult specific product labeling for details.

Quetiapine Fumarate

Oral

Tablets, film-coated	25 mg (of quetiapine)	**Seroquel®**, AstraZeneca
	50 mg (of quetiapine)	**Seroquel®**, AstraZeneca
	100 mg (of quetiapine)	**Seroquel®**, AstraZeneca
	200 mg (of quetiapine)	**Seroquel®**, AstraZeneca
	300 mg (of quetiapine)	**Seroquel®**, AstraZeneca
	400 mg (of quetiapine)	**Seroquel®**, AstraZeneca

Risperidone

■ Risperidone has been described as an atypical or second-generation antipsychotic agent.

Uses

■ **Psychotic Disorders** Risperidone is used for the symptomatic management of psychotic disorders. Drug therapy is integral to the management of acute psychotic episodes and accompanying violent behavior in patients with schizophrenia and generally is required for long-term stabilization to sustain symptom remission or control and to minimize the risk of relapse. Antipsychotic agents are the principal class of drugs used for the management of all phases of schizophrenia. Patient response and tolerance to antipsychotic agents are variable, and patients who do not respond to or tolerate one drug may be successfully treated with an agent from a different class or with a different adverse effect profile.

Schizophrenia and Other Psychotic Disorders Efficacy of oral risperidone for the management of psychotic disorders has been established by controlled studies of 4–8 weeks' duration principally in patients with schizophrenic disorders in hospital settings. Schizophrenia is a major psychotic disorder that frequently has devastating effects on various aspects of the patient's life and carries a high risk of suicide and other life-threatening behaviors. Manifestations of schizophrenia involve multiple psychologic processes, including perception (e.g., hallucinations), ideation, reality testing (e.g., delusions), emotion (e.g., flatness, inappropriate affect), thought processes (e.g., loose associations), behavior (e.g., catatonia, disorganization), attention, concentration, motivation (e.g., avolition, impaired intention and planning), and judgment. The principal manifestations of this disorder usually are described in terms of positive and negative (deficit) symptoms, and more recently, disorganized symptoms. Positive symptoms include hallucinations, delusions, bizarre behavior, hostility, uncooperativeness, and paranoid ideation, while negative symptoms include restricted range and intensity of emotional expression (affective flattening), reduced thought and speech productivity (alogia), anhedonia, apathy, and decreased initiation of goal-directed behavior (avolition). Disorganized symptoms include disorganized speech (thought disorder) and behavior and poor attention. For additional information on the symptomatic management of schizophrenia, including treatment recommendations and results of the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study, see Schizophrenia and Other Psychotic Disorders under Uses: Psychotic Disorders, in the Phenothiazines General Statement 28:16.08.24.

In clinical studies principally in patients with schizophrenia, oral risperidone was more effective than placebo and at least as effective as typical (e.g., haloperidol, perphenazine) and certain atypical (e.g., olanzapine) antipsychotics in the treatment of schizophrenia. Data from limited clinical studies indicate that risperidone improves both positive and negative manifestations of schizophrenia, but that such improvements may not be substantially greater than those achieved by haloperidol, a typical antipsychotic. Risperidone was more effective than haloperidol in preventing relapse in adult outpatients with clinically stable schizophrenia or schizoaffective disorders who were assigned to receive either drug for a minimum of 1 year. In this study, approximately 25% of patients who received usual dosages of risperidone had relapsed by the end of the study compared with approximately 40% of those receiving usual dosages of haloperidol. In these studies, improvement in manifestations of schizophrenia was based on the results of various psychiatric rating scales, including the Brief Psychiatric Rating Scale (BPRS) that assesses factors such as anergy, thought disturbances, activation, hostility/suspiciousness, and anxiety/depression; the BPRS psychosis cluster that assesses factors such as conceptual disorganization, hallucinatory behavior, suspiciousness, and unusual thought content in actively psychotic schizophrenic patients; the Scale for the Assessment of Negative Symptoms (SANS); the Positive and Negative Syndrome Scale (PANSS); and the Clinical Global Impression (CGI) scale.

Because of their safety and efficacy, some authorities consider conventional antipsychotic agents or risperidone to be reasonable first-line drugs for the management of the acute phase of schizophrenia. Risperidone may be particularly useful in patients who experience extrapyramidal reactions with typical antipsychotic agents since the drug appears to cause fewer extrapyramidal reactions at clinically effective dosages. Some authorities state that risperidone or newer atypical antipsychotic agents (such as olanzapine) also may be advantageous in patients who have not responded adequately to therapy with a conventional antipsychotic agent. However, the efficacy of atypical antipsychotics, other than clozapine, in treatment-resistant schizophrenia has yet to be established, and the possible clinical benefits of risperidone therapy should be weighed against the potential drawbacks, including its higher cost compared with standard agents and the lack of a parenteral preparation of the drug.

Geriatric Considerations. Although risperidone has been studied for use in the management of psychosis and aggression in institutionalized geriatric patients with moderate to severe dementia of the Alzheimer's† type (Alzheimer's disease, presenile or senile dementia), vascular dementia‡, or a combination of the 2 types of dementia (i.e., mixed dementia†), there is evidence that use of the drug in geriatric patients with dementia may be associated with an increased risk of adverse cerebrovascular events. In randomized, placebo-controlled studies in nursing home residents with dementia, oral risperidone at a dosage of approximately 1 mg daily was more effective than placebo in decreasing psychotic and behavioral symptoms (e.g., aggression, agitation) of dementia, as assessed by the Behavioral Pathology in Alzheimer's Disease scale (BEHAVE-AD) and the Cohen-Mansfield Agitation Inventory (CMAI). However, evidence from these studies showed a significantly higher incidence of adverse cerebrovascular events such as stroke and transient ischemic attacks (TIAs) associated with risperidone therapy relative to placebo. In addition, geriatric patients with dementia-related psychosis treated with atypical antipsychotic agents appear to be at an increased risk of death compared with that among patients receiving placebo. (See Cautions: Geriatric Precautions.) Risperidone is not approved for the treatment with dementia-related psychosis.

■ **Bipolar Disorder** Risperidone is used alone or in conjunction with lithium or valproate for the management of manic and mixed episodes associated with bipolar I disorder. Efficacy of risperidone monotherapy in the treatment of acute manic and mixed episodes has been demonstrated in 2 placebo-controlled trials of 3 weeks' duration in patients who met the DSM-IV criteria for bipolar I disorder with acute manic or mixed episodes with or without psychotic features. The principal rating instrument used for assessing manic symptoms in these trials was the Young Mania Rating Scale (Y-MRS), an 11-item clinician-rated scale traditionally used to assess the degree of manic symptomatology in a range from 0 (no manic features) to 60 (maximum score). In the first 3-week, placebo-controlled trial, which was limited to patients with manic episodes, risperidone monotherapy was given at an initial dosage of 3 mg daily and subsequently in a flexible dosage ranging from 1–6 mg daily; the mean modal dosage was 4.1 mg daily. In the second 3-week, placebo-controlled trial, patients also were given an initial dosage of risperidone 3 mg daily and subsequently a flexible dosage ranging from 1–6 mg daily; the mean modal dosage was 5.6 mg daily. Risperidone was found to be superior to placebo in the reduction of the Y-MRS total score in both studies.

Efficacy of risperidone when used in conjunction with lithium or valproate in the treatment of acute manic or mixed episodes has been demonstrated in one placebo-controlled trial of 3 weeks' duration in patients who met the DSM-IV criteria for bipolar I disorder (with or without a rapid cycling course) and who met diagnostic criteria for an acute manic or mixed episode (with or without psychotic features). In this study, inpatients and outpatients with bipolar disorder experiencing manic or mixed episodes who had not adequately responded to lithium or valproate monotherapy were randomized to receive risperidone, haloperidol, or placebo in conjunction with their original therapy. Risperidone therapy was given in an initial dosage of 2 mg daily and subsequently given in a flexible dosage ranging from 1–6 mg daily; the mean modal

dosage was 3.8 mg daily. Lithium and valproate were given in conjunction with risperidone and plasma drug concentrations were maintained within therapeutic ranges of 0.6–1.4 mEq/L for lithium and 50–120 mcg/mL for valproate. Addition of risperidone to lithium or valproate was shown to be superior to continued monotherapy with lithium or valproate as assessed by reduction of Y-MRS total score.

In a second 3-week, placebo-controlled trial, inpatients and outpatients with bipolar mania receiving lithium, valproate (as divalproex), or carbamazepine therapy with inadequately controlled manic or mixed symptoms were randomized to receive risperidone or placebo in conjunction with their original therapy. Risperidone was given in a flexible dosage range of 1–6 mg daily, with an initial dosage of 2 mg daily; the mean modal dosage was 3.7 mg daily. Addition of risperidone to lithium, valproate, or carbamazepine therapy (with plasma drug concentrations maintained within therapeutic ranges of 0.6–1.4 mEq/L, 50–120 mcg/mL, or 4–12 mcg/mL, respectively) was not found to be superior to lithium, valproate, or carbamazepine given alone as assessed by reduction of the Y-MRS total score. A possible explanation for the failure of this trial was enzymatic induction of clearance of risperidone and its principal active metabolite, 9-hydroxyrisperidone, by carbamazepine in the subgroup of patients receiving combined therapy with these drugs, resulting in subtherapeutic plasma concentrations of risperidone and 9-hydroxyrisperidone.

For the initial management of less severe manic or mixed episodes in patients with bipolar disorder, current American Psychiatric Association (APA) recommendations state that monotherapy with lithium, valproate (e.g., valproate sodium, valproic acid, divalproex), or an antipsychotic such as olanzapine may be adequate. For more severe manic or mixed episodes, combined therapy with an antipsychotic and lithium or valproate is recommended as first-line therapy. For further information on the management of bipolar disorder, see Uses: Bipolar Disorder, in Lithium Salts 28:28.

The manufacturer states that efficacy of risperidone has not been systematically evaluated for long-term use (i.e., exceeding 3 weeks) in the treatment of acute manic episodes or for prophylactic use in patients with bipolar disorder.

■ **Autistic Disorder** Risperidone is used for the management of irritability associated with autistic disorder in children and adolescents, including symptoms of aggression towards others, deliberate self-injuriousness, temper tantrums, and quickly changing moods.

Short-term efficacy of risperidone in children and adolescents with autistic disorder has been demonstrated in 2 placebo-controlled trials of 8 weeks' duration in children and adolescents (aged 5–16 years) who met the DSM-IV criteria for autistic disorder. Over 90% of the patients in these 2 trials were under 12 years of age and the majority weighed over 20 kg (weight range: 16–104.3 kg). The principal rating instruments used for assessing efficacy in these trials were the Aberrant Behavior Checklist (ABC) and the Clinical Global Impression-Change (CGI-C) scale. The primary outcome measure in both trials was the change from baseline to endpoint in the Irritability subscale of the ABC (ABC-I), which measures the emotional and behavioral symptoms of autism, including aggression toward others, deliberate self-injuriousness, temper tantrums, and rapidly changing moods. The CGI-C rating at endpoint was a co-primary outcome measure in one of the studies.

In the first 8-week, placebo-controlled trial, children and adolescents with autistic disorder aged from 5 to 16 years received twice daily placebo or risperidone 0.5–3.5 mg daily on a weight-adjusted basis, starting at 0.25 mg daily or 0.5 mg daily if baseline weight was less than 20 kg or 20 kg or greater, respectively; dosage was then titrated according to clinical response. Risperidone (mean modal dosage of 1.9 mg/day; equivalent to 0.06 mg/kg daily) was found to substantially improve scores on the ABC-I subscale and the CGI-C scale compared with placebo in this study.

In the second 8-week, placebo-controlled trial, children and adolescents with autistic disorder aged from 5–12 years were given an initial risperidone dosage of 0.01 mg/kg daily, which was then titrated up to 0.02–0.06 mg/kg daily based on clinical response. Risperidone (mean modal dosage of 0.05 mg/kg daily; equivalent to 1.4 mg daily) improved scores on the ABC-I subscale compared with placebo.

The efficacy of risperidone for long-term use (i.e., longer than 8 weeks) in children and adolescents with autistic disorder has been demonstrated in an open-label extension of the first 8-week, placebo-controlled trial in which patients received risperidone for 4 or 6 months (depending on whether they received risperidone or placebo in the double-blind study). During the open-label treatment period, patients were maintained on a mean modal risperidone dosage of 1.8–2.1 mg daily (equivalent to 0.05–0.07 mg/kg daily).

Children and adolescents who maintained their positive response to risperidone (defined as at least a 25% improvement on the ABC-I subscale and a CGI-C rating of much improved or very much improved) during the 4–6 month open-label treatment period (average duration of therapy was 140 days) were randomized to receive either risperidone or placebo during an 8-week, double-blind withdrawal trial. A substantially lower relapse rate was observed in the risperidone group compared with the placebo group during the pre-planned interim analysis of data from this trial. Based on the interim analysis results, the study was terminated since a statistically significant effect on relapse prevention was demonstrated. Relapse was defined as at least a 25% worsening on the most recent assessment of the ABC-I subscale (in relation to baseline for the randomized withdrawal phase). The manufacturer states that clinicians who elect to use risperidone in children and adolescents with autistic disorder for extended periods should periodically re-evaluate the long-term risks and benefits of the drug for the individual patient.

Although not curative, pharmacologic agents, such as risperidone, generally are used in children and adolescents with autistic disorder to reduce behavioral disturbances associated with autism and to help facilitate the child's or adolescent's adjustment and engagement in intensive, targeted educational interventions. In clinical studies, risperidone was not found to improve certain core symptoms of autism (e.g., language deficits, impaired social relatedness). However, the drug was more effective than placebo for improving scores on subscales for sensory motor behaviors, affectual reactions, and sensory responses in a controlled study. The possible risks, including clinically important weight gain, tardive dyskinesia, withdrawal dyskinesia, and other extrapyramidal reactions associated with the drug, should be considered.

Risperidone also has been used for the treatment in a limited number of adults† with autistic disorder and other pervasive developmental disorders.

Dosage and Administration

■ **Administration** Risperidone is administered orally or by IM injection.

Oral Administration Risperidone is administered orally, either in a once-daily dose or in 2 equally divided doses daily. Because risperidone can cause orthostatic hypotension, twice-daily oral administration may be preferable during initiation of therapy and in patients who may be more susceptible to orthostatic hypotension, such as geriatric or debilitated patients. If once-daily dosing is being considered in geriatric or debilitated patients, it is recommended that the patient be titrated on a twice-daily regimen for 2–3 days at the target dose. Subsequent switching to the once-daily dosing regimen can be done thereafter. Some experts state that once-daily administration of risperidone may be sufficient in most patients receiving maintenance therapy because of the extended half-life of the drug's principal active metabolite (9-hydroxyrisperidone).

In children and adolescents receiving risperidone for the management of irritability associated with autistic disorder who experience persistent somnolence, administering the drug once daily at bedtime, twice-daily administration, or a reduction in dosage may be helpful.

Since food reportedly does not affect the rate or extent of GI absorption of risperidone, the drug can be administered without regard to meals. Compatibility tests show that risperidone oral solution is compatible in the following beverages: water, coffee, orange juice, and low-fat milk; such testing also indicates that risperidone oral solution is *not* compatible in cola or tea.

Patients receiving risperidone orally disintegrating tablets should be instructed not to remove a tablet from the blister until just prior to dosing. The tablet should not be pushed through the foil. With dry hands, the blister backing should be peeled completely off the blister. The tablet should then be gently removed and immediately placed on the tongue, where it rapidly disintegrates in saliva, and then subsequently swallowed with or without liquid. Risperidone orally disintegrating tablets should not be divided or chewed.

IM Administration The commercially available risperidone powder for injection containing the drug in extended-release microspheres must be reconstituted prior to administration using the components of the dose pack supplied by the manufacturer. The dose pack should be allowed to reach room temperature before reconstituting the injection. Risperidone extended-release microspheres should be reconstituted using only the diluent in the prefilled syringe supplied by the manufacturer. The entire contents of the prefilled syringe should be injected into the vial, and the vial should be shaken vigorously while the plunger rod is held down with the thumb for at least 10 seconds to ensure a homogeneous suspension; the reconstituted suspension should appear uniform, thick, and milky. The manufacturer's prescribing information should be consulted for additional details on use of the components of the dose pack to reconstitute and administer risperidone injection. The manufacturer states that different dosage strengths of IM risperidone should not be combined in a single administration.

Following reconstitution, immediate use is recommended because the suspension will settle over time. If more than 2 minutes pass before administration, the vial should again be vigorously shaken to resuspend the drug. The contents of the vial must be used within 6 hours of reconstitution and should not be exposed to temperatures exceeding 25°C.

The entire contents of the vial should be administered by deep IM injection into the upper outer quadrant of the gluteal area every 2 weeks, alternating buttocks. The injection should *not* be administered IV.

■ **Dosage** ***Schizophrenia*** **Oral Dosage.** Risperidone has a bell-shaped dose-response curve, with therapeutic efficacy of oral dosages of 12–16 mg daily lower than that of dosages of 4–8 mg daily in adults. Because dosage information contained in the manufacturer's labeling principally is derived from early clinical studies of the drug in patients not typical of the general population of patients treated in the community (i.e., in hospitalized, chronically-ill schizophrenic patients accustomed to high-dose antipsychotic therapies), dosage of risperidone should be individualized according to the patient's response and tolerance. Clinicians also may consider consulting published protocols for specific dosage information, particularly in geriatric or younger patients, and in those experiencing their first psychotic episode.

The manufacturer's labeling states that the initial oral dosage of risperidone in adults generally is 1 mg twice daily, with dosage increase in increments of 1 mg twice daily on the second and third day, as tolerated, to a target dosage

of 6–8 mg daily (administered once daily or in 2 equally divided doses). However, more recent evidence from open labeled studies and clinical experience with the drug indicates that an initial dosage of 1–2 mg daily, with dosage increases in increments of 0.5–1 mg daily titrated over 6–7 days, as tolerated, to a target dose of 4 mg daily may be more appropriate for the management of schizophrenia in most otherwise healthy adult patients. Because steady-state plasma concentrations of 9-hydroxyrisperidone (an active metabolite of risperidone) may not be attained for 7 days at a given dosage, subsequent dosage adjustments generally should be made at intervals of at least 7 days. Lower initial dosages (e.g., 1 mg daily) and slower dosage titrations to an initial target dosage of 2 mg daily may be appropriate for younger patients and in those being treated for their first psychotic episode; dosage may then be titrated up to 4 mg daily depending on clinical response at the lower dosage and adverse neurologic effects. Such patients appear to benefit optimally from risperidone dosage of 1–3 mg daily. A substantial number of patients being treated for their first psychotic episode start to develop extrapyramidal symptoms once dosages are increased above 2 mg daily. Dosage reductions should be considered in any patient who develops extrapyramidal symptoms.

While antipsychotic efficacy has been established in clinical trials at oral dosages ranging from 4–16 mg daily, maximum efficacy of the drug was observed in most patients at risperidone dosages of 4–8 mg daily. In addition, the manufacturer and some clinicians state that dosages exceeding 6 mg daily, when given in 2 divided doses, did not result in further improvement but were associated with increases in some adverse effects, including extrapyramidal manifestations. Therefore, the manufacturer states that dosages exceeding 6 mg (in 2 divided doses) daily generally are not recommended and those exceeding 16 mg daily have not been evaluated for safety. In a single study of once-daily dosing, efficacy results generally were stronger for 8 mg than for 4 mg.

The manufacturer states that there are no systematically collected data that specifically address switching from other antipsychotic agents to risperidone or concomitant administration with other antipsychotic agents. While immediate discontinuance of the previous antipsychotic treatment may be acceptable for some patients with schizophrenia, gradual discontinuance of the drug may be appropriate for most patients. In all cases, the period of overlapping antipsychotic administration should be minimized. The first risperidone dose should be administered in place of the next scheduled parenteral antipsychotic dose in schizophrenic patients being switched from long-acting (depot) parenteral antipsychotic therapy to oral risperidone therapy.

The optimum duration of oral risperidone therapy currently is not known, but maintenance therapy with risperidone 2–8 mg daily has been shown to be effective for up to 2 years. Patients should be reassessed periodically to determine the need for continued therapy with the drug. If risperidone therapy is reinitiated after a drug-free period, the manufacturer recommends that the appropriate recommended schedule of careful dosage titration be employed.

IM Dosage. For the management of schizophrenia, the recommended initial adult IM dosage of risperidone injection extended-release microspheres is 25 mg administered by deep IM injection in the gluteal area every 2 weeks. The manufacturer recommends that patients first receive oral risperidone to establish tolerability of the drug before the extended-release risperidone injection is used. To ensure that adequate plasma antipsychotic concentrations are maintained prior to the main release of risperidone from the injection site, therapy with oral risperidone or another oral antipsychotic agent (e.g., for patients being switched from other oral antipsychotic therapy to IM risperidone) should be given with the first IM injection of risperidone, and such oral therapy should be continued for 3 weeks, then discontinued. If risperidone injection is used in patients previously receiving other oral antipsychotic agents, the need for continuing any concomitant therapy for managing extrapyramidal manifestations should be periodically reevaluated.

Some patients not responding to the initial dosage of 25 mg every 2 weeks may benefit from increasing the IM dosage to 37.5 or 50 mg every 2 weeks. However, the dosage should not be increased more frequently than every 4 weeks, and clinical effects of the increased dosage should not be expected earlier than 3 weeks after the first injection of the higher dose. The maximum IM dosage should not exceed 50 mg every 2 weeks since higher dosages were associated with an increased incidence of adverse effects, but no additional clinical benefit was observed.

Although no controlled studies have been conducted to establish the optimum duration of IM risperidone therapy in patients with schizophrenia, oral risperidone has been shown to be effective in delaying time to relapse with longer term use. It is recommended that responding patients be continued on treatment with IM risperidone at the lowest dose needed. Patients should periodically be reassessed to determine the need for continued treatment.

If therapy with IM risperidone is reinitiated after a drug-free period, oral risperidone (or another oral antipsychotic agent) should again be administered for supplementation.

Bipolar Disorder For the management of acute manic and mixed episodes associated with bipolar disorder as monotherapy or as combined therapy in adults, an initial risperidone oral dosage of 2–3 mg given once daily was found to be effective in clinical trials. Dosage may be increased or decreased by 1 mg daily at intervals of not less than 24 hours, reflecting the procedures in the placebo-controlled trials. In these trials, the short-term (i.e., 3-week) antimanic efficacy of risperidone was demonstrated in a flexible dosage ranging from 1 to 6 mg daily. Safety of dosages exceeding 6 mg daily has not been established.

The optimum duration of risperidone therapy for bipolar disorder currently is not known. While it is generally agreed that pharmacologic treatment beyond an acute response in mania is desirable, both for maintenance of the initial response and for prevention of new manic episodes, there are no systematically obtained data to support the use of risperidone beyond 3 weeks. Therefore, the manufacturer states that clinicians who elect to use risperidone for extended periods should periodically reevaluate the long-term risks and benefits of the drug for the individual patient.

Autistic Disorder For the management of irritability associated with autistic disorder in children 5 years of age and older and adolescents, an initial risperidone oral dosage of 0.25 mg daily is recommended for patients weighing less than 20 kg and 0.5 mg daily is recommended for patients weighing 20 kg or more. The drug may be administered either once or twice daily.

Dosage should be individualized according to clinical response and tolerability of the patient. After a minimum of 4 days following initiation of therapy, the dosage may be increased to the recommended dosage of 0.5 mg daily for patients weighing less than 20 kg and 1 mg daily for patients weighing 20 kg or more; this dosage should then be maintained for a minimum of 14 days. In patients not responding adequately, increases in dosage may be considered at intervals of 2 weeks or longer in increments of 0.25 mg daily for patients weighing less than 20 kg or 0.5 mg daily for patients weighing 20 kg or more. Exercise caution with risperidone dosages in smaller children who weigh less than 15 kg. Safety and effectiveness in pediatric patients less than 5 years of age not established.

In clinical trials, 90% of patients who responded to risperidone therapy (based on at least 25% improvement in the Irritability subscale of the Aberrant Behavior Checklist [ABC-I]) received dosages from 0.5–2.5 mg daily. The maximum daily dosage in one of the pivotal trials, when the therapeutic effect reached a plateau, was 1 mg in patients weighing less than 20 kg, 2.5 mg in patients weighing 20 kg or more, and 3 mg in patients weighing more than 45 kg. Dosage data for children weighing less than 15 kg currently are lacking.

Once adequate clinical response has been achieved, consider a gradual reduction in dosage to achieve an optimal balance of efficacy and safety. Patients experiencing excessive somnolence may benefit from a once-daily dosage administered at bedtime or administering half the daily dosage twice daily, or a reduction in dosage.

The manufacturer states that clinicians who elect to use risperidone in children and adolescents with autistic disorder for extended periods should periodically reevaluate the long-term risks and benefits of the drug for the individual patient.

Geriatric Patients and Others at Risk of Orthostatic Hypotension Like other α-adrenergic blocking agents, risperidone can induce orthostatic hypotension (e.g., manifested as dizziness, tachycardia, and occasionally syncope), particularly during initiation of therapy with the drug. The manufacturer and some clinicians state that the risk of this effect can be minimized by limiting the initial oral dosage of risperidone to 1 mg twice daily in otherwise healthy adults and to 0.5 mg once or twice daily in geriatric or debilitated patients, in patients with renal or hepatic impairment, and in those predisposed to, or at risk from, hypotension. Dosages in such patients should then be increased gradually at increments of not more than 0.5 mg twice daily as necessary and tolerated. Increases beyond a dosage level of 1.5 mg twice daily generally should occur at intervals of at least 7 days. However, other clinicians recommend initiating risperidone therapy at a dosage of 0.25 mg daily in geriatric patients and gradually increasing the dosage as tolerated. (See Cautions: Geriatric Precautions.) Most geriatric patients should not be maintained at an oral dosage exceeding 3 mg daily.

For geriatric patients with schizophrenia, the recommended IM risperidone dosage of the extended-release injection is 25 mg every 2 weeks. Oral risperidone (or another oral antipsychotic agent) should be given with the first risperidone extended-release injection and should be continued for 3 weeks to ensure that adequate antipsychotic plasma concentrations are maintained prior to the main release phase of risperidone from the injection site.

Elderly patients and patients with a predisposition to hypotensive reactions or for whom such reactions would pose a particular risk should be instructed in nonpharmacologic interventions that help reduce the occurrence of orthostatic hypotension (e.g., sitting on the edge of the bed for several minutes before attempting to stand in the morning, slowly rising from a seated position). These patients should avoid sodium depletion or dehydration and circumstances that accentuate hypotension (e.g., alcohol intake, high ambient temperature). Monitoring of orthostatic vital signs should be considered.

Particular caution also is warranted in patients with known cardiovascular disease (e.g., history of myocardial infarction or ischemia, heart failure, conduction abnormalities), cerebrovascular disease, or conditions that would predispose to hypotension (e.g., dehydration, hypovolemia, concomitant antihypertensive therapy) and in those for whom such reactions would pose a risk, and cautious dosage titration and careful monitoring are necessary in such patients. Dosage reduction should be considered in any patient in whom hypotension develops.

■ **Dosage in Renal and Hepatic Impairment** Because elimination of risperidone may be reduced and the risk of adverse effects, particularly hypotension, increased in patients with renal impairment, oral risperidone therapy should be initiated at a reduced dosage of 0.5 mg twice daily in adults and increased as necessary and tolerated at increments of 0.5 mg twice daily; increases beyond a dosage level of 1.5 mg twice daily should be made at intervals of at least 7 days. Likewise, this reduced oral dosage should be employed in

patients with hepatic impairment because of the risk of an increased free fraction of risperidone in such patients.

If IM risperidone is used for management of schizophrenia in adult patients with renal or hepatic impairment, the patient should be treated with titrated doses of oral risperidone prior to initiating treatment with the extended-release injection. The recommended starting oral risperidone dosage is 0.5 mg twice daily during the first week, which can be increased to 1 mg twice daily or 2 mg once daily during the second week. If a dosage of at least 2 mg daily of oral risperidone is well tolerated, an IM dosage of 25 mg of the extended-release injection can be administered every 2 weeks. Oral supplementation should be continued for 3 weeks after the first injection until the main release of risperidone from the injection site has begun. In some patients, slower titration may be medically appropriate.

Cautions

Although risperidone differs chemically from the phenothiazines, the drug may be capable of producing many of the toxic manifestations of phenothiazine derivatives. Not all adverse effects of the phenothiazines have been reported with risperidone, but the possibility that they may occur should be considered. Adverse effects of risperidone and the phenothiazines are numerous and may involve nearly all organ systems. Although these effects usually are reversible when dosage is reduced or the drug is discontinued, some effects may be irreversible and, rarely, fatal. In some patients, unexpected death associated with antipsychotic therapy has been attributed to cardiac arrest or asphyxia resulting from failure of the gag reflex. (See Cautions: Cardiovascular Effects.) In other cases, the cause of death could not be determined or definitely attributed to antipsychotic drug therapy.

The most frequent adverse effects of oral risperidone reported in at least 5% of adult patients with schizophrenia who received the drug in 2 short-term (6–8 week) clinical studies and with an incidence of at least twice that of those who received placebo included nervous system (e.g., anxiety, dizziness, extrapyramidal symptoms, somnolence), GI (e.g., constipation, dyspepsia, nausea), dermatologic (e.g., rash), respiratory (e.g., rhinitis), and cardiovascular (e.g., tachycardia) effects. Approximately 9% of patients receiving risperidone in phase 2 or 3 studies discontinued treatment because of adverse effects compared with about 7% of those receiving placebo and 10% of those receiving an active control drug (haloperidol). Adverse effects commonly associated with discontinuance of therapy and considered to be possibly or probably related to risperidone include extrapyramidal symptoms, dizziness, hyperkinesia, somnolence, and nausea.

The most frequent adverse effects of oral risperidone reported in at least 5% of adult patients with bipolar mania who received the drug as monotherapy in the US placebo-controlled trial and with an incidence of at least twice that of those receiving placebo included nervous system (e.g., somnolence, dystonia, akathisia, parkinsonism, vision abnormalities) and GI (e.g., dyspepsia, nausea, increased salivation) effects. In the US placebo-controlled trial of risperidone in conjunction with mood stabilizers (lithium or valproate), the most common adverse effects associated with risperidone administration were somnolence, dizziness, parkinsonism, increased saliva, akathisia, abdominal pain, and urinary incontinence. In the US placebo-controlled trial of risperidone monotherapy, approximately 8% of patients receiving risperidone discontinued therapy because of adverse effects compared with about 6% of those receiving placebo. Adverse effects associated with discontinuance of therapy in this study and considered to be possibly, probably, or very likely related to risperidone included paroniria, somnolence, dizziness, extrapyramidal reaction, and involuntary muscle contractions; each of these occurred in 1 risperidone-treated patient (0.7%) but in none of those receiving placebo. In the US placebo-controlled trial of risperidone used in conjunction with mood stabilizers, there was no overall difference in the incidence of discontinuance because of adverse effects (4% for risperidone and 4% for placebo).

The most frequent adverse effects of oral risperidone reported in at least 5% of pediatric patients with autistic disorder who received the drug in 2 placebo-controlled trials and with an incidence of at least twice that of those receiving placebo included nervous system (e.g., somnolence, fatigue, tremor, dystonia, dizziness, parkinsonism, automatism, dyskinesia, confusion), GI (e.g., increased appetite, increased salivation, constipation, dry mouth), respiratory (e.g., upper respiratory tract infection), cardiovascular effects (e.g., tachycardia), and weight gain. Somnolence was the most frequent adverse effect in these trials, occurring in 67% of the risperidone-treated patients and in 23% of patients receiving placebo. Average weight gain over 8 weeks was 2.6 kg for the risperidone-treated patients compared with 0.9 kg for patients receiving placebo. Extrapyramidal symptoms occurred in approximately 28% of the risperidone-treated patients compared with 10% of those receiving placebo.

The most frequent adverse effects associated with use of risperidone extended-release IM injection reported in at least 5% of adult patients with schizophrenia in clinical trials and with an incidence of at least twice that of those receiving placebo included somnolence, akathisia, parkinsonism, dyspepsia, constipation, dry mouth, fatigue, and increased weight.

■ **Nervous System Effects** ***Tardive Dyskinesia*** Like other antipsychotic agents (e.g., phenothiazines), risperidone has been associated with tardive dyskinesias. Although it has been suggested that atypical antipsychotics appear to have a lower risk of tardive dyskinesia, whether antipsychotic drugs differ in their potential to cause tardive dyskinesia is as yet unknown. In one open-label study, an annual incidence of tardive dyskinesia of 0.3% was reported in patients with schizophrenia who received approximately 8–9 mg of oral risperidone daily for at least 1 year. The prevalence of this syndrome appears to be highest among geriatric patients (particularly females). The risk of developing tardive dyskinesia and the likelihood that it will become irreversible also appear to increase with the duration of therapy and cumulative dose of antipsychotic agents administered; however, the syndrome may occur, although much less frequently, after relatively short periods of treatment with low dosages. For additional information on tardive dyskinesia, see Tardive Dyskinesia under Cautions: Nervous System Effects, in the Phenothiazines General Statement 28:16.08.24.

Extrapyramidal Reactions Extrapyramidal reactions occurred in 17% of patients with schizophrenia receiving oral risperidone dosages of 10 mg daily or less and in 34% of patients receiving dosages of 16 mg daily in clinical studies. Although the incidence of extrapyramidal manifestations in patients receiving risperidone dosages of 10 mg daily or less was similar to that reported in patients receiving placebo, the incidence increased as the dosage of the drug increased, suggesting a dose-related effect. At recommended therapeutic dosages of risperidone (4–8 mg daily) for schizophrenia, the severity of extrapyramidal reactions appears to be comparable to placebo and clozapine 400 mg daily, and substantially less than that associated with haloperidol 10 or 20 mg daily. Similarly, the severity of parkinsonian symptoms, as assessed on the parkinsonism subscale of the Extrapyramidal Symptom Rating Scale (ESRS), is also linearly related to risperidone dosages of 2–16 mg daily, with the incidence of parkinsonian symptoms at risperidone dosages of 6 mg daily or less comparable to that of placebo and substantially less than that seen with haloperidol dosages of 20 mg daily.

Neuroleptic malignant syndrome (NMS), a potentially fatal symptom complex, has been reported in patients receiving antipsychotic agents. NMS requires immediate discontinuance of the drug and intensive symptomatic and supportive care. For additional information on NMS, see Neuroleptic Malignant Syndrome under Nervous System Effects: Extrapyramidal Reactions in Cautions, in the Phenothiazines General Statement 28:16.08.24.

Other Nervous System Effects Dose-related somnolence was a commonly reported adverse effect associated with risperidone treatment. Approximately 8% of adult patients with schizophrenia receiving 16 mg of oral risperidone daily and 1% of patients receiving placebo reported somnolence in studies utilizing direct questioning or a checklist to detect adverse events, respectively.

Insomnia, agitation, and anxiety have been reported in 20–26% of patients receiving risperidone. In addition, headache, dizziness, and aggressive reaction have been reported in 12–14, 4–7, and 1–3% of schizophrenia patients, respectively.

Adverse nervous system effects reported in 1% or more of patients with schizophrenia who received risperidone in clinical studies include increased sleep duration or dream activity, diminished sexual desire, fatigue, and nervousness. Impaired concentration, depression, apathy, catatonic reaction, euphoria, increased libido, amnesia, dysarthria, vertigo, stupor, paraesthesia,malaise, seizure, and confusion also have been reported in 0.1–1% of patients. In addition, aphasia, cholinergic syndrome, choreoathetosis, coma, delirium, emotional lability, hypoesthesia, hypotonia, hyperreflexia, leg cramps, migraine, nightmares, tongue paralysis, torticollis, withdrawal syndrome, and yawning have been reported in fewer than 0.1% of patients. Mania also has been reported during postmarketing surveillance; however, a causal relationship to the drug has not been established.

■ **Cardiovascular Effects** ***Orthostatic Hypotension*** Orthostatic hypotension associated with dizziness, tachycardia, and in some patients, syncope, especially during the initial dose-titration period has been reported in patients receiving risperidone, probably reflecting the drug's α-adrenergic antagonistic properties. The risk of orthostatic hypotension and syncope may be minimized by limiting initial doses in geriatric patients and patients with renal or hepatic impairment. (See Dosage and Administration.) Monitoring of orthostatic vital signs should be considered in patients for whom this is of concern. A dose reduction should be considered if hypotension occurs. Risperidone should be used with particular caution in patients with known cardiovascular disease (history of myocardial infarction or ischemia, heart failure, or conduction abnormalities), cerebrovascular disease, or conditions that would predispose to hypotension (e.g., dehydration, hypovolemia). Clinically important hypotension has been observed with concomitant use of risperidone and antihypertensive drug therapy.

Other Cardiovascular Effects Pooled analysis of results of placebo-controlled studies indicates that risperidone therapy is not associated with statistically significant changes in ECG parameters (e.g., PR, QT, or QT_c intervals, heart rate). In pivotal clinical studies, however, tachycardia, which may be dose dependent, occurred in 3 or 5% of patients with schizophrenia receiving daily oral dosages of risperidone of 10 mg or less or 16 mg, respectively. In addition, palpitation, hypertension, hypotension, AV block, and myocardial infarction have occurred in 1% or more of patients receiving risperidone. Ventricular tachycardia, angina pectoris, atrial premature complexes (APCs, PACs), T-wave inversions, ventricular extrasystoles, ST depression, and myocarditis have occurred in fewer than 0.1% of patients receiving the drug in clinical trials. Atrial fibrillation, pulmonary embolism, cerebrovascular disorders (including stroke and transient ischemic attack) (see Cautions: Geriatric Precautions), and rarely, sudden death and/or cardiopulmonary arrest also have been reported

during postmarketing surveillance; however, a causal relationship to the drug has not been established.

■ **Endocrine and Metabolic Effects** Severe hyperglycemia, sometimes associated with ketoacidosis, hyperosmolar coma, or death, has been reported in patients receiving certain atypical antipsychotic agents, including risperidone. While confounding factors such as an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population make it difficult to establish with certainty the relationship between use of agents in this drug class and glucose abnormalities, epidemiologic studies suggest an increased risk of treatment-emergent hyperglycemia-related adverse events in patients treated with the atypical antipsychotic agents included in the studies (e.g., risperidone, clozapine, olanzapine, quetiapine).

Precise risk estimates for hyperglycemia-related adverse events in patients treated with atypical antipsychotics currently are not available. While some evidence suggests that the risk for diabetes may be greater with some atypical antipsychotics (e.g., clozapine, olanzapine) than with others (e.g., risperidone, quetiapine) in the class, available data are conflicting and insufficient to provide reliable estimates of relative risk associated with use of the various atypical antipsychotics.

Similar to other antipsychotic agents, risperidone causes elevated prolactin concentrations, which may persist during chronic use of the drug. Risperidone appears to be associated with a higher level of prolactin elevation than other currently available antipsychotic agents. The clinical importance of elevated serum prolactin concentrations is as yet unknown for most patients receiving these drugs. Gynecomastia and breast pain in men have been reported in fewer than 0.1% of patients. In addition, galactorrhea, amenorrhea, and impotence have been reported with agents that increase serum prolactin concentrations, including risperidone.

Hyponatremia, weight gain or loss, increased serum creatine kinase (CK, creatine phosphokinase, CPK) concentrations, thirst, and diabetes mellitus have been reported in 0.1–1% of schizophrenia patients receiving oral risperidone in clinical studies. In addition, decreased serum iron concentrations, cachexia, dehydration, disorders in antidiuretic hormone, hypokalemia, hypoproteinemia, hyperphosphatemia, hypertriglyceridemia, hyperuricemia, and hypoglycemia have been reported in fewer than 0.1% of patients. Precocious puberty and pituitary adenomas also have been reported during postmarketing surveillance; however, a causal relationship to the drug has not been established.

■ **GI Effects** Adverse GI effects that have been reported in 5–13% of patients with schizophrenia receiving oral risperidone in clinical studies include constipation, nausea, dyspepsia, and vomiting. Abdominal pain, increased salivation, and toothache also have been reported in 1–4% of patients receiving risperidone in clinical studies. In addition, anorexia and reduced salivation were reported in 1% or more of patients receiving risperidone in clinical trials. Flatulence, diarrhea, increased appetite, stomatitis, melena, dysphagia, hemorrhoids, and gastritis have also been reported in 0.1–1% of patients. In addition, fecal incontinence, eructation, gastroesophageal reflux, gastroenteritis, esophagitis, lingual discoloration, cholelithiasis, lingual edema, diverticulitis, gingivitis, discolored feces, GI hemorrhage, and hematemesis have been reported in fewer than 0.1% of patients receiving the drug in clinical trials. Although a causal relationship to risperidone has not been established, intestinal obstruction has been reported during postmarketing surveillance.

■ **Respiratory Effects** Rhinitis has been reported in 8–10% of patients with schizophrenia receiving oral risperidone and was the most common adverse respiratory effect reported during clinical studies. In addition, cough, sinusitis, pharyngitis, upper respiratory infections, and dyspnea have been reported in 1–3% of patients receiving risperidone in clinical studies. Hyperventilation, bronchospasm, pneumonia, and stridor also have been reported in 0.1–1% of patients receiving risperidone in clinical studies. Asthma, increased sputum, and aspiration have been rarely reported in fewer than 0.1% of patients. Although a causal relationship to the drug has not been established, apnea also has been reported during postmarketing surveillance.

■ **Dermatologic Effects and Sensitivity Reactions** Rash and dry skin have been reported in about 2–5% of patients with schizophrenia receiving oral risperidone in clinical studies. In addition, adverse dermatologic effects that have been reported in 1% or more of patients receiving risperidone include seborrhea and increased pigmentation. Increased or decreased sweating, acne, alopecia, hyperkeratosis, pruritus, and skin exfoliation were reported in 0.1–1% of patients in clinical trials. Bullous eruption, skin ulceration, aggravated psoriasis, furunculosis, verruca, dermatitis lichenoid, hypertrichosis, genital pruritus, and urticaria have been rarely reported.

Although a causal relationship has not been established, hypersensitivity reactions, including anaphylaxis, angioedema, and photosensitivity have been reported in patients receiving risperidone.

■ **Genitourinary Effects** Adverse genitourinary effects reported in 1% or more of patients with schizophrenia receiving oral risperidone include polyuria, polydipsia, menorrhagia, orgasmic dysfunction, and vaginal dryness. In addition, urinary incontinence, hematuria, dysuria, nonpuerperal lactation, amenorrhea, breast or perineal pain in females, leukorrhea, mastitis, dysmenorrhea, intermenstrual bleeding, and vaginal hemorrhage have been reported in 0.1–1% of patients receiving risperidone in clinical studies. Urinary retention, cystitis, and renal insufficiency also have been reported in fewer than 0.1% of patients.

In male patients, erectile dysfunction and ejaculation failure were reported in up to 1% of schizophrenia patients receiving oral risperidone in clinical studies. In addition, rare cases of priapism have been reported. While a causal relationship to risperidone use has not been established, other drugs with α-adrenergic blocking effects have been reported to cause priapism, and it is possible that risperidone may share this capacity. Severe priapism may require surgical intervention.

■ **Musculoskeletal Effects** Back or chest pain and arthralgia have been reported in 2–3% of patients with schizophrenia receiving oral risperidone in clinical studies. In addition, myalgia has been reported in 0.1–1% of patients. Arthrosis, synostosis, bursitis, arthritis, and skeletal pain also have occurred in fewer than 0.1% of patients.

■ **Hematologic Effects** Anemia, hypochromic anemia, epistaxis, and purpura have been reported in 0.1–1% of adult patients with schizophrenia and granulocytopenia has been reported in 0.1–1% of children and adolescents with autistic disorder receiving oral risperidone in clinical studies. Normocytic anemia, leukocytosis, lymphadenopathy, leukopenia, Pelger-Huet anomaly, hemorrhage, superficial phlebitis, thrombophlebitis, and thrombocytopenia also have been reported in fewer than 0.1% of patients. In addition, thrombotic thrombocytopenic purpura occurred in at least one patient (a 28 year-old female patient) receiving risperidone in a large, open-labeled study. This patient experienced jaundice, fever, and bruising but eventually recovered after receiving plasmapheresis. The relationship of this adverse event to risperidone therapy is unknown.

■ **Hepatic Effects** Increased SGOT and increased SGPT have been reported in 0.1–1% of patients with schizophrenia receiving oral risperidone in clinical studies. In addition, hepatic failure, cholestatic hepatitis, cholecystitis, cholelithiasis, hepatitis, and hepatocellular damage have been reported in fewer than 0.1% of patients. Although a causal relationship to the drug has not been established, jaundice also has been reported during postmarketing surveillance.

■ **Ocular and Otic Effects** Abnormal vision has been reported in 1–2% of patients with schizophrenia receiving oral risperidone in clinical studies. Abnormal accommodation and xerophthalmia also have been reported in 0.1–1% of patients receiving risperidone in clinical studies. In addition, diplopia, ocular pain, blepharitis, photopsia, photophobia, abnormal lacrimation, tinnitus, hyperacusis, and decreased hearing have been reported in fewer than 0.1% of patients.

■ **Other Adverse Effects** Chest pain and fever have been reported in 2–3% of patients with schizophrenia receiving oral risperidone in clinical studies. Although a causal relationship to the drug has not been established, pancreatitis and aggravated parkinsonian syndrome has been reported during postmarketing surveillance.

■ **Precautions and Contraindications** Risperidone shares many of the toxic potentials of other antipsychotic agents (e.g., phenothiazines), and the usual precautions associated with therapy with these agents should be observed. (See Cautions, in the Phenothiazines General Statement 28:16.08.24.)

Because severe hyperglycemia, sometimes associated with ketoacidosis, hyperosmolar coma, or death, has been reported in patients receiving certain atypical antipsychotic agents, including risperidone, the manufacturers of atypical antipsychotic agents state that patients with preexisting diabetes mellitus in whom therapy with an atypical antipsychotic is initiated should be closely monitored for worsening of glucose control; those with risk factors for diabetes (e.g., obesity, family history of diabetes) should undergo fasting blood glucose testing upon therapy initiation and periodically throughout treatment. (See Cautions: Endocrine and Metabolic Effects.) Any patient who develops manifestations of hyperglycemia during treatment with an atypical antipsychotic should undergo fasting blood glucose testing. In some cases, patients who developed hyperglycemia while receiving an atypical antipsychotic have required continuance of antidiabetic treatment despite discontinuance of the antipsychotic; in other cases hyperglycemia resolved with discontinuance of the suspect drug. For further information on the management of diabetes risks in patients receiving atypical antipsychotics, see Hyperglycemia and Diabetes Mellitus under Cautions: Precautions and Contraindications, in Clozapine 28:16.08.04.

Because of the possibility of orthostatic hypotension, caution should be observed in patients with known cardiovascular disease (e.g., history of myocardial infarction or ischemia, heart failure, conduction abnormalities), cerebrovascular disease (see Cautions: Geriatric Precautions), conditions that would predispose patients to hypotension (e.g., dehydration, hypovolemia), and patients receiving antihypertensive agents. Since patients with a recent history of myocardial infarction or unstable heart disease were excluded from clinical studies, clinicians should be aware that risperidone has not been evaluated or used to any appreciable extent in such patients. Patients receiving risperidone should be advised of the risk of orthostatic hypotension, especially during the period of initial dosage titration. (See Cautions: Cardiovascular Effects.)

Patients with parkinsonian syndrome or dementia with Lewy bodies who receive antipsychotics, including risperidone, reportedly have an increased sensitivity to antipsychotic agents. Clinical manifestations of this increased sensitivity have been reported to include confusion, obtundation, postural instability with more frequent falling, extrapyramidal adverse effects, and clinical features consistent with neuroleptic malignant syndrome. (For additional information on extrapyramidal adverse effects and neuroleptic malignant syndrome, see Cautions: Nervous System Effects, in the Phenothiazines General Statement 28:16.08.24.)

Plasma concentrations of risperidone and its principal active metabolite, 9-hydroxyrisperidone, are increased in patients with severe renal impairment (creatinine clearance less than 30 mL/minute per1.73 m^2), and an increased free fraction of risperidone occurs in patients with severe hepatic impairment. Therefore, lower initial dosages should be used in such patients. (See Dosage and Administration.)

Individuals with phenylketonuria (i.e., homozygous genetic deficiency of phenylalanine hydroxylase) and other individuals who must restrict their intake of phenylalanine should be warned that risperidone 0.5-, 1-, 2-, 3-. or 4-mg orally disintegrating tablets contain aspartame (e.g., NutraSweet®) which is metabolized in the GI tract to provide about 0.14, 0.28, or 0.-42, 0.63, or 0.84 mg of phenylalanine, respectively, following oral administration.

Because seizures have occurred in 0.3% of patients receiving risperidone in clinical studies, the drug should be administered with caution to patients with a history of seizures.

Esophageal dysmotility and aspiration have been associated with the use of antipsychotic agents, including risperidone. Because aspiration pneumonia is a common cause of morbidity and mortality in patients with advanced dementia of the Alzheimer's type, risperidone and other antipsychotic drugs should be used with caution in patients at risk for aspiration pneumonia.

Because both hypothermia and hyperthermia have been associated with risperidone therapy, the drug should be administered with caution in patients who will be exposed to temperature extremes.

Because risperidone has the potential to impair judgment, thinking, or motor skills, patients should be cautioned about operating hazardous machinery, including driving automobiles, until they are reasonably certain that risperidone therapy does not adversely affect them.

Risperidone has an antiemetic effect in animals; this effect also may occur in humans, and may mask manifestations of overdosage with certain drugs or may obscure the cause of vomiting in various disorders such as intestinal obstruction, Reye's syndrome or brain tumor.

Patients should be advised to inform their clinician if they are taking, or plan to take, any prescription or nonprescription drugs, or have any concomitant illnesses (e.g., diabetes mellitus). Patients also should be advised to avoid alcohol while taking risperidone.

Risperidone is contraindicated in patients with known hypersensitivity to the drug.

■ **Pediatric Precautions** The manufacturer states that safety and effectiveness of risperidone in children with schizophrenia or acute mania associated with bipolar I disorder have not been established. However, efficacy and safety of the drug in the treatment of irritability associated with autistic disorder have been established in 2 placebo-controlled trials of 8 weeks' duration in 156 children and adolescents aged from 5–16 years. (See Uses: Autistic Disorder.) Additional safety information also was assessed from a long-term study in patients with autistic disorder and from short- and long-term studies in more than 1200 pediatric patients with other psychiatric disorders who were of similar age and weight and who received similar risperidone dosages as patients treated for irritability associated with autistic disorder. Safety and effectiveness of risperidone in pediatric patients with autistic disorder younger than 5 years of age have not been established.

In clinical trials in 1885 children and adolescents with autistic disorder or other psychiatric disorders treated with risperidone, 2 patients (0.1%) reportedly developed tardive dyskinesia, which resolved upon discontinuance of therapy. In addition, approximately 15% of children and adolescents receiving 0.5–2.5 mg daily dosages of risperidone developed withdrawal dyskinesia during the discontinuance phase of one long-term (6 month), open-label study.

In long-term, open-label trials in patients with autistic disorder or other psychiatric disorders, a mean body weight gain of 7.5 kg after 12 months of risperidone therapy was reported, which was higher than the normal expected weight gain (i.e., 3–3.5 kg per year adjusted for age, based on the Centers for Disease Control and Prevention normative data). The majority of the weight increase occurred within the first 6 months of drug exposure. Average percentiles at baseline and at 12 months were 49 and 60 for weight, 48 and 53 for height, and 50 and 62 for body mass index, respectively. When treating pediatric patients with risperidone, the manufacturer recommends that weight gain should be assessed against that expected with normal growth.

Somnolence frequently occurred in placebo-controlled trials in pediatric patients with autistic disorder. Most cases were mild to moderate in severity, occurred early during therapy (peak incidence during the first 2 weeks of therapy), and were transient (median duration of 16 days). Patients experiencing persistent somnolence may benefit from a change in dosage regimen.

Risperidone has been shown to elevate prolactin concentrations in children and adolescents as well as adults. In double-blind, placebo-controlled, 8-week trials in children and adolescents aged from 5–17 years, 49% of risperidone-treated patients had elevated prolactin concentrations compared with 2% of those receiving placebo.

In clinical trials conducted in 1885 children and adolescents with autistic disorder or other psychiatric disorders, galactorrhea and gynecomastia reportedly occurred in 0.8 and 2.3% of risperidone-treated patients, respectively.

The manufacturer states that the long-term effects of risperidone on growth and maturation have not been fully evaluated.

■ **Geriatric Precautions** Clinical studies of risperidone for the management of schizophrenia did not include sufficient numbers of patients 65 years of age and older to determine whether geriatric patients respond differently than younger patients. However, serious adverse effects, including an increased risk of death, have been reported in geriatric patients receiving risperidone or other atypical antipsychotic agents in clinical trials in patients with dementia-related psychosis. Risperidone is not approved for the treatment of dementia-related psychosis. (See Geriatric Considerations in Uses: Psychotic Disorders.)

Adverse cerebrovascular events (e.g., stroke, transient ischemic attack), some of which resulted in fatalities, have been reported in clinical studies of risperidone for the management of psychosis in geriatric patients (mean age 85 years; range 73–97) with dementia. Analysis of pooled data from 4 randomized, placebo-controlled studies indicates that adverse cerebrovascular events occurred in approximately 4% of geriatric patients with dementia of the Alzheimer's type, vascular dementia, or mixed dementia receiving risperidone compared with 2% of those receiving placebo. Although many of the patients who experienced adverse cerebrovascular events during the course of these studies had at least one risk factor for cerebrovascular events (e.g., arrhythmia, atherosclerosis, atrial fibrillation, diabetes, heart failure, hypertension, prior history of stroke or transient ischemic attack), the total number of such patients was too small to permit definitive conclusions about the relationship between known risk factors for cerebrovascular events and risperidone therapy. An increased risk of adverse cerebrovascular events has not been identified to date in clinical studies of risperidone for the management of schizophrenia.

An increased risk of death has been reported among geriatric patients with dementia-related psychosis treated with atypical antipsychotic drugs compared with that among patients receiving placebo. Analyses of 17 placebo-controlled trials (average duration of 10 weeks) revealed an approximate 1.6- to 1.7-fold increase in mortality among geriatric patients receiving atypical antipsychotic drugs (i.e., risperidone, aripiprazole, olanzapine, quetiapine) compared with that in patients receiving placebo. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5% compared with a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature.

A higher incidence of mortality also was observed in geriatric patients with dementia-related psychosis receiving risperidone and furosemide concurrently in placebo-controlled trials when compared with that in patients receiving risperidone alone or placebo and furosemide concurrently. The increase in mortality in patients receiving risperidone and furosemide concurrently was observed in 2 out of 4 clinical trials. The pathological mechanism for this finding remains to be established and no consistent pattern for the cause of death was observed. An increased incidence of mortality in geriatric patients with dementia-related psychosis was observed with risperidone regardless of concurrent furosemide administration.

Risperidone dosage generally should be titrated carefully in geriatric patients, usually initiating therapy at the low end of the dosage range. The greater frequency of decreased hepatic, renal, and/or cardiac function and of concomitant disease and drug therapy observed in the elderly also should be considered. Although geriatric patients exhibit a greater tendency to orthostatic hypotension, the manufacturer states that its risk may be minimized by limiting the initial oral dosage to 0.5 mg twice daily followed by careful titration and close monitoring of orthostatic vital signs in patients for whom this is of concern. More recent evidence however, indicates that even lower initial dosages and slower dosage titration are better tolerated in these patients. Therefore, some clinicians recommend initiating oral risperidone therapy at 0.25 mg daily, and gradually increasing dosages, as tolerated, to a dosage of 2 mg daily in these patients. Higher oral dosages (e.g., 3 or 4 mg daily) may be required in some patients, but are usually associated with greater incidence of extrapyramidal reactions. Most geriatric patients should *not* be maintained at an oral risperidone dosage exceeding 3 mg daily. (See Geriatric Patients and Others at Risk of Orthostatic Hypotension under Dosage and Administration: Dosage.)

■ **Mutagenicity and Carcinogenicity** Risperidone did not exhibit mutagenic potential in in vitro chromosomal aberration studies in human lymphocytes or Chinese hamster cells, mouse lymphoma assay, in vitro rat hepatocyte DNA-repair assay, in vivo micronucleus test in mice, the sex-linked recessive lethal test in Drosophila, or in microbial (Ames) test systems.

Statistically significant increases in pituitary gland adenomas and mammary gland adenocarcinomas were observed in female mice receiving risperidone dosages of 0.63, 2.5, and 10 mg/kg (equivalent to 2.4, 9.4, and 37.5 times the maximum recommended human dosage for schizophrenia on a mg/kg basis or 0.2, 0.75, and 3 times the maximum recommended human dosage on a mg/m^2 basis, respectively) for 18 months. In addition, statistically significant increases were observed in mammary gland adenocarcinomas in both male and female rats, and mammary gland neoplasms and endocrine pancreas adenomas in male rats receiving risperidone dosages of 0.63, 2.5, and 10 mg/kg (equivalent to 0.4, 1.5, and 6 times the maximum recommended human dosage for schizophrenia on a mg/kg basis or 0.2, 0.75, and 3 times the maximum recommended human dosage on a mg/m^2 basis, respectively) for 25 months.

Although an increase in mammary neoplasms has been found in rodents following long-term administration of prolactin-stimulating antipsychotic agents, no clinical or epidemiologic studies conducted to date have shown an association between long-term administration of prolactin-stimulating drugs and mammary tumorigenesis in humans. Current evidence is considered too limited to be conclusive, and further study is needed to determine the clinical importance in most patients of elevated serum prolactin concentrations associated with antipsychotic agents. Since in vitro tests indicate that approximately

one-third of human breast cancers are prolactin-dependent, risperidone should be used with caution in patients with previously detected breast cancer.

■ **Pregnancy, Fertility, and Lactation** Reproductive studies in rats and rabbits using risperidone dosages of 0.4–6 times the maximum recommended human dosage on a mg/m² basis have not revealed evidence of fetal malformation. However, risperidone has been shown to cross the placenta in rats, and an increased rate of stillborn rat pups occurred at dosages 1.5 times higher than the maximum recommended human dosage on a mg/m² basis. In 3 reproductive studies in rats, there was an increase in pup deaths during the first 4 days of lactation at dosages 0.1–3 times the human dosage on a mg/m² basis. It is not known whether these deaths resulted from a direct effect on the fetuses or pups or to effects on the dams. In a separate reproductive study in rats, an increased number of pup daths (at birth or by the day after birth) and a decrease in birth weight were observed in pups of dams treated with risperidone dosages that were 3 times the maximum recommended human dosage on a mg/m² basis. Risperidone also appeared to impair maternal behavior, as evidenced by reduced weight gain and decreased survival (from day 1–4 of lactation) in pups born to control dams but reared by risperidone-treated dams.

Although there are no adequate and controlled studies to date in humans, one case of agenesis of the corpus callosum has been reported in an infant exposed to risperidone in utero; however, a causal relationship to risperidone therapy is unknown. Reversible extrapyramidal adverse effects in the neonate also were observed following postmarketing use of risperidone during the third trimester of pregnancy. Risperidone should be used during pregnancy only when the potential benefits justify the possible risks to the fetus. The effect of risperidone on labor and delivery in humans is unknown.

Risperidone (0.16–5 mg/kg) has been shown to impair mating, but not fertility, in Wistar rats in 3 reproductive studies at dosages 0.1–3 times the maximum recommended human dosage on a mg/m² basis. The effect appeared to be in females since impaired mating behavior was not noted in the Segment I study in which males only were treated. Sperm motility and serum testosterone concentrations were decreased in beagles at dosages 0.6–10 times the human dose on a mg/m² basis. Serum testosterone and sperm parameters partially recovered but remained decreased after treatment was discontinued. A no-effect dosage was not found in these studies in either rats or dogs.

Risperidone and its principal active metabolite, 9-hydroxyrisperidone, are distributed into milk. The manufacturer states that women receiving risperidone should avoid nursing.

Description

Risperidone is a benzisoxazole-derivative antipsychotic agent and is chemically unrelated to other antipsychotic agents. While risperidone shares some of the pharmacologic actions of other antipsychotic agents, the drug has been described as an atypical or second-generation antipsychotic agent since many of its CNS effects differ from those of typical or first-generation agents (e.g., butyrophenones, phenothiazines). The exact mechanism of antipsychotic action of risperidone has not been fully elucidated but, like that of clozapine, appears to be more complex than that of most other antipsychotic agents and may involve antagonism of central type 2 serotonergic ($5\text{-}HT_2$) receptors and central dopamine D_2 receptors.

SumMon® (see Users Guide). For additional information on this drug until a more detailed monograph is developed and published, the manufacturer's labeling should be consulted. It is *essential* that the labeling be consulted for detailed information on the usual cautions, precautions, and contraindications concerning potential drug interactions and/or laboratory test interferences and for information on acute toxicity.

Preparations

Excipients in commercially available drug preparations may have clinically important effects in some individuals; consult specific product labeling for details.

Risperidone

Oral		
Solution	1 mg/mL	**Risperdal®**, Janssen
Tablets	0.25 mg	**Risperdal®** (scored), Janssen
	0.5 mg	**Risperdal®** (scored), Janssen
	1 mg	**Risperdal®** (scored), Janssen
	2 mg	**Risperdal®** (scored), Janssen
	3 mg	**Risperdal®** (scored), Janssen
	4 mg	**Risperdal®** (scored), Janssen
Tablets, orally disintegrating	0.5 mg	**Risperdal® M-TAB®**, Janssen
	1 mg	**Risperdal® M-TAB®**, Janssen
	2 mg	**Risperdal® M-TAB®**, Janssen
	3 mg	**Risperdal® M-TAB®**, Janssen
	4 mg	**Risperdal® M-TAB®**, Janssen
Parenteral		
For injectable suspension, extended-release, for IM use	25 mg	**Risperdal® Consta®** (available as dose pack containing a SmartSite® needle-free vial access device, a Needle-Pro® safety needle, and with 2-mL prefilled syringe diluent), Janssen
	37.5 mg	**Risperdal® Consta®** (available as dose pack containing a SmartSite® needle-free vial access device, a Needle-Pro® safety needle, and with 2-mL prefilled syringe diluent), Janssen
	50 mg	**Risperdal® Consta®** (available as dose pack containing a SmartSite® needle-free vial access device, a Needle-Pro® safety needle, and with 2-mL prefilled syringe diluent), Janssen

†Use is not currently included in the labeling approved by the US Food and Drug Administration

Ziprasidone

■ Ziprasidone has been referred to as an atypical or second-generation antipsychotic agent.

Uses

■ **Psychotic Disorders** *Schizophrenia* Ziprasidone is used for the symptomatic management of schizophrenia. Drug therapy is integral to the management of acute psychotic episodes and accompanying violent behavior in patients with schizophrenia and generally is required for long-term stabilization to sustain symptom remission or control and to minimize the risk of relapse. Antipsychotic agents are the principal class of drugs used for the management of all phases of schizophrenia. Patient response and tolerance to antipsychotic agents are variable, and patients who do not respond to or tolerate one drug may be successfully treated with an agent from a different class or with a different adverse effect profile.

Because of ziprasidone's greater capacity to prolong the QT/QT_c-interval compared with that of several other antipsychotic agents, use of ziprasidone may be reserved for patients whose disease fails to respond adequately to appropriate courses of other antipsychotic agents. (See Prolongation of QT interval under Warnings/Precautions: Warnings, in Cautions.) However, it should be noted that patients with a history of resistance to antipsychotic therapy (i.e., failed to respond to adequate courses of 2 or more antipsychotic agents) usually were excluded in clinical studies of ziprasidone.

Efficacy of oral ziprasidone was evaluated in 5 placebo-controlled studies of variable duration (4 short-term [4–6 weeks] and one long-term [52 weeks]), principally in patients with schizophrenic disorders in hospital settings. Ziprasidone appears to be superior to placebo in improving both positive and negative manifestations in acute exacerbations of schizophrenia and in reducing the rate of relapse for up to 52 weeks.

Although results of a limited comparative study suggest that oral ziprasidone hydrochloride dosages of 160 mg daily may be as effective as oral haloperidol 15 mg daily in reducing positive symptoms of schizophrenia, a reliable and valid comparison of ziprasidone and oral haloperidol cannot be made at this time based solely on this study due to its relatively small sample size (90 patients), high dropout rate (51.1%), and brief duration (4 weeks). Data from one unpublished comparative study also suggest that ziprasidone hydrochloride (mean dosage of 130 mg daily) may be as effective as olanzapine (mean dosage of 11 mg daily) in the treatment of schizophrenia.

Ziprasidone is used IM for the management of acute agitation in patients with schizophrenia for whom treatment with ziprasidone is appropriate and who require an IM antipsychotic agent for rapid control of behaviors that interfere with diagnosis and care (e.g., threatening behaviors, escalating or urgently distressing behavior, self-exhausting behavior). The efficacy of IM ziprasidone for the management of acute agitation in schizophrenia was established in single-day controlled trials in hospital settings. Because there is no experience regarding the safety of administering ziprasidone IM to schizophrenic patients already receiving oral ziprasidone, concomitant use of oral and IM formulations of ziprasidone is *not* recommended.

For additional information on the symptomatic management of schizophrenia, including treatment recommendations and results of the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE), see Schizophrenia and Other Psychotic Disorders under Uses: Psychotic Disorders, in the Phenothiazines General Statement 28:16.08.24.

■ **Bipolar Disorder** Ziprasidone is used for the treatment of acute manic and mixed episodes (with or without psychotic features) associated with bipolar I disorder. According to DSM-IV criteria, manic episodes are distinct periods lasting 1 week or longer (or less than 1 week if hospitalization is required) of abnormally and persistently elevated, expansive, or irritable mood accompanied by at least 3 (or 4 if the mood is only irritability) of the following 7

Risperidone

Dosing & Indications

- **Adult Dose**

  - Risperdal(R) orally disintegrating tablets are bioequivalent to Risperdal(R) tablets
  - previous oral antipsychotics should be continued for 3 weeks following the initiation of therapy with risperidone long-acting injection to ensure that adequate therapeutic concentrations are maintained until the main release phase of risperidone from the injection site has begun
  - Bipolar I disorder: (oral, monotherapy or in combination with lithium or valproate) initial, 2 to 3 mg ORALLY once a day; maintenance, dosage adjustments should be made in increments of 1 mg/day at intervals of at least 24 hours; doses higher than 6 mg/day have not been evaluated in clinical trials
  - Bipolar I disorder: (IM, monotherapy or in combination with lithium or valproate) establish tolerability to oral risperidone prior to initiation of treatment with the risperidone long-acting IM injection; initial, 25 mg IM every 2 weeks; oral risperidone or another antipsychotic medication should be given with the initial injection and should be continued for 3 weeks and then discontinued
  - Bipolar I disorder: (IM, monotherapy or in combination with lithium or valproate) maintenance, dose may be increased to 37.5 mg or 50 mg IM at intervals of at least 4 weeks; clinical effects of dose adjustment should not be expected earlier than 3 weeks after the injection of the higher dose; MAX 50 mg IM every 2 weeks
  - Schizophrenia: (oral) initial, 2 mg/day ORALLY, administered either once or twice daily; increase as tolerated in increments of 1 to 2 mg/day (or slower) at intervals not less than 24 hours, to a recommended dose of 4 to 8 mg/day; doses above 6 mg/day for twice-daily dosing were not shown to be more efficacious than lower doses; the safety of doses above 16 mg/day has not been evaluated in clinical trials
  - Schizophrenia: (oral) maintenance, 2 mg/day to 8 mg/day
  - Schizophrenia: (oral) if risperidone is discontinued, restart with the initial titration schedule
  - Schizophrenia: (oral) when switching from other antipsychotic agents, minimize the period of overlapping administration.
  - Schizophrenia: (oral) when switching from depot antipsychotics, initiate risperidone therapy in place of the next scheduled injection
  - Schizophrenia: (IM) establish tolerability to oral risperidone prior to initiation of treatment with the risperidone long-acting IM injection; initial, 25 mg IM every 2 weeks; oral risperidone or another antipsychotic medication should be given with the initial injection and should be continued for 3 weeks and then discontinued
  - Schizophrenia: (IM) maintenance, dose may be increased to 37.5 mg or 50 mg IM at intervals of at least 4 weeks; clinical effects of dose adjustment should not be expected earlier than 3 weeks after the injection of the higher dose; MAX 50 mg IM every 2 weeks

- **Pediatric Dose**

  - safety and effectiveness of long-acting risperidone injection has not been established in pediatric patients younger than 18 years
  - safety and effectiveness of oral risperidone in pediatric patients younger than 13 years with schizophrenia have not been established
  - safety and effectiveness of oral risperidone in pediatric patients younger than 10 years with bipolar mania has not been established
  - safety and effectiveness or oral risperidone in pediatric patients younger than 5 years with autistic disorder have not been established
  - Autistic disorder - Irritability: dosing individualized according to the response and tolerability, over a dose range of 0.5 to 3 mg/day
  - Autistic disorder - Irritability: (5 years or older; weight less than 20 kg) initial, 0.25 mg ORALLY once a day or half the total daily dose given twice daily; may increase after a minimum of 4 days to 0.5 mg/day; maintenance, 0.5 mg ORALLY once a day or half the total daily dose given twice daily; maintain the dose for a minimum of 14 days and may increase doses at 2-week intervals or longer,

in increments of 0.25 mg per day to achieved sufficient clinical response; dosing data in children weighing less than 15 kg is not available
- Autistic disorder - Irritability: (age 5 years or older; weight 20 kg or greater) initial, 0.5 mg ORALLY once a day or half the total daily dose given twice daily; may increase after a minimum of 4 days to 1 mg/day; maintenance, 1 mg ORALLY once a day or half the total daily dose given twice daily; maintain the dose for a minimum of 14 days; may increase doses at 2-week intervals or longer, in increments of 0.5 mg per day to achieve sufficient clinical response
- Autistic disorder - Irritability: in patients with persistent somnolence, administering a once daily dose at bedtime, or half the daily dose twice daily, or a reduced dose may be beneficial
- Bipolar I disorder: (10 years or older) initial, 0.5 mg ORALLY once daily as a single dose in the morning or evening; adjust dosage at intervals not less than 24 hours and in increments of 0.5 to 1 mg/day up to a recommended dose of 2.5 mg/day
- Bipolar I disorder: in patients with persistent somnolence, administering half the daily dose twice daily may be beneficial
- Schizophrenia: (13 years or older) initial, 0.5 mg ORALLY once daily as a single dose in the morning or evening; adjust dosage at intervals not less than 24 hours and in increments of 0.5 to 1 mg/day up to a recommended dose of 3 mg/day
- Schizophrenia: in patients with persistent somnolence, administering half the daily dose twice daily may be beneficial
- Schizophrenia: if risperidone is discontinued, restart with the initial titration schedule
- Schizophrenia: when switching from other antipsychotic agents, minimize the period of overlapping administration.
- Schizophrenia: when switching from depot antipsychotics, initiate risperidone therapy in place of the next scheduled injection

- **Dose Adjustments**

- concomitant CYP3A4 inducers (eg, carbamazepine, phenytoin, rifampin, phenobarbital): titrate dose to desired effect
- concomitant CYP2D6 inhibitors (eg, fluoxetine, paroxetine): titrate dose to desired effect
- debilitated patients (oral): initial dose 0.5 mg ORALLY twice a day; dosage increases in these patients should be in increments of no more than 0.5 mg twice a day, with increases to dosages above 1.5 mg twice a day occurring at intervals of at least 1 week. If a once-a-day dosing regimen is being considered, it is recommended that the patient be titrated on a twice-a-day regimen for 2 to 3 days at the target dose and then switched to once-daily dosing
- geriatric (oral): initial dose 0.5 mg ORALLY twice a day; increase dose in increments of no more than 0.5 mg twice a day, with increases to dosages above 1.5 mg twice a day occurring at intervals of at least 1 week. If a once-a-day dosing regimen is desired, initiate and titrate on a twice-a-day regimen for 2 to 3 days to the target dose; switch to a once-a-day dosing regimen can be done thereafter
- geriatric (IM): 25 mg IM every 2 weeks
- hepatic impairment (IM): administer titrated doses of ORAL risperidone prior to starting IM therapy in these patients; initial, 0.5 mg ORALLY twice daily for 1 week, then dose may be increased to 1 mg twice daily OR 2 mg once daily in the second week; if a 2 mg ORAL dose is well tolerated, 12.5 mg or 25 mg of the long-acting injection may be given IM every 2 weeks
- hepatic impairment, severe (oral): initial dose, 0.5 mg ORALLY twice daily; increase dose in increments of no more than 0.5 mg twice a day, with increases to dosages above 1.5 mg twice a day occurring at intervals of at least 1 week
- hypotension (oral): patients either predisposed to hypotension or for whom hypotension would pose a risk, initial dose 0.5 mg ORALLY twice a day; increase dose in increments of no more than 0.5 mg twice a day, with increases to dosages above 1.5 mg twice a day occurring at intervals of at least 1 week
- poor tolerability to psychotropic medications: although the efficacy has not been confirmed in clinical trials, 12.5 mg IM may be given
- renal impairment, severe (oral): initial dose, 0.5 mg ORALLY twice daily; increase dose in increments of no more than 0.5 mg twice a day, with increases to dosages above 1.5 mg twice a day occurring at intervals of at least 1 week
- renal impairment (IM): administer titrated doses of ORAL risperidone prior to starting IM therapy in

these patients; initial, 0.5 mg ORALLY twice daily for one week, then dose may be increased to 1 mg twice daily OR 2 mg once daily in the second week; if a 2 mg ORAL dose is well tolerated, 12.5 mg or 25 mg of the long-acting injection may be given IM every 2 weeks

- **FDA Labeled Indications**
  - Autistic disorder - Irritability
    - FDA Approval:
      Adult, no
      Pediatric, yes 5 years or older, oral only
    - Efficacy:
      Pediatric, Effective
    - Strength of Recommendation:
      Pediatric, Class IIa
    - Strength of Evidence:
      Pediatric, Category B
  - Bipolar I disorder
    - FDA Approval:
      Adult, yes oral and IM
      Pediatric, yes 10 years or older, oral only
    - Efficacy:
      Adult, Effective
      Pediatric, Evidence favors efficacy
    - Strength of Recommendation:
      Adult, Class IIa
      Pediatric, Class IIb
    - Strength of Evidence:
      Adult, Category B
      Pediatric, Category B
  - Schizophrenia
    - FDA Approval:
      Adult, yes oral and IM
      Pediatric, yes 13 years or older, oral only
    - Efficacy:
      Adult, Effective
      Pediatric, Evidence favors efficacy
    - Strength of Recommendation:
      Adult, Class IIa
      Pediatric, Class IIb
    - Strength of Evidence:
      Adult, Category B
      Pediatric, Category B

- **Non-FDA Labeled Indications**
  - Behavioral syndrome - Mental retardation
    - FDA Approval:
      Adult, no
      Pediatric, no
    - Efficacy:
      Adult, Evidence favors efficacy
      Pediatric, Evidence favors efficacy
    - Strength of Recommendation:
      Adult, Class IIb
      Pediatric, Class IIb
    - Strength of Evidence:
      Adult, Category B
      Pediatric, Category B
  - Gilles de la Tourette's syndrome
    - FDA Approval:
      Adult, no
      Pediatric, no
    - Efficacy:
      Adult, Evidence favors efficacy
      Pediatric, Evidence favors efficacy
    - Strength of Recommendation:
      Adult, Class IIb
      Pediatric, Class IIb
    - Strength of Evidence:
      Adult, Category B
      Pediatric, Category B
  - Pervasive developmental disorder
    - FDA Approval:
      Adult, no
      Pediatric, no
    - Efficacy:
      Pediatric, Evidence favors efficacy
    - Strength of Recommendation:
      Pediatric, Class IIb
    - Strength of Evidence:
      Pediatric, Category B

Black Box WARNING

Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death compared with placebo. Although the causes of death in clinical trials were varied, most of the deaths appeared to be either cardiovascular (eg, heart failure, sudden death) or infectious (eg, pneumonia) in nature. Observational studies suggest that antipsychotic drugs may increase mortality. It is unclear from the observational studies to what extent these mortality findings may be attributed to the antipsychotic drug as opposed to patient characteristics. Risperidone is not approved for the treatment of patients with dementia-related psychosis. Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Risperidone is not approved for the treatment of patients with dementia-related psychosis.

Contraindications/Warnings

- **Contraindications**

  - hypersensitivity to risperidone, paliperidone (an active metabolite of risperidone) or to any product component

- **Precautions**

  - elderly patients with dementia-related psychosis (unapproved use); increased risk of death and increased risk of cerebrovascular events (cerebrovascular accidents and TIA, some fatal); most deaths were attributed to cardiovascular events (eg, heart failure or sudden death) or infections (eg, pneumonia)
  - agranulocytosis, leukopenia, and neutropenia have been reported; risk factors include preexisting low WBC and history of drug-induced leukopenia or neutropenia; monitoring recommended; discontinue if significant WBC decline with no other causative factors or if patient has severe neutropenia (ie, absolute neutrophil count less than 1000/mm(3))
  - cardiovascular or cerebrovascular disease or conditions that predispose patients to hypotension (eg, dehydration, hypovolemia, antihypertensive medications); increased risk of orthostatic hypotension
  - conditions that may contribute to elevated body temperature; disruption of body temperature regulation has been reported with antipsychotic agents
  - diabetes mellitus or risk factors for diabetes mellitus (eg, obesity, family history); increased risk of worsening of glucose control or severe hyperglycemia; monitoring recommended
  - dyslipidemia, which may increase cardiovascular or cerebrovascular risk has been reported
  - elderly patients, especially elderly women; increased risk of tardive dyskinesia
  - elderly patients; increased risk of orthostatic hypotension, especially during the initial dose-titration period (oral)
  - esophageal dysmotility and aspiration may occur; use cautiously in patients at risk for aspiration pneumonia
  - hepatic impairment; increase in the free fraction of risperidone reported with severe impairment; dosage adjustment recommended
  - hyperglycemia (some cases extreme and associated with ketoacidosis, hyperosmolar coma, or death) has been reported with atypical antipsychotic use; monitoring recommended
  - hyperprolactinemia; may result in galactorrhea, amenorrhea, gynecomastia, impotence, hypogonadism, and decreased bone density; incidence of hyperprolactinemia appears to be higher with risperidone relative to other antipsychotic agents
  - increased duration of therapy and/or higher cumulative doses; increased risk of tardive dyskinesia
  - neuroleptic malignant syndrome (NMS), potentially fatal, has been reported in association with antipsychotic drugs; immediately discontinue drug if NMS is suspected
  - patients with phenylketonuria; contains phenylalanine, a component of aspartame (oral disintegrating tablet)
  - Parkinson disease or dementia with Lewy bodies; increased sensitivity to antipsychotic medications
  - priapism has been reported; severe cases may require surgical intervention
  - renal impairment; increased plasma concentrations reported with severe impairment (CrCl less than 30 mL/min/1.73 m(2)); dosage adjustment recommended
  - seizure disorder, history, or conditions that lower seizure threshold
  - suicide risk; close monitoring of high-risk patients recommended
  - tardive dyskinesia, potentially irreversible; discontinue treatment if appropriate

- weight gain, which may increase cardiovascular or cerebrovascular risk has been reported; monitoring recommended
- report suspected adverse reactions to the US Food and Drug Administration at 1-800-FDA-1088 or www.fda.gov/medwatch

- **Pregnancy Category**

  - C (FDA)
  - B3 (AUS)

- **Breast Feeding**

  - Micromedex: Infant risk cannot be ruled out.

Drug Interactions

- **Contraindicated**

  - ◇ Bepridil (theoretical)
  - ◇ Cisapride (theoretical)
  - ◇ Levomethadyl (theoretical)
  - ◇ Mesoridazine (theoretical)
  - ◇ Metoclopramide (theoretical)
  - ◇ Pimozide (theoretical)
  - ◇ Terfenadine (theoretical)
  - ◇ Thioridazine (theoretical)

- **Major**

  - ◇ Acecainide (theoretical)
  - ◇ Ajmaline (probable)
  - ◇ Amiodarone (theoretical)
  - ◇ Amisulpride (theoretical)
  - ◇ Amitriptyline (theoretical)
  - ◇ Amoxapine (theoretical)
  - ◇ Aprindine (theoretical)
  - ◇ Arsenic Trioxide (theoretical)
  - ◇ Asenapine (theoretical)
  - ◇ Astemizole (theoretical)
  - ◇ Azimilide (theoretical)
  - ◇ Bretylium (theoretical)
  - ◇ Chloral Hydrate (theoretical)
  - ◇ Chloroquine (theoretical)
  - ◇ Chlorpromazine (theoretical)
  - ◇ Citalopram (probable)
  - ◇ Clarithromycin (theoretical)
  - ◇ Desipramine (theoretical)
  - ◇ Dibenzepin (theoretical)
  - ◇ Disopyramide (probable)
  - ◇ Dofetilide (theoretical)
  - ◇ Dolasetron (theoretical)
  - ◇ Doxepin (theoretical)
  - ◇ Droperidol (theoretical)
  - ◇ Encainide (theoretical)
  - ◇ Enflurane (theoretical)
  - ◇ Erythromycin (theoretical)
  - ◇ Flecainide (theoretical)

- Fluconazole (theoretical)
- Foscarnet (theoretical)
- Gemifloxacin (theoretical)
- Ginkgo Biloba (probable)
- Halofantrine (theoretical)
- Haloperidol (theoretical)
- Halothane (theoretical)
- Hydromorphone (theoretical)
- Hydroquinidine (probable)
- Ibutilide (theoretical)
- Imipramine (theoretical)
- Isoflurane (theoretical)
- Isradipine (theoretical)
- Lidoflazine (theoretical)
- Linezolid (probable)
- Lithium (probable)
- Lorcainide (theoretical)
- Mefloquine (theoretical)
- Milnacipran (theoretical)
- Nortriptyline (theoretical)
- Octreotide (theoretical)
- Pazopanib (theoretical)
- Pentamidine (theoretical)
- Pirmenol (probable)
- Prajmaline (probable)
- Probucol (theoretical)
- Procainamide (probable)
- Prochlorperazine (theoretical)
- Propafenone (theoretical)
- Protriptyline (theoretical)
- Quetiapine (probable)
- Sematilide (theoretical)
- Sertindole (theoretical)
- Simvastatin (probable)
- Sotalol (theoretical)
- Spiramycin (theoretical)
- Sulfamethoxazole (theoretical)
- Sultopride (theoretical)
- Tedisamil (theoretical)
- Telithromycin (theoretical)
- Tetrabenazine (theoretical)
- Tramadol (theoretical)
- Trifluoperazine (theoretical)
- Trimethoprim (theoretical)
- Trimipramine (theoretical)
- Vasopressin (theoretical)
- Zolmitriptan (theoretical)
- Zotepine (theoretical)

- **Moderate**

  - Bupropion (probable)
  - Carbamazepine (probable)
  - Cimetidine (probable)
  - Fluoxetine (probable)
  - Fosphenytoin (probable)
  - Itraconazole (established)
  - Ketoconazole (established)

- Lamotrigine (probable)
- Levorphanol (probable)
- Methadone (probable)
- Midodrine (probable)
- Paroxetine (established)
- Phenobarbital (probable)
- Phenytoin (probable)
- Ranitidine (probable)
- Ritonavir (probable)
- Valproic Acid (probable)

Adverse Effects

- **COMMON**

  - Dermatologic: Rash (oral, adults, 1% to 4%; pediatrics, up to 11%; IM, less than 4%)
  - Endocrine metabolic: Hyperprolactinemia (oral, adults, less than 1%; pediatrics, 49% to 87%; IM, less than 4%), Weight increased (oral, adult, 8.7% to 20.9%; pediatric, 14% to 32.6%; IM, adult, 8% to 10%)
  - Gastrointestinal: Constipation (oral, 8% to 21%; IM, 5% to 7%), Diarrhea (oral, 1% to 8%; IM, less than 4%), Excessive salivation (oral, 1% to 10%; IM, 1% to 4%), Increased appetite (oral, adult, more than 5%; pediatric, 4% to 47%; IM, 4%), Indigestion (oral, 2% to 10%; IM, 6%), Nausea (oral, 4% to 16%; IM, 3% to 4%), Upper abdominal pain (oral, adult, more than 5%; pediatric, 13% to 16%), Vomiting (oral, 10% to 25%; IM, less than 4%), Xerostomia (oral, 4% to 15%; IM, up to 7%)
  - Neurologic: Akathisia (oral, up to 10%; IM, 4% to 11%), Dizziness (oral, 4% to 16%; IM, 3% to 11%), Dystonia (oral, adult, 3% to 5%; pediatric, 2% to 6%; IM, adult, less than 4%), Parkinsonism (oral, 6% to 28%; IM, 8% to 15%), Sedated (oral, adult, 3% to 6%; pediatric, 8% to 29%), Tremor (oral, 2% to 12%; IM, 3% to 24%)
  - Ophthalmic: Blurred vision (oral, 1% to 7%; IM, 2% to 3%)
  - Psychiatric: Anxiety (oral, up to 16% IM, less than 4%)
  - Respiratory: Cough (oral, adults, 2%; pediatrics, 24%; IM, 2% to 4%), Nasal congestion (oral, adult, 4% to 6%; pediatric, 13%), Nasopharyngitis (oral, adult, 3% to 4%; pediatric, 21%), Pain in throat (oral, adult, more than 5%; pediatric, 3% to 10%), Upper respiratory infection (oral, 2% to 8%; IM, 2% and 6%)
  - Other: Fatigue (oral, adult, 1% to 3%; pediatric, 18% to 42%; IM, 3% to 9%), Pain, General (IM, 1% to 4%)

- **SERIOUS**

  - Cardiovascular: Prolonged QT interval, Sudden cardiac death, Syncope (oral, up to 1%; IM, up to 2%)
  - Endocrine metabolic: Diabetic ketoacidosis, Hypothermia
  - Gastrointestinal: Pancreatitis
  - Hematologic: Agranulocytosis, Leukopenia, Neutropenia, Thrombocytopenia, Thrombotic thrombocytopenic purpura
  - Neurologic: Cerebrovascular accident (oral, less than 5%; IM, less than 4%), Seizure (oral, 0.3%; IM, 0.3%), Tardive dyskinesia (oral, less than 5%; IM, less than 4%)
  - Reproductive: Priapism
  - Respiratory: Pulmonary embolism
  - Other: Neuroleptic malignant syndrome (oral, adults, less than 1%; pediatrics, less than 5%)

Name Info

- **US Trade Names**

- Risperdal

- Risperdal Consta
- Risperdal M-Tab
- RisperiDONE M-Tab

- **Class**
  - Antipsychotic
  - Benzisoxazole

- **Regulatory Status**
  - RX

- **Generic Availability**
  - Yes

Mechanism of Action/Pharmacokinetics

- **Mechanism of Action**
  - The mechanism by which risperidone exerts its antipsychotic effect is unknown. Risperidone is a selective monoaminergic antagonist with a strong affinity for serotonin Type 2 (5-HT2) receptors and a slightly weaker affinity for dopamine Type 2 (D2) receptors. The antipsychotic activity of risperidone may be mediated through antagonism at a combination of these receptor sites, particularly through blockade of cortical serotonin receptors and limbic dopamine systems. Risperidone also has moderate affinity for the alpha 1-adrenergic, alpha 2-adrenergic, and H1-histaminergic receptors. The affinity of risperidone for the serotonin 5-HT1A, 5-HT1C, and 5-HT1D receptors is low to moderate, while its affinity for dopamine D1 and the haloperidol-sensitive sigma site is weak. Risperidone has negligible affinity for cholinergic-muscarinic, beta-adrenergic, and serotonin 5-HT1B and 5-HT3 receptors.

- **Pharmacokinetics**
  - **Absorption**
    - ◇ Tmax, IM: 29 to 31 days
    - ◇ Tmax, Oral, adult: 1 hour
    - ◇ Tmax, Oral, pediatric: 2 hours
    - ◇ Bioavailability, oral: 70%
    - ◇ Effects of food: none
  - **Distribution**
    - ◇ Vd: 1.1 L/kg (1 to 2 L/kg)
    - ◇ Protein binding, adults: 90% (risperidone); 77% (9-hydroxyrisperidone)
    - ◇ Protein binding, adolescents: 85.3% (risperidone), 71.9% (9-hydroxyrisperidone)
    - ◇ Protein binding, children: 88.3% (risperidone); 75% (9-hydroxyrisperidone)
  - **Metabolism**
    - ◇ Hepatic: extensively via CYP2D6 pathway
    - ◇ 9-hydroxy-risperidone: active
  - **Excretion**

- Fecal: 14% (risperidone and its metabolites)
- Risperidone, Renal: adults, 70%; adolescents, 7.4%; children, 4.3%;
- 9-hydroxyrisperidone, Renal: adolescents, 26%; children, 23.9%
- Renal clearance: 0.96 L/hr
- Total body clearance: adults, 3.2 to 3.3 L/hr in poor CYP2D6 metabolizers; 13.7 L/hr (risperidone) and 5 L/hr (risperidone plus 9-hydroxyrisperidone) in extensive CYP2D6 metabolizers
- Total body clearance: adolescent, 18.1 L/hr; children, 13.5 L/hr

- **Elimination Half Life**

  - 3 to 20 hours (oral); 2.9 to 6 days (IM)
  - active moiety: 8 days
  - 9-hydroxyrisperidone: 21 to 30 hours

Administration/Monitoring

- **Administration**

  - Intramuscular

    - Intramuscular: (long-acting injection) administer by deep IM injection into the deltoid or gluteal muscles; must be administered with only the appropriate needle supplied in the dose pack, alternating between the 2 arms or 2 buttocks; do not inject intravenously
    - Intramuscular: (long-acting injection) do not combine different dosage strengths in a single administration
    - Intramuscular: (long-acting injection) reconstitute only with diluent supplied in the dose pack; use immediately after reconstitution, but may be stored at room temperature (not exceeding 77 degrees F (25 degrees C)) for up to 6 hours; shake vigorously to resuspend just prior to administration

  - Oral

    - Oral: (orally disintegrating tablets) consume tablet immediately once it is removed from the blister unit; tablets disintegrate in the mouth within seconds and can be swallowed subsequently with or without liquid
    - Oral: (orally disintegrating tablets) do not split or chew
    - Oral: (orally disintegrating tablets) peel back foil to expose tablet; do not push the tablet through the foil backing
    - Oral: (solution) may be administered directly from the calibrated pipette, or can be mixed with water, coffee, orange juice, or low-fat milk; it is NOT compatible with cola or tea
    - Oral: may be taken with or without meals

- **Monitoring**

  - improvement in the signs and symptoms of bipolar disorder (manic or mixed episodes), schizophrenia, or irritability associated with autistic disorder are indicative of efficacy
  - personal and family history of obesity, diabetes mellitus, and cardiovascular disease, baseline, and updated annually
  - CBC with differential; frequently during the first few months of therapy in patients with preexisting low WBC or a history of drug-induced leukopenia or neutropenia
  - fasting blood glucose test; baseline, at week 12, and annually in all patients; more frequently for patients with risk factors for diabetes mellitus; diabetic patients should be closely monitored for worsening glucose control
  - fasting lipid profile; baseline, at week 12, and every 5 years thereafter
  - blood pressure; baseline, at week 12, and annually thereafter; more frequently in patients with risk factors for hypertension

- waist circumference; baseline, and annually thereafter
- weight and BMI; baseline, at week 4, at week 8, at week 12, following initiation and change in therapy, and quarterly thereafter
- orthostatic vital signs in patients predisposed to hypotension
- tardive dyskinesia; baseline, and annually thereafter; every 6 months in patients with higher risk (ie, elderly, patients who have experienced acute dystonic reactions, akathisia, or other clinically significant extrapyramidal side effects)
- suicide risk; patients at high-risk for suicide should be closely supervised during therapy

How Supplied

- Generic
  - ◇ Oral Solution: 1 MG/ML
  - ◇ Oral Tablet: 0.25 MG, 0.5 MG, 1 MG, 2 MG, 3 MG, 4 MG
  - ◇ Oral Tablet, Disintegrating: 0.25 MG, 0.5 MG, 1 MG, 2 MG, 3 MG, 4 MG
- Risperdal Consta
  - ◇ Intramuscular Powder for Suspension, Extended Release: 12.5 MG, 25 MG, 37.5 MG, 50 MG
- Risperdal M-Tab
  - ◇ Oral Tablet, Disintegrating: 0.5 MG, 1 MG, 2 MG
- Risperdal M-TAB
  - ◇ Oral Tablet, Disintegrating: 3 MG, 4 MG
- Risperdal
  - ◇ Oral Solution: 1 MG/ML
  - ◇ Oral Tablet: 0.25 MG, 0.5 MG, 1 MG, 2 MG, 3 MG, 4 MG
- RisperiDONE M-Tab
  - ◇ Oral Tablet, Disintegrating: 0.5 MG, 1 MG, 2 MG, 3 MG, 4 MG

Toxicology

- **Clinical Effects**
  - RISPERIDONE
    - ◇ USES: An atypical antipsychotic used to treat schizophrenia. PHARMACOLOGY: A benzisoxazole derivative with high antagonist affinity for dopamine (D2) and serotonin (5-HT2) receptors. TOXICOLOGY: Dopamine receptor blockade results in extrapyramidal symptoms, and alpha1-adrenergic effects are responsible for orthostatic hypotension. Its affinity, albeit low affinity, for histamine receptors contributes to anticholinergic effects. EPIDEMIOLOGY: Unintentional and deliberate poisonings of atypical antipsychotics are common and occasionally severe. MILD TO MODERATE TOXICITY: Tachycardia and hypotension are common. Depressed mental status, somnolence and extrapyramidal symptoms are also fairly common. In most cases, symptoms manifest mainly as mild central nervous system effects and reversible cardiovascular and neuromuscular effects. SEVERE TOXICITY: QTc prolongation, extrapyramidal symptoms likely. Respiratory depression, seizure, or coma could potentially occur, as well as neuroleptic malignant syndrome. ADVERSE EFFECTS: COMMON: Nausea, diarrhea, constipation, dizziness, somnolence, tachycardia, orthostatic hypotension, and extrapyramidal disorder.
- **Treatment of Exposure**
  - RISPERIDONE

- Support: MANAGEMENT OF MILD TO MODERATE TOXICITY: Management will primarily be symptomatic and supportive. Treat seizures with benzodiazepines. Manage mild hypotension with IV fluids. MANAGEMENT OF SEVERE TOXICITY: Treat seizures with benzodiazepines. Treat hypotension with IV fluids and pressors (norepinephrine preferred) if needed. Treat ventricular dysrhythmias with sodium bicarbonate, use lidocaine or amiodarone if bicarbonate unsuccessful. Manage severe extrapyramidal symptoms with anticholinergics and/or benzodiazepines. Although rare, treat neuroleptic malignant syndrome with benzodiazepines, bromocriptine, consider dantrolene, as well as cooling and supportive measures.
- Decontamination: PREHOSPITAL: Prehospital gastrointestinal decontamination is not recommended due to the potential for somnolence, seizures and dystonic reaction. HOSPITAL: Administer activated charcoal if the overdose is recent, the patient is not vomiting, and is able to maintain airway.
- Airway management: Insure adequate ventilation and perform endotracheal intubation early in patients with serious cardiac toxicity, coma or significant CNS depression.
- Antidote: None
- Seizure: Administer IV benzodiazepines; add propofol, or barbiturates if seizures recur or persist.
- Hypotensive episode: Treat hypotension with intravenous fluids, if hypotension persists administer vasopressors. Norepinephrine is preferred; the manufacturer recommends avoidance of epinephrine and dopamine since beta stimulation may worsen hypotension in the setting of risperidone-induced alpha blockade.
- Conduction disorder of the heart: Obtain an ECG, institute continuous cardiac monitoring and administer oxygen. Evaluate for hypoxia, acidosis, and electrolyte disorders (particularly hypokalemia, hypocalcemia, and hypomagnesemia). Sodium bicarbonate is generally first line therapy for QRS widening and ventricular dysrhythmias, administer 1 to 2 mEq/kg, repeat as needed to maintain blood pH between 7.45 and 7.55. In patients unresponsive to bicarbonate, consider lidocaine or amiodarone.
- Neuroleptic malignant syndrome: Oral bromocriptine, benzodiazepines or oral or IV dantrolene in conjunction with cooling and other supportive measures.
- Monitoring of patient: Monitor vital signs and mental status. Obtain an ECG and institute continuous cardiac monitoring. Monitor serum electrolytes including sodium, potassium, and magnesium, as well as glucose; obtain CBC.
- Enhanced elimination procedure: Hemodialysis and hemoperfusion are UNLIKELY to be of value because of the high degree of protein binding.
- Patient disposition: HOME CRITERIA: Children less than 12 years of age who are naive to risperidone can be observed at home following an unintentional ingestion of 1 mg or less and are only experiencing mild sedation. All patients, 12 years of age or older, who are naive to risperidone, can be observed at home following an unintentional ingestion of 5 mg or less and are experiencing only mild sedation. All patients who are taking risperidone on a chronic basis can be observed at home if they have unintentionally ingested no more than 5 times their current single dose (not daily dose) of risperidone and are only experiencing mild sedation. Patients who have not developed signs or symptoms more than 6 hours after ingestion are unlikely to develop toxicity. OBSERVATION CRITERIA: Any patient with a deliberate ingestion or more than minor symptoms should be referred to a healthcare facility. Children less than 12 years of age who are naive to risperidone should be referred to a healthcare facility following an unintentional ingestion of more than 1 mg. All patients, 12 years of age or older, who are naive to risperidone should be referred to a healthcare facility following an unintentional ingestion of more than 5 mg. All patients who are taking risperidone on a chronic basis should be referred to a healthcare facility following an acute ingestion of more than 5 times their current single dose (not daily dose) of risperidone. ADMISSION CRITERIA: Patients with deliberate ingestions demonstrating cardiotoxicity, or persistent neurotoxicity should be admitted. CONSULT CRITERIA: Consult a medical toxicologist or Poison Center for assistance in managing patients with severe toxicity or in whom the diagnosis is unclear.

- **Range of Toxicity**
  - RISPERIDONE

- TOXICITY: SUMMARY: CHILD: In drug naive children, an ingestion of 1 mg in a child less than 12 years of age should be considered potentially toxic, and an ingestion of more than 5 mg should be considered potentially toxic in a child 12 years or older. In children who are using risperidone on a regular basis, a does of more than 5 times their current single dose (not daily dose) should be considered potentially toxic. ADULT: Overdose of 270 mg in an adult resulted in dysrhythmias (supraventricular tachycardia, atrial flutter, prolonged QTc, bradycardia) and extrapyramidal symptoms. An adult developed tachycardia and QTc prolongation after ingesting an estimated dose of greater than 60 mg of risperidone. PEDIATRIC: A 15-year-old girl developed transient lethargy, hypotension, and tachycardia after ingesting 110 mg of risperidone. THERAPEUTIC DOSE: ADULT: 4 to 16 mg/day, with therapeutic effects usually in the range of 4 to 6 mg/day.

Clinical Teaching

- Patient should avoid activities requiring mental alertness or coordination until drug effects are realized, as drug may cause dizziness and somnolence.
- Drug may impair heat regulation. Advise patient to use caution with activities leading to an increased core temperature, such as strenuous exercise, exposure to extreme heat, or dehydration.
- Advise patient to rise from a sitting/lying position slowly, as drug may cause orthostatic hypotension.
- This drug may cause constipation, dyspepsia, akathisia, agitation, anxiety, and weight gain.
- Patient should report signs/symptoms of extrapyramidal effects, tardive dyskinesia (jerky muscle movements, tongue thrusting, facial grimacing/ticks, random movements of extremities), or neuroleptic malignant syndrome (sweating, fever, stupor, unstable blood pressure, muscular rigidity, autonomic dysfunction).
- Advise diabetic patients to monitor for signs/symptoms of hyperglycemia and to report difficulties with glucose control.
- Instruct elderly patients to immediately report signs/symptoms of arrhythmia, heart failure, pneumonia, transient ischemic attack, or cerebrovascular accident.
- Patient should not drink alcohol or use medicines that cause drowsiness while taking this drug.
- Advise patients using injectable form to call healthcare professional if a dose is missed, as drug should be given on a regular schedule.

Last Modified: September 12, 2013

Images & Imprints

Ingredients: Risperidone (1 MG)
Color: White
Shape: Oblong
Pattern: Solid
Imprint: R 1; JANSSEN
NDC: 12280-0019-15, 13411-0123-03, 16590-0572-30, 16590-0572-60, 21695-0113-15, 49999-0633-15, 50458-0300-01, 50458-0300-06, 50458-0300-50, 54868-3512-00, 55289-0491-30, 58864-0038-15, 58864-0038-30, 68115-0928-60

Ingredients: Risperidone (2 MG)
Color: Orange
Shape: Oblong
Pattern: Solid
Imprint: R 2; JANSSEN
NDC: 13411-0124-03, 16590-0575-30, 16590-0575-60, 18837-0335-60, 49999-0634-30, 49999-0634-60, 50458-0320-01, 50458-0320-06, 50458-0320-50, 55289-0465-30, 68115-0856-60

Ingredients: Risperidone (3 MG)
Color: Yellow
Shape: Oblong
Pattern: Solid
Imprint: R 3; JANSSEN
NDC: 13411-0125-03, 21695-0115-60, 35356-0106-60, 50458-0330-01, 50458-0330-06, 50458-0330-50, 68115-0783-60

Ingredients: Risperidone (4 MG)
Color: Green
Shape: Oblong
Pattern: Solid
Imprint: R 4; JANSSEN
NDC: 13411-0126-03, 50458-0350-01, 50458-0350-06, 55289-0519-30

Ingredients: Risperidone (0.5 MG)
Color: Dark Red
Shape: Oblong
Pattern: Solid
Imprint: Ris 0.5; JANSSEN
NDC: 49999-0911-15, 50458-0302-01, 50458-0302-06, 50458-0302-50, 54868-4874-00, 68115-0827-60

Ingredients: Risperidone (0.25 MG)
Color: Dark Yellow
Shape: Oblong
Pattern: Solid
Imprint: Ris 0.25; JANSSEN
NDC: 50458-0301-01, 50458-0301-50

Ingredients: Risperidone (0.25 MG)
Color: Dark Yellow
Shape: Oblong
Pattern: Solid
Imprint: Ris 0.25; JANSSEN
NDC: 50458-0301-04, 68115-0694-60

Ingredients: Risperidone (1 MG/ML)
NDC: 50458-0305-03, 50458-0305-10

Ingredients: Risperidone (1 MG)
Color: Light Pink
Shape: Square
Pattern: Solid
Imprint: R1
NDC: 50458-0315-28, 50458-0315-30

Ingredients: Risperidone (2 MG)
Color: Light Pink
Shape: Circle
Pattern: Solid
Imprint: R2
NDC: 50458-0325-28

Ingredients: Risperidone (0.5 MG)
Color: Light Pink
Shape: Circle
Pattern: Solid
Imprint: R0.5
NDC: 50458-0395-28, 50458-0395-30

Ingredients: Risperidone (2 MG)
Color: Orange
Shape: Capsule-shape
Pattern: Solid
Imprint: R2; PATR
NDC: 50458-0593-10, 50458-0593-50, 50458-0593-60

Warranty and Disclaimer

The information above is for use only by healthcare professionals in conjunction with clinical data and their professional judgment.

- Thomson Reuters
- Title:
  - DrugPoints® System
- Date Posted:
  - 9/30/2013 4:36:26 PM CDT (UTC -05:00)
- Date Accessed:
  - 10/9/2013 2:20:38 PM CDT (UTC -05:00)
- Electronic Address:
  - http://online.statref.com/Document.aspx?fxId=6&docId=1506
- Location In Title:
  - DRUGPOINTS® SYSTEM
    "R" Monographs
    Risperidone

Overview® (see Users Guide). For additional information on this drug until a more detailed monograph is developed and published, the manufacturer's labeling should be consulted. It is *essential* that the manufacturer's labeling be consulted for more detailed information on usual cautions, precautions, contraindications, potential drug interactions, laboratory test interferences, and acute toxicity.

Preparations

Excipients in commercially available drug preparations may have clinically important effects in some individuals; consult specific product labeling for details.

Paliperidone

Oral

Tablets, extended-release	3 mg	**Invega®, Janssen**
	6 mg	**Invega®, Janssen**
	9 mg	**Invega®, Janssen**

Quetiapine Fumarate

■ Quetiapine is considered an atypical or second-generation antipsychotic agent.

Uses

■ **Psychotic Disorders** Quetiapine is used for the symptomatic management of psychotic disorders (e.g., schizophrenia). Drug therapy is integral to the management of acute psychotic episodes and accompanying violent behavior in patients with schizophrenia and generally is required for long-term stabilization to sustain symptom remission or control and to minimize the risk of relapse. Antipsychotic agents are the principal class of drugs used for the management of all phases of schizophrenia. Patient response and tolerance to antipsychotic agents are variable, and patients who do not respond to or tolerate one drug may be successfully treated with an agent from a different class or with a different adverse effect profile.

Schizophrenia Short-term efficacy of quetiapine for the management of schizophrenia has been established by placebo-controlled studies of 6 weeks' duration principally in hospitalized patients with schizophrenia. Schizophrenia is a major psychotic disorder that frequently has devastating effects on various aspects of the patient's life and carries a high risk of suicide and other life-threatening behaviors. Manifestations of schizophrenia involve multiple psychologic processes, including perception (e.g., hallucinations), ideation, reality testing (e.g., delusions), emotion (e.g., flatness, inappropriate affect), thought processes (e.g., loose associations), behavior (e.g., catatonia, disorganization), attention, concentration, motivation (e.g., avolition, impaired intention and planning), and judgment. The principal manifestations of this disorder usually are described in terms of positive and negative (deficit) symptoms, and more recently, disorganized symptoms. Positive symptoms include hallucinations, delusions, bizarre behavior, hostility, uncooperativeness, and paranoid ideation, while negative symptoms include restricted range and intensity of emotional expression (affective flattening), reduced thought and speech productivity (alogia), anhedonia, apathy, and decreased initiation of goal-directed behavior (avolition). Disorganized symptoms include disorganized speech (thought disorder) and behavior and poor attention.

In clinical studies in patients with schizophrenia, quetiapine was more effective than placebo in reducing the severity of symptoms associated with this disorder. Quetiapine appears to improve both positive and negative manifestations of schizophrenia. Results from comparative clinical studies and meta-analyses suggest that quetiapine is at least as effective as chlorpromazine or haloperidol in reducing positive and negative symptoms of schizophrenia.

The American Psychiatric Association (APA) considers certain atypical antipsychotic agents (i.e., quetiapine, aripiprazole, olanzapine, risperidone, ziprasidone) first-line drugs for the management of the acute phase of schizophrenia (including first psychotic episodes), principally because of the decreased risk of adverse extrapyramidal effects and tardive dyskinesia, with the understanding that the relative advantages, disadvantages, and cost-effectiveness of conventional and atypical antipsychotic agents remain controversial. The APA states that, with the possible exception of clozapine for the management of treatment-resistant symptoms, there currently is no definitive evidence that one atypical antipsychotic agent will have superior efficacy compared with another agent in the class, although meaningful differences in response may be observed in individual patients. Conventional antipsychotic agents may be considered first-line therapy in patients who have been treated successfully in the past with or who prefer conventional agents. The choice of an antipsychotic agent should be individualized, considering past response to therapy, adverse effect profile (including the patient's experience of subjective effects such as dysphoria), and the patient's preference for a specific drug, including route of administration.

Although the efficacy of quetiapine for long-term use has not been established in controlled studies, the manufacturer states that beneficial effects of the drug were maintained for up to 4 years in some patients during an open-label extension study in patients who achieved an initial response to treatment during double-blind clinical studies. If quetiapine is used for extended periods, the need for continued therapy should be reassessed periodically on an individualized basis. (See Dosage and Administration: Dosage.)

For additional information on the symptomatic management of schizophrenia, including treatment recommendations and results of the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study, see Schizophrenia and Other Psychotic Disorders under Uses: Psychotic Disorders, in the Phenothiazines General Statement 28:16.08.24.

■ **Bipolar Disorder** Quetiapine is used alone or in conjunction with lithium or divalproex sodium for the management of acute manic episodes associated with bipolar I disorder. Efficacy of quetiapine monotherapy in the treatment of acute manic episodes has been demonstrated in 2 placebo-controlled studies of 12 weeks' duration in patients who met the DSM-IV criteria for bipolar disorder and who met diagnostic criteria for an acute manic episode (with or without psychotic features). Patients with rapid cycling and mixed episodes were excluded from these studies. The principal rating instrument used for assessing manic symptoms in these studies was the Young Mania Rating Scale (YMRS) score, an 11-item clinician rated scale traditionally used to assess the degree of manic symptomatology in a range from 0 (no manic features) to 60 (maximum score). In these studies, quetiapine was shown to be superior to placebo in reduction of the YMRS total score after 3 and 12 weeks of treatment.

Efficacy of quetiapine when used in combination with lithium or divalproex sodium in the management of acute manic episodes has been demonstrated in a placebo-controlled study of 3 weeks' duration in patients who met the DSM-IV criteria for bipolar I disorder with acute manic episodes (with or without psychotic features). Patients with rapid cycling and mixed episodes were excluded from enrollment and patients included in the study may or may not have received an adequate course of therapy with lithium or divalproex sodium prior to randomization. Quetiapine was shown to be superior to placebo when added to lithium or divalproex sodium alone in the reduction of YMRS total score. However, in a similarly designed study, quetiapine was associated with an improvement of YMRS scores but did not demonstrate superiority to placebo.

For the initial management of less severe manic or mixed episodes in patients with bipolar disorder, current APA recommendations state that monotherapy with lithium, valproate (e.g., valproate sodium, valproic acid, divalproex), or an antipsychotic (e.g., olanzapine) may be adequate. For more severe manic or mixed episodes, combination therapy with an antipsychotic and lithium or valproate is recommended as first-line therapy. For further information on the management of bipolar disorder, see Uses: Bipolar Disorder, in Lithium Salts 28:28.

Quetiapine also is used for the treatment of depressive episodes associated with bipolar disorder. Efficacy of quetiapine in the treatment of depressive episodes has been demonstrated in 2 randomized, double-blind, placebo-controlled studies of 8 weeks' duration in patients with bipolar I or II disorder (with or without a rapid cycling course). Patients in these studies received fixed daily quetiapine dosages of 300 or 600 mg once daily. The principal rating instrument used for assessing depressive symptoms in these studies was the Montgomery-Asberg Depression Rating Scale (MADRS), a 10-item clinician-rated scale with scores ranging from 0 to 60. In both studies, quetiapine was found to be superior to placebo in reduction of MADRS scores at week 8, with improvements in scores evident within one week of treatment. In addition, patients receiving 300 mg of quetiapine daily demonstrated significant improvements compared to placebo recipients in overall quality of life and satisfaction related to various areas of functioning.

Dosage and Administration

■ **Administration** Quetiapine is administered orally. While food reportedly can marginally increase the peak concentration and oral bioavailability of quetiapine, the drug generally can be administered without regard to meals.

Dispensing and Administration Precautions Because of similarity in spelling between Seroquel® (the trade name for quetiapine fumarate) and Serzone® (the former trade name for nefazodone hydrochloride, an antidepressant agent; no longer commercially available in the US under this trade name), dispensing errors have been reported to the US Food and Drug Administration (FDA) and the manufacturer of Seroquel® (AstraZeneca). According to the medication error reports, the overlapping strengths (100 and 200 mg), dosage forms (tablets), and dosing intervals (twice daily) and the fact that these 2 drugs were stored closely together in pharmacies also were critical in causing these errors. Therefore, extra care should be exercised in ensuring the accuracy of both oral and written prescriptions for Seroquel® and Serzone®. Although the Serzone brand was discontinued in June 2004, clinicians may continue to refer to nefazodone by the former brand name in prescribing. Some experts recommend that pharmacists assess the measures of avoiding dispensing errors and implement them as appropriate (e.g., by verifying all orders for these agents by spelling both the trade and generic names to prescribers, using computerized name alerts, attaching reminders to drug containers and pharmacy shelves, separating the drugs on pharmacy shelves, counseling patients). (See Dispensing and Administration Precautions under Warnings/Precautions: General Precautions in Cautions.)

■ **Dosage** Dosage of quetiapine fumarate is expressed in terms of quetiapine and must be carefully adjusted according to individual requirements and response, using the lowest possible effective dosage.

Higher maintenance dosages of quetiapine may be required in patients receiving the antipsychotic drug concomitantly with phenytoin or other hepatic enzyme-inducing agents (e.g., carbamazepine, barbiturates, rifampin, glucocorticoids), and an increase in the maintenance dosage of quetiapine may be required to reestablish efficacy in patients receiving such concomitant therapy. (See Drug Interactions: Drugs Affecting Hepatic Microsomal Enzymes and also Phenytoin.)

Patients receiving quetiapine should be monitored for possible worsening of depression, suicidality, or unusual changes in behavior, especially at the beginning of therapy or during periods of dosage adjustments. (See Worsening of Depression and Suicidality Risk under Warnings/Precautions: Warnings, in Cautions.)

The manufacturer states that if quetiapine therapy is reinitiated after a drug-free period of less than 1 week, dosage titration is not necessary. However, if quetiapine therapy is reinitiated after a drug-free period exceeding 1 week, dosage generally should be titrated as with initial therapy.

Schizophrenia For the management of schizophrenia, the recommended initial dosage of quetiapine in adults is 25 mg twice daily. Dosage may be increased in increments of 25–50 mg 2 or 3 times daily on the second or third day, as tolerated, to a target dosage of 300–400 mg daily in 2 or 3 divided doses by the fourth day. Because steady-state plasma concentrations of quetiapine may not be attained for 1–2 days at a given dosage, subsequent dosage adjustments generally should be made at intervals of not less than 2 days, usually in increments or decrements of 25–50 mg twice daily. Effective dosages of quetiapine in clinical trials generally ranged from 150–750 mg daily. While the manufacturer states that increasing quetiapine dosages beyond 300 mg daily usually does not result in additional therapeutic effect, dosages of 400–500 mg daily apparently have been required in some patients, and a dosage range of 300–800 mg daily has been recommended. Safety of quetiapine in dosages exceeding 800 mg daily has not been established.

The optimum duration of quetiapine therapy currently is not known, but the efficacy of maintenance therapy with antipsychotic agents used in the treatment of schizophrenia is well established. Patients responding to quetiapine therapy should continue to receive the drug as long as clinically necessary and tolerated but at the lowest possible effective dosage, and the need for continued therapy with the drug should be reassessed periodically. The American Psychiatric Association (APA) states that prudent long-term treatment options in patients with remitted first- or multiple-episodes include either indefinite maintenance therapy or gradual discontinuance of the antipsychotic agent with close follow-up and a plan to reinstitute treatment upon symptom recurrence. Discontinuance of antipsychotic therapy should be considered only after a period of at least 1 year of symptom remission or optimal response while receiving the antipsychotic agent. In patients who have had multiple previous psychotic episodes or 2 psychotic episodes within 5 years, indefinite maintenance antipsychotic treatment is recommended.

If antipsychotic therapy is to be discontinued in patients with schizophrenia, precautions should include slow, gradual dose reduction over many months, more frequent clinician visits, and use of early intervention strategies. Patients and their family and caregivers should be advised about early signs of relapse, and clinicians should collaborate with them to develop plans for action should they emerge. The treatment program should be designed to respond quickly to evidence of prodromal symptoms or behaviors or exacerbations of schizophrenic symptoms.

Bipolar Disorder For the management of depressive episodes associated with bipolar I or II disorder, the recommended dosage of quetiapine in adults is 50 mg administered once daily at bedtime on the first day of therapy. The dosage of quetiapine should then be increased to 100 mg once daily on the second day of therapy, 200 mg once daily on the third day of therapy, and 300 mg once daily on the fourth day of therapy. In clinical trials demonstrating clinical efficacy, quetiapine was given in a dosing schedule of 50, 100, 200, and 300 mg once daily on days 1–4, respectively; patients who received 600 mg daily received 500 mg daily on day 5 and 600 mg daily on day 8. Although antidepressant efficacy was demonstrated with quetiapine at dosages of 300 mg daily and 600 mg daily, no additional benefit was seen in the 600-mg daily group.

For the management of acute mania associated with bipolar I disorder (alone or in conjunction with lithium or divalproex sodium), the recommended initial dosage of quetiapine in adults is 100 mg daily, administered in 2 divided doses. The dosage of quetiapine should be increased in increments of up to 100 mg daily in 2 divided doses to 400 mg daily on the fourth day of therapy. Subsequent dosage adjustments up to 800 mg daily by the sixth day of therapy should be made in increments not exceeding 200 mg daily. Data indicate that most patients respond to 400–800 mg daily. The safety of quetiapine dosages exceeding 800 mg daily has not been established.

The APA states that for patients treated with an antipsychotic agent during an acute episode in bipolar disorder, the need for ongoing antipsychotic treatment should be reassessed upon entering the maintenance phase. The APA recommends that antipsychotics be slowly tapered and discontinued unless they are required to control persistent psychosis or provide prophylaxis against recurrence. While maintenance therapy with atypical antipsychotics may be considered, there currently is limited evidence regarding their efficacy in the maintenance phase compared with that of agents such as lithium or valproate. The manufacturer of quetiapine states that efficacy of the drug has not been systematically evaluated for more than 12 weeks as monotherapy of acute manic episodes associated with bipolar I disorder or for more than 3 weeks as combined therapy with divalproex or lithium. In addition, the manufacturer of quetiapine states that efficacy of the drug has not been systematically evaluated for more than 8 weeks in the management of depressive episodes in patients with bipolar I or II disorder. If quetiapine is used for extended periods, the need for continued therapy should be reassessed periodically on an individualized basis.

Switching to or Concomitant Use with Other Antipsychotic Agents The manufacturer states that there are no systematically collected data that specifically address switching from other antipsychotic agents to quetiapine or concerning concomitant use of quetiapine with other antipsychotic agents. Although abrupt discontinuance of the previous antipsychotic agent may be acceptable for some patients with schizophrenia, gradual discontinuance may be most appropriate for others. In all cases, the period of overlapping antipsychotic administration should be minimized. In patients being switched from long-acting (depot) parenteral antipsychotic therapy to oral quetiapine therapy, the first oral dose of quetiapine should be administered in place of the next scheduled dose of the long-acting preparation. The need for continuing existing drugs used for the symptomatic relief of extrapyramidal manifestations should be reevaluated periodically.

■ **Special Populations** The manufacturer states that because quetiapine is substantially metabolized in the liver and because the pharmacokinetics of quetiapine appear to be altered in patients with hepatic impairment, an initial dosage of 25 mg daily should be used in adults with hepatic impairment. The dosage should be increased by 25–50 mg daily according to clinical response and tolerability until an effective dosage is reached.

Although elimination of quetiapine was reduced in patients with severe renal impairment (e.g., creatinine clearance of 10–30 mL/minute), the plasma quetiapine concentrations were similar to those in patients with normal renal function; therefore, the manufacturer states that dosage adjustment is not necessary in such patients.

Geriatric or debilitated patients and patients predisposed to hypotension or in whom hypotension would pose a risk (e.g., patients with dehydration or hypovolemia, those receiving antihypertensive drugs, patients with known cardiovascular or cerebrovascular disease) should have a slower rate of dosage titration and should receive lower target dosages of quetiapine. The risk of orthostatic hypotension can be minimized by limiting the initial dosage of quetiapine to 25 mg twice daily. If orthostatic hypotension occurs during titration to the target dosage, the manufacturer recommends a return to the previous dosage in the titration schedule

Cautions

■ **Contraindications** Known hypersensitivity to quetiapine or any ingredient in the formulation.

■ **Warnings/Precautions** ***Warnings*** **Increased Mortality in Geriatric Patients with Dementia-related Psychosis.** Geriatric patients with dementia-related psychosis treated with atypical antipsychotic drugs appear to be at an increased risk of death compared with that among patients receiving placebo. Analyses of 17 placebo-controlled trials (average duration of 10 weeks) revealed an approximate 1.6- to 1.7-fold increase in mortality among geriatric patients receiving atypical antipsychotic drugs (i.e., quetiapine, aripiprazole, olanzapine, risperidone) compared with that in patients receiving placebo. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5% compared with a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. The manufacturer states that quetiapine is not approved for the treatment of dementia-related psychosis. (See Dosage and Administration: Special Populations and see also Geriatric Use under Warnings/Precautions: Specific Populations, in Cautions.)

Worsening of Depression and Suicidality Risk. Worsening of depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior may occur in both adult and pediatric (see Pediatric Use under Warnings/Precautions: Specific Populations, in Cautions) patients with major depressive disorder or other psychiatric disorders, whether or not they are taking antidepressants. This risk may persist until clinically important remission occurs with therapy. Suicide is a known risk of depression and certain other psychiatric disorders, and these disorders themselves are the strongest predictors of suicide. However, there has been a long-standing concern that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients during the early phases of treatment. Pooled analyses of short-term, placebo-controlled studies of antidepressants (i.e., selective serotonin-reuptake inhibitors and other antidepressants) have shown an increased risk of suicidality in children, adolescents, and young adults (18–24 years of age) with major depressive disorder and other psychiatric disorders. An increased suicidality risk was not demonstrated with antidepressants compared to placebo in adults older than 24 years of age and a reduced risk was observed in adults 65 years of age or older.

The US Food and Drug Administration (FDA) recommends that all patients being treated with antidepressants for any indication be appropriately moni-

tored and closely observed for clinical worsening, suicidality, and unusual changes in behavior, particularly during initiation of therapy (i.e., the first few months) and during periods of dosage adjustments. Families and caregivers of patients being treated with antidepressants for major depressive disorder or other indications, both psychiatric and nonpsychiatric, also should be advised to monitor patients on a daily basis for the emergence of agitation, irritability, or unusual changes in behavior as well as the emergence of suicidality, and to report such symptoms immediately to a health-care provider.

Although a causal relationship between the emergence of symptoms such as anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia, hypomania, and/or mania and either the worsening of depression and/or the emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality. Consequently, consideration should be given to changing the therapeutic regimen or discontinuing therapy in patients whose depression is persistently worse or in patients experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidality, particularly if such manifestations are severe, abrupt in onset, or were not part of the patient's presenting symptoms. FDA also recommends that the drugs be prescribed in the smallest quantity consistent with good patient management, in order to reduce the risk of overdosage.

Bipolar Disorder. It is generally believed (though not established in controlled trials) that treating a major depressive episode with an antidepressant alone may increase the likelihood of precipitating a mixed or manic episode in patients at risk for bipolar disorder. Therefore, patients should be adequately screened for bipolar disorder prior to initiating treatment with an antidepressant; such screening should include a detailed psychiatric history (e.g., family history of suicide, bipolar disorder, and depression). Quetiapine is approved for use in treating bipolar depression in adults. (See Bipolar Disorder under Uses.)

Neuroleptic Malignant Syndrome. Neuroleptic malignant syndrome (NMS), a potentially fatal syndrome requiring immediate discontinuance of the drug and intensive symptomatic treatment, has been reported in patients receiving antipsychotic agents, including quetiapine. For additional information on NMS, see Extrapyramidal Reactions under Cautions: Nervous System Effects, in the Phenothiazines General Statement 28:16.08.24.

Tardive Dyskinesia. Use of antipsychotic agents, including quetiapine, may be associated with tardive dyskinesias, a syndrome of potentially irreversible, involuntary, dyskinetic movements. For additional information on tardive dyskinesia, see Tardive Dyskinesia under Cautions: Nervous System Effects, in the Phenothiazines General Statement 28:16.08.24.

Hyperglycemia and Diabetes Mellitus. Severe hyperglycemia, sometimes associated with ketoacidosis, hyperosmolar coma, or death, has been reported in patients receiving all atypical antipsychotic agents, including quetiapine. While confounding factors such as an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population make it difficult to establish with certainty the relationship between use of agents in this drug class and glucose abnormalities, epidemiologic studies suggest an increased risk of treatment-emergent hyperglycemia-related adverse events in patients treated with the atypical antipsychotic agents included in the studies (e.g., quetiapine, clozapine, olanzapine, risperidone).

Precise risk estimates for hyperglycemia-related adverse events in patients treated with atypical antipsychotics currently are not available. While some evidence suggests that the risk for diabetes may be greater with some atypical antipsychotics (e.g., clozapine, olanzapine) than with others in the class (e.g., quetiapine, risperidone), available data are conflicting and insufficient to provide reliable estimates of relative risk associated with use of the various atypical antipsychotics.

The manufacturers of atypical antipsychotic agents state that patients with preexisting diabetes mellitus in whom therapy with an atypical antipsychotic is initiated should be closely monitored for worsening of glucose control; those with risk factors for diabetes (e.g., obesity, family history of diabetes) should undergo fasting blood glucose testing upon therapy initiation and periodically throughout treatment. Any patient who develops manifestations of hyperglycemia (e.g., polydipsia, polyphagia, polyuria, weakness) during treatment with an atypical antipsychotic should undergo fasting blood glucose testing. In some cases, patients who developed hyperglycemia while receiving an atypical antipsychotic have required continuance of antidiabetic treatment despite discontinuance of the suspect drug; in other cases, hyperglycemia resolved with discontinuance of the antipsychotic.

For further information on the risk of hyperglycemia and diabetes mellitus associated with atypical antipsychotic agents, see Cautions: Endocrine and Metabolic Effects and see also Hyperglycemia and Diabetes Mellitus under Cautions: Precautions and Contraindications, in Clozapine 28:16.08.04.

Sensitivity Reactions Contact dermatitis, maculopapular rash, and photosensitivity reactions were reported infrequently during clinical trials. Anaphylaxis and Stevens-Johnson syndrome have been reported during postmarketing surveillance.

General Precautions **Cardiovascular Effects.** Orthostatic hypotension with associated dizziness, tachycardia, and/or syncope, particularly during the initial dosage titration period, has been reported. The risk of orthostatic hypotension and syncope may be minimized by limiting initial dosage. (See Dosage and Administration: Special Populations.) Use with caution in patients with known cardiovascular (e.g., history of myocardial infarction or ischemia, heart failure, conduction abnormalities) or cerebrovascular disease and/or conditions that would predispose patients to hypotension (e.g., dehydration, hypovolemia, concomitant antihypertensive therapy).

Ocular Effects. The development of cataracts in association with quetiapine was observed in animal studies. Lens changes also have been reported in some patients receiving long-term quetiapine therapy, although a causal relationship has not been established. Because the possibility of lens changes cannot be excluded, the manufacturer recommends ophthalmologic examination of the lens by methods adequate to detect cataract formation (e.g., slit lamp exam) be performed at the initiation of quetiapine therapy, or shortly thereafter, and at 6-month intervals during chronic quetiapine therapy.

Nervous System Effects. Seizures occurred in 0.6% of patients receiving quetiapine in controlled clinical trials. Use with caution in patients with a history of seizures or with conditions known to lower the seizure threshold (e.g., dementia of the Alzheimer's type, geriatric patients).

Somnolence occurred in 16–18 or 34% of patients receiving quetiapine as monotherapy (for the treatment of schizophrenia or bipolar disorder) or in conjunction with lithium or divalproex sodium (for the treatment of bipolar disorder), respectively, during clinical studies compared with 4–11% of those receiving placebo.

Endocrine Effects. Dose-related decreases in total and free thyroxine (T4) of approximately 20% were observed in patients receiving quetiapine dosages at the higher end of the therapeutic dosage range during clinical studies. These decreases were maximal during the first 2–4 weeks of therapy and were maintained without adaptation or progression during more chronic therapy. Generally, these changes were not considered clinically important and were reversible upon discontinuance of quetiapine, regardless of duration of therapy. Increases in TSH were observed in about 0.4 or 12% of patients receiving quetiapine alone or in conjunction with lithium or divalproex sodium, respectively. In patients receiving quetiapine monotherapy, thyroid replacement therapy was necessary in some patients who experienced increases in TSH.

Although not observed in patients receiving quetiapine during clinical trials, increases in prolactin concentrations and associated increases in mammary gland neoplasia were reported in animal studies.

Metabolic Effects. During clinical studies, 23 or 21% of patients with schizophrenia or acute mania receiving quetiapine gained at least 7% of their baseline weight compared with 6–7% of those receiving placebo. In patients receiving quetiapine as adjunctive therapy for acute mania, 13% gained at least 7% of their baseline weight compared with 4% of those receiving placebo.

Increases from baseline in cholesterol and triglyceride concentrations of 11 and 17%, respectively, were reported in patients receiving quetiapine compared with slight decreases in patients receiving placebo in clinical studies in patients with schizophrenia. These changes were weakly related to increases in weight observed in patients receiving quetiapine. For additional information on metabolic effects, see Hyperglycemia and Diabetes Mellitus under Warnings/Precautions, in Cautions.

Hepatic Effects. Asymptomatic, transient, and reversible increases in serum transaminases, principally ALT, have been reported in patients receiving quetiapine; these changes usually occurred within the first 3 weeks and resolved despite continued quetiapine therapy.

Sexual Dysfunction. One case of drug-induced priapism was reported in clinical studies of quetiapine.

Body Temperature Regulation. Although not reported in clinical studies with quetiapine, disruption of the body's ability to reduce core body temperature has been associated with use of antipsychotic agents. Use caution when quetiapine is administered in patients exposed to conditions that may contribute to an elevation in core body temperature (e.g., dehydration, extreme heat, strenuous exercise, concomitant use of anticholinergic agents).

GI Effects. Esophageal dysmotility and aspiration have been associated with the use of antipsychotic agents. Use with caution in patients at risk for aspiration pneumonia (e.g., geriatric patients, those with advanced Alzheimer's dementia).

Suicide. Attendant risk with bipolar disorder and psychotic illnesses; closely supervise high-risk patients. In clinical studies in patients with bipolar depression, the incidence of treatment-emergent suicidal ideation or suicide attempt in quetiapine-treated patients was low (1.7–2.6%) and similar to that observed with placebo (2%). Prescribe in the smallest quantity consistent with good patient management to reduce the risk of overdosage. (See Worsening of Depression and Suicidality Risk under Warnings/Precautions: Warnings, in Cautions.)

Dispensing and Administration Precautions. Because of similarity in spelling between Seroquel® (the trade name for quetiapine fumarate) and Serzone® (the former trade name for nefazodone hydrochloride, an antidepressant agent; no longer commercially available in the US under this trade name), dispensing errors have been reported to the US Food and Drug Administration (FDA) and the manufacturer of Seroquel® (AstraZeneca). According to the medication error reports, the overlapping strengths (100 and 200 mg), dosage forms (tablets), and dosing intervals (twice daily) and the fact that these 2 drugs were stored closely together in pharmacies also were critical in causing these errors. These medication errors may be associated with adverse CNS (e.g., mental status deterioration, hallucination, paranoia, muscle weakness, lethargy, dizziness) and GI effects (e.g., nausea, vomiting, diarrhea). As of November 2001,

4 patients had required emergency room visits and 3 patients reportedly had been hospitalized because of dispensing errors involving these 2 agents. One female patient 25 years of age experienced fever and respiratory arrest after mistakenly taking Seroquel® for 3 days instead of taking Serzone®, and eventually died, although a causal relationship has not been established. FDA also is concerned that several patients unintentionally ingested Serzone® or Seroquel® for a prolonged period of time before the error was discovered. Therefore, extra care should be exercised in ensuring the accuracy of both oral and written prescriptions for Seroquel® and Serzone®. Although the Serzone brand was discontinued in June 2004, clinicians may continue to refer to nefazodone by the former brand name in prescribing. Some experts recommend that pharmacists assess the measures of avoiding dispensing errors and implement them as appropriate (e.g., by verifying all orders for these agents by spelling both the trade and generic names to prescribers, using computerized name alerts, attaching reminders to drug containers and pharmacy shelves, separating the drugs on pharmacy shelves, counseling patients).

Patients should be advised to question the dispensing pharmacist regarding any changes in the appearance of their prescription in terms of shape, color, or size of the tablets. Dispensing errors involving Seroquel® (quetiapine) and Serzone® (nefazodone) should be reported to the manufacturers or directly to the FDA MedWatch program by phone (800-FDA-1088), by fax (800-FDA-0178), by the Internet (http://www.fda.gov/medwatch), or by mail (FDA Safety Information and Adverse Event Reporting Program, FDA, 5600 Fishers Lane, Rockville, MD 20852-9787).

Specific Populations **Pregnancy.** Category C. (See Users Guide.)

Lactation. Quetiapine is distributed into milk in animals. Not known whether quetiapine is distributed into milk in humans. The manufacturer states that women receiving quetiapine should not breast-feed.

Pediatric Use. Safety and efficacy not established in children younger than 18 years of age.

FDA warns that a greater risk of suicidal thinking or behavior (suicidality) occurred during first few months of antidepressant treatment (4%) compared with placebo (2%) in children and adolescents with major depressive disorder, obsessive-compulsive disorder (OCD), or other psychiatric disorders based on pooled analyses of 24 short-term, placebo-controlled trials of 9 antidepressant drugs (selective serotonin-reuptake inhibitors [SSRIs] and other antidepressants). However, a more recent meta-analysis of 27 placebo-controlled trials of 9 antidepressants (SSRIs and others) in patients younger than 19 years of age with major depressive disorder, OCD, or non-OCD anxiety disorders suggests that the benefits of antidepressant therapy in treating these conditions may outweigh the risks of suicidal behavior or suicidal ideation. No suicides occurred in these pediatric trials.

Carefully consider these findings when assessing potential benefits and risks of quetiapine in a child or adolescent for any clinical use. (See Worsening of Depression and Suicidality Risk under Warnings/Precautions: Warnings, in Cautions.)

Geriatric Use. In clinical studies, approximately 7% of 3400 patients were 65 years of age or older. While no substantial differences in safety relative to younger adults were observed, factors that decrease pharmacokinetic clearance, increase the pharmacodynamic response, or cause poorer tolerance (e.g., orthostasis) may be present in geriatric patients. (See Dosage and Administration: Special Populations and see also Increased Mortality in Geriatric Patients with Dementia-related Psychosis under Warnings/Precautions: Warnings, in Cautions.)

In pooled data analyses, a *reduced* risk of suicidality was observed in adults 65 years of age or older with antidepressant therapy compared with placebo. (See Worsening of Depression and Suicidality Risk under Warnings/Precautions: Warnings, in Cautions.)

Hepatic Impairment. Increased plasma concentrations expected in patients with hepatic impairment; dosage adjustment may be necessary. (See Dosage and Administration: Special Populations.)

Renal Impairment. Clearance may be decreased in patients with severe renal impairment, but dosage adjustment is not necessary.

■ **Common Adverse Effects** The most common adverse effects reported in 5% or more of patients receiving quetiapine therapy for schizophrenia or bipolar disorder and at a frequency twice that reported among patients receiving placebo in clinical trials include somnolence, sedation, asthenia, lethargy, dizziness, dry mouth, constipation, increased ALT, weight gain, dyspepsia, abdominal pain, postural hypotension, and pharyngitis.

Drug Interactions

■ **Drugs Affecting Hepatic Microsomal Enzymes** Inhibitors of cytochrome P-450 (CYP) isoenzyme 3A4 (e.g., erythromycin, fluconazole, itraconazole, ketoconazole): potential pharmacokinetic interaction (increased serum quetiapine concentrations). Use with caution.

Inducers of CYP3A4 (e.g., barbiturates, carbamazepine, glucocorticoids, phenytoin, rifampin): potential pharmacokinetic interaction (increased quetiapine metabolism and decreased serum quetiapine concentrations). Dosage adjustment may be necessary if these drugs are initiated or discontinued in patients receiving quetiapine. (See Drug Interactions: Phenytoin.)

■ **Drugs Metabolized by Hepatic Microsomal Enzymes** Substrates of CYP1A2, CYP3A4, CYP2C9, CYP2C19, or CYP2D6: pharmacokinetic interaction unlikely.

■ **Alcohol** Potential pharmacologic interaction (additive CNS effects). Avoid alcoholic beverages during quetiapine therapy.

■ **Cimetidine** Concomitant use of cimetidine (400 mg 3 times daily for 4 days) and quetiapine (150 mg 3 times daily) decreased mean clearance of quetiapine by 20%. However, dosage adjustment of quetiapine is not necessary.

■ **Divalproex** Potential pharmacokinetic interaction. Increased maximum plasma quetiapine concentrations, with no effect on extent of quetiapine absorption or mean clearance. Decreased maximum plasma valproic acid concentrations and extent of absorption (not clinically important).

■ **Fluoxetine, Haloperidol, Imipramine, Risperidone** No effect on steady-state pharmacokinetics of quetiapine observed.

■ **Hypotensive Agents** Potential pharmacologic interaction (additive hypotensive effects).

■ **Levodopa and Dopamine Agonists** Potential pharmacologic interaction (antagonistic effects).

■ **Lithium** No effect on steady-state lithium pharmacokinetics observed.

■ **Lorazepam** Potential pharmacokinetic interaction (decreased clearance of lorazepam). Concomitant use of quetiapine (250 mg 3 times daily) and lorazepam (single 2-mg dose) resulted in a 20% decrease in the mean clearance of lorazepam.

■ **Phenytoin** Concomitant use of quetiapine (250 mg 3 times daily) and phenytoin (100 mg 3 times daily) resulted in a fivefold increase in quetiapine clearance. An increase in quetiapine dosage may be required; caution advised if phenytoin is withdrawn and replaced with a noninducer of CYP3A4 (e.g., valproate).

■ **Thioridazine** Potential pharmacokinetic interaction (increased oral clearance of quetiapine).

■ **Other CNS Agents** Potential pharmacologic interaction (additive CNS effects). Use with caution.

Description

Quetiapine is a dibenzothiazepine-derivative antipsychotic agent. The drug is pharmacologically similar to clozapine, but differs pharmacologically from other currently available first-generation (typical) antipsychotic agents (e.g., phenothiazines, butyrophenones). Because of these pharmacologic differences, quetiapine is considered an atypical or second-generation antipsychotic agent.

The exact mechanism of quetiapine's antipsychotic action in schizophrenia and its mood stabilizing action in bipolar disorder has not been fully elucidated but may involve antagonism at serotonin type 1 (5-hydroxytryptamine [5-HT_{1A}]) and type 2 (5-HT_{2A}, 5-HT_{2C}) receptors, and at dopamine (D_1, D_2) receptors.

Current evidence suggests that the clinical potency and antipsychotic efficacy of both typical and atypical antipsychotic drugs generally are related to their affinity for and blockade of central dopamine D_2 receptors; however, antagonism at dopamine D_2 receptors does not appear to account fully for the antipsychotic effects of quetiapine. Results of in vivo and in vitro studies indicate that quetiapine is a comparatively weak antagonist at dopamine D_2 receptors. Receptor binding studies show quetiapine is a weak antagonist at D_1 receptors. Although their role in eliciting the pharmacologic effects of antipsychotic agents remains to be fully elucidated, dopamine D_3, D_4, and D_5 receptors also have been identified; quetiapine possesses no affinity for the dopamine D_4 receptor.

The therapeutic effects of antipsychotic drugs are thought to be mediated by dopaminergic blockade in the mesolimbic and mesocortical areas of the CNS, while antidopaminergic effects in the neostriatum appear to be associated with extrapyramidal effects. The apparently low incidence of extrapyramidal effects associated with quetiapine therapy suggests that the drug is more active in the mesolimbic than in the neostriatal dopaminergic system. In contrast to typical antipsychotic agents (e.g., chlorpromazine) but like other atypical antipsychotic drugs (e.g., clozapine), quetiapine does not cause sustained elevations in serum prolactin concentrations and therefore is unlikely to produce adverse effects such as amenorrhea, galactorrhea, and impotence.

Quetiapine exhibits α_1- and α_2-adrenergic blocking activity; blockade of α_1-adrenergic receptors may explain the occasional orthostatic hypotension associated with the drug. Quetiapine also blocks histamine H_1 receptors, which may explain the sedative effects associated with the drug. Quetiapine possesses little or no affinity for β-adrenergic, γ-aminobutyric acid (GABA), benzodiazepine, or muscarinic receptors.

Quetiapine is extensively metabolized in the liver principally via sulfoxidation and oxidation to inactive metabolites. In vitro studies suggest that the cytochrome P-450 (CYP) 3A4 isoenzyme is involved in the metabolism of quetiapine to the inactive sulfoxide metabolite, which is the principal metabolite. The mean terminal half-life of quetiapine is about 6 hours. Following oral administration of a single dose of quetiapine, approximately 73 and 20% of the dose is excreted in urine and feces, respectively; less than 1% of the dose is excreted unchanged. Based on in vitro studies, quetiapine and 9 of its metabolites do not appear likely to inhibit CYP isoenzymes 1A2, 3A4, 2C9, 2C19, or 2D6.

Advice to Patients

Risk of suicidality; importance of patients, family, and caregivers being alert to and immediately reporting emergence of suicidality, worsening de-

pression, or unusual changes in behavior, especially during the first few months of therapy or during periods of dosage adjustment. FDA recommends providing written patient information (medication guide) explaining risks of suicidality each time the drug is dispensed.

Risk of orthostatic hypotension, especially during initial dosage titration and at times of reinitiation of therapy or increases in dosage.

Risk of somnolence and impairment of judgment, thinking, or motor skills; avoid driving, operating machinery, or performing hazardous tasks until effects on the individual are known.

Importance of avoiding alcohol during quetiapine therapy.

Importance of informing clinicians of existing or contemplated concomitant therapy, including prescription and OTC drugs, as well as any concomitant illnesses (e.g., diabetes mellitus).

Importance of women informing clinicians if they are or plan to become pregnant or plan to breast-feed.

Importance of avoiding overheating or dehydration.

Importance of informing patients of other important precautionary information. (See Cautions.)

Overview® (see Users Guide). For additional information on this drug until a more detailed monograph is developed and published, the manufacturer's labeling should be consulted. It is *essential* that the manufacturer's labeling be consulted for more detailed information on usual cautions, precautions, contraindications, potential drug interactions, laboratory test interferences, and acute toxicity.

Preparations

Excipients in commercially available drug preparations may have clinically important effects in some individuals; consult specific product labeling for details.

Quetiapine Fumarate

Oral

Tablets, film-coated	25 mg (of quetiapine)	**Seroquel®**, AstraZeneca
	50 mg (of quetiapine)	**Seroquel®**, AstraZeneca
	100 mg (of quetiapine)	**Seroquel®**, AstraZeneca
	200 mg (of quetiapine)	**Seroquel®**, AstraZeneca
	300 mg (of quetiapine)	**Seroquel®**, AstraZeneca
	400 mg (of quetiapine)	**Seroquel®**, AstraZeneca

Risperidone

■ Risperidone has been described as an atypical or second-generation antipsychotic agent.

Uses

■ **Psychotic Disorders** Risperidone is used for the symptomatic management of psychotic disorders. Drug therapy is integral to the management of acute psychotic episodes and accompanying violent behavior in patients with schizophrenia and generally is required for long-term stabilization to sustain symptom remission or control and to minimize the risk of relapse. Antipsychotic agents are the principal class of drugs used for the management of all phases of schizophrenia. Patient response and tolerance to antipsychotic agents are variable, and patients who do not respond to or tolerate one drug may be successfully treated with an agent from a different class or with a different adverse effect profile.

Schizophrenia and Other Psychotic Disorders Efficacy of oral risperidone for the management of psychotic disorders has been established by controlled studies of 4–8 weeks' duration principally in patients with schizophrenic disorders in hospital settings. Schizophrenia is a major psychotic disorder that frequently has devastating effects on various aspects of the patient's life and carries a high risk of suicide and other life-threatening behaviors. Manifestations of schizophrenia involve multiple psychologic processes, including perception (e.g., hallucinations), ideation, reality testing (e.g., delusions), emotion (e.g., flatness, inappropriate affect), thought processes (e.g., loose associations), behavior (e.g., catatonia, disorganization), attention, concentration, motivation (e.g., avolition, impaired intention and planning), and judgment. The principal manifestations of this disorder usually are described in terms of positive and negative (deficit) symptoms, and more recently, disorganized symptoms. Positive symptoms include hallucinations, delusions, bizarre behavior, hostility, uncooperativeness, and paranoid ideation, while negative symptoms include restricted range and intensity of emotional expression (affective flattening), reduced thought and speech productivity (alogia), anhedonia, apathy, and decreased initiation of goal-directed behavior (avolition). Disorganized symptoms include disorganized speech (thought disorder) and behavior and poor attention. For additional information on the symptomatic management of schizophrenia, including treatment recommendations and results of the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study, see Schizophrenia and Other Psychotic Disorders under Uses: Psychotic Disorders, in the Phenothiazines General Statement 28:16.08.24.

In clinical studies principally in patients with schizophrenia, oral risperidone was more effective than placebo and at least as effective as typical (e.g., haloperidol, perphenazine) and certain atypical (e.g., olanzapine) antipsychotics in the treatment of schizophrenia. Data from limited clinical studies indicate that risperidone improves both positive and negative manifestations of schizophrenia, but that such improvements may not be substantially greater than those achieved by haloperidol, a typical antipsychotic. Risperidone was more effective than haloperidol in preventing relapse in adult outpatients with clinically stable schizophrenia or schizoaffective disorders who were assigned to receive either drug for a minimum of 1 year. In this study, approximately 25% of patients who received usual dosages of risperidone had relapsed by the end of the study compared with approximately 40% of those receiving usual dosages of haloperidol. In these studies, improvement in manifestations of schizophrenia was based on the results of various psychiatric rating scales, including the Brief Psychiatric Rating Scale (BPRS) that assesses factors such as anergy, thought disturbances, activation, hostility/suspiciousness, and anxiety/depression; the BPRS psychosis cluster that assesses factors such as conceptual disorganization, hallucinatory behavior, suspiciousness, and unusual thought content in actively psychotic schizophrenic patients; the Scale for the Assessment of Negative Symptoms (SANS); the Positive and Negative Syndrome Scale (PANSS); and the Clinical Global Impression (CGI) scale.

Because of their safety and efficacy, some authorities consider conventional antipsychotic agents or risperidone to be reasonable first-line drugs for the management of the acute phase of schizophrenia. Risperidone may be particularly useful in patients who experience extrapyramidal reactions with typical antipsychotic agents since the drug appears to cause fewer extrapyramidal reactions at clinically effective dosages. Some authorities state that risperidone or newer atypical antipsychotic agents (such as olanzapine) also may be advantageous in patients who have not responded adequately to therapy with a conventional antipsychotic agent. However, the efficacy of atypical antipsychotics, other than clozapine, in treatment-resistant schizophrenia has yet to be established, and the possible clinical benefits of risperidone therapy should be weighed against the potential drawbacks, including its higher cost compared with standard agents and the lack of a parenteral preparation of the drug.

Geriatric Considerations. Although risperidone has been studied for use in the management of psychosis and aggression in institutionalized geriatric patients with moderate to severe dementia of the Alzheimer's† type (Alzheimer's disease, presenile or senile dementia), vascular dementia†, or a combination of the 2 types of dementia (i.e., mixed dementia†), there is evidence that use of the drug in geriatric patients with dementia may be associated with an increased risk of adverse cerebrovascular events. In randomized, placebo-controlled studies in nursing home residents with dementia, oral risperidone at a dosage of approximately 1 mg daily was more effective than placebo in decreasing psychotic and behavioral symptoms (e.g., aggression, agitation) of dementia, as assessed by the Behavioral Pathology in Alzheimer's Disease scale (BEHAVE-AD) and the Cohen-Mansfield Agitation Inventory (CMAI). However, evidence from these studies showed a significantly higher incidence of adverse cerebrovascular events such as stroke and transient ischemic attacks (TIAs) associated with risperidone therapy relative to placebo. In addition, geriatric patients with dementia-related psychosis treated with atypical antipsychotic agents appear to be at an increased risk of death compared with that among patients receiving placebo. (See Cautions: Geriatric Precautions.) Risperidone is not approved for the treatment with dementia-related psychosis.

■ **Bipolar Disorder** Risperidone is used alone or in conjunction with lithium or valproate for the management of manic and mixed episodes associated with bipolar I disorder. Efficacy of risperidone monotherapy in the treatment of acute manic and mixed episodes has been demonstrated in 2 placebo-controlled trials of 3 weeks' duration in patients who met the DSM-IV criteria for bipolar I disorder with acute manic or mixed episodes with or without psychotic features. The principal rating instrument used for assessing manic symptoms in these trials was the Young Mania Rating Scale (Y-MRS), an 11-item clinician-rated scale traditionally used to assess the degree of manic symptomatology in a range from 0 (no manic features) to 60 (maximum score). In the first 3-week, placebo-controlled trial, which was limited to patients with manic episodes, risperidone monotherapy was given at an initial dosage of 3 mg daily and subsequently in a flexible dosage ranging from 1–6 mg daily; the mean modal dosage was 4.1 mg daily. In the second 3-week, placebo-controlled trial, patients also were given an initial dosage of risperidone 3 mg daily and subsequently a flexible dosage ranging from 1–6 mg daily; the mean modal dosage was 5.6 mg daily. Risperidone was found to be superior to placebo in the reduction of the Y-MRS total score in both studies.

Efficacy of risperidone when used in conjunction with lithium or valproate in the treatment of acute manic or mixed episodes has been demonstrated in one placebo-controlled trial of 3 weeks' duration in patients who met the DSM-IV criteria for bipolar I disorder (with or without a rapid cycling course) and who met diagnostic criteria for an acute manic or mixed episode (with or without psychotic features). In this study, inpatients and outpatients with bipolar disorder experiencing manic or mixed episodes who had not adequately responded to lithium or valproate monotherapy were randomized to receive risperidone, haloperidol, or placebo in conjunction with their original therapy. Risperidone therapy was given in an initial dosage of 2 mg daily and subsequently given in a flexible dosage ranging from 1–6 mg daily; the mean modal

Quetiapine Fumarate

Dosing & Indications

- **Adult Dose**

- quetiapine regular-release may be switched to quetiapine extended-release at the equivalent total daily dose taken once daily; individual dosage adjustments may be required
- Bipolar disorder, depressed phase: regular-release tablets, 50 mg ORALLY once a day on day 1, then 100 mg once daily on day 2, then 200 mg once daily on day 3, then 300 mg once daily on day 4 (all doses given at bedtime); patients requiring higher doses should receive 400 mg on day 5, increased to 600 mg on day 8 (week 1)
- Bipolar disorder, depressed phase: extended-release tablets, 50 mg ORALLY on day 1, then 100 mg on day 2, then 200 mg on day 3, then 300 mg on day 4; administer once daily in the evening
- Bipolar disorder, depressed phase: reinitiation of therapy: if less than 1 week off of quetiapine, titration of dose is not required and maintenance dose may be reinitiated; if greater than 1 week off of quetiapine, initial titration schedule should be followed
- Bipolar disorder, maintenance; Adjunct: regular-release tablets, 400 mg to 800 mg per day ORALLY divided twice daily; generally continuation of stabilization dose
- Bipolar disorder, maintenance; Adjunct: extended-release tablets, total daily dose of 400 mg to 800 mg ORALLY divided and administered twice daily; generally continuation of stabilization dose; periodically reassess for need and appropriate dose for maintenance treatment
- Bipolar disorder, maintenance; Adjunct: reinitiation of therapy: if less than 1 week off of quetiapine, titration of dose is not required and maintenance dose may be reinitiated; if greater than 1 week off of quetiapine, initial titration schedule should be followed
- Major depressive disorder; Adjunct: extended-release tablets, initial 50 mg ORALLY once daily in the evening; increase to 150 mg once daily in the evening on day 3; recommended dosage range is 150 to 300 mg/day; MAX dosage 300 mg/day.
- Major depressive disorder; Adjunct: reinitiation of therapy: if less than 1 week off of quetiapine, titration of dose is not required and maintenance dose may be reinitiated; if greater than 1 week off of quetiapine, initial titration schedule should be followed
- Manic bipolar I disorder: regular-release tablets, initial, 50 mg ORALLY twice daily, may increase dosage by increments up to 50 mg twice daily on the second and third day, to a target dose 400 mg per day by the fourth day given in 2 divided doses
- Manic bipolar I disorder: regular-release tablets, further dosage adjustments in increments of not more than 200 mg/day up to 800 mg/day by day 6 may be made; usual effective dosage range is 400 to 800 mg/day; MAX dosage 800 mg/day
- Manic bipolar I disorder: extended-release tablets, 300 mg ORALLY in the evening on day 1 and 600 mg in the evening on day 2; adjust between 400 and 800 mg daily beginning on day 3 depending on patient response and tolerance
- Manic bipolar I disorder: reinitiation of therapy: if less than 1 week off of quetiapine, titration of dose is not required and maintenance dose may be reinitiated; if greater than 1 week off of quetiapine, initial titration schedule should be followed
- Schizophrenia: regular-release tablets, initial, 25 mg ORALLY twice daily, may increase total daily dosage by 25 to 50 mg divided into 2 to 3 doses on the second and third day, as tolerated, to a target dose range of 300 to 400 mg daily by the fourth day
- Schizophrenia: regular-release tablets, dosage adjustments, if indicated, should generally occur at intervals of not less than 2 days in dose increments/decrements of 25 to 50 mg divided twice a day; usual effective dosage range is 150 to 750 mg/day, MAX dose 800 mg/day
- Schizophrenia: extended-release tablets, initial, 300 mg ORALLY once daily, preferably in the evening; titrate to a target dose range of 400 to 800 mg daily; dose increases may occur at intervals of at least 1 day in increments of up to 300 mg/day; MAX dose 800 mg/day
- Schizophrenia: reinitiation of therapy: if less than 1 week off of quetiapine, titration of dose is not required and maintenance dose may be reinitiated; if greater than 1 week off of quetiapine, initial titration schedule should be followed
- Schizophrenia, maintenance: extended-release tablets, 400 to 800 mg ORALLY once daily, preferably in the evening; periodically reassess for need and appropriate dose for maintenance treatment

- Schizophrenia, maintenance: reinitiation of therapy: if less than 1 week off of quetiapine, titration of dose is not required and maintenance dose may be reinitiated; if greater than 1 week off of quetiapine, initial titration schedule should be followed

- **Pediatric Dose**

  - safety and efficacy of quetiapine regular-release tablets not established in pediatric patients except for the treatment of schizophrenia in children 13 to 17 years of age, the acute treatment of manic episodes in bipolar I disorder in children 10 to 17 years of age, and the maintenance treatment of bipolar I disorder in patients 10 to 17 years of age
  - safety and efficacy of quetiapine extended-release tablets not established in pediatric patients
  - Bipolar disorder, maintenance; Adjunct: initiate medication therapy only after thorough diagnostic evaluation; total treatment program includes medication and psychological, educational, and social interventions
  - Bipolar disorder, maintenance; Adjunct: 10 to 17years of age, regular-release tablets, lowest dose needed to maintain remission; periodically reassess for need for maintenance treatment
  - Bipolar disorder, maintenance; Adjunct: reinitiation of therapy: if less than 1 week off of quetiapine, titration of dose is not required and maintenance dose may be reinitiated; if greater than 1 week off of quetiapine, initial titration schedule should be followed
  - Manic bipolar I disorder: initiate medication therapy only after thorough diagnostic evaluation; total treatment program includes medication and psychological, educational, and social interventions
  - Manic bipolar I disorder: 10 to 17years of age, regular-release tablets, 50 mg/day ORALLY on day 1, 100 mg/day on day 2, 200 mg/day on day 3, 300 mg/day on day 4 and 400 mg/day on day 5 administered 2 to 3 times daily, depending upon patient response and tolerability
  - Manic bipolar I disorder: 10 to 17years of age, regular-release tablets, further dosage adjustments in increments of not more than 100 mg/day up to the recommended dosage range of 400 to 600 mg/day may occur based upon patient response and tolerability; MAX dosage 600 mg/day
  - Manic bipolar I disorder: reinitiation of therapy: if less than 1 week off of quetiapine, titration of dose is not required and maintenance dose may be reinitiated; if greater than 1 week off of quetiapine, initial titration schedule should be followed
  - Schizophrenia: initiate medication therapy only after thorough diagnostic evaluation; total treatment program includes medication and psychological, educational and social interventions
  - Schizophrenia: 13 to 17 years, regular-release tablets, 50 mg/day ORALLY on day 1, 100 mg/day on day 2, 200 mg/day on day 3, 300 mg/day on day 4 and 400 mg/day on day 5 administered 2 to 3 times daily depending upon patient response and tolerability
  - Schizophrenia: 13 to 17 years, regular-release tablets, further dosage adjustments in increments of not more than 100 mg/day up to the recommended dosage range of 400 to 800 mg/day may occur based upon patient response and tolerability; MAX dosage 800 mg/day
  - Schizophrenia: reinitiation of therapy: if less than 1 week off of quetiapine, titration of dose is not required and maintenance dose may be reinitiated; if greater than 1 week off of quetiapine, initial titration schedule should be followed

- **Dose Adjustments**

  - hepatic impairment (regular-release tablets): initial dose, 25 mg/day; increase dose daily in increments of 25 to 50 mg/day to an effective dose based on response and tolerability
  - hepatic impairment (extended-release tablets): initiate with 50 mg/day; increase in increments of 50 mg/day depending on patient response and tolerance
  - elderly (regular-release tablets): use a slower dose escalation and lower target dose
  - elderly (extended-release tablets): initiate with 50 mg/day; increase in increments of 50 mg/day depending on patient response and tolerance
  - debilitated patients (extended-release and regular-release tablets): use a slower dose escalation and lower target dose
  - patients predisposed to hypotensive reactions: (extended-release and regular-release tablets): use a slower dose escalation and lower target dose

- **FDA Labeled Indications**

- Bipolar disorder, depressed phase
  - FDA Approval:
    Adult, yes
    Pediatric, no
  - Efficacy:
    Adult, Evidence favors efficacy
  - Strength of Recommendation:
    Adult, Class IIa
  - Strength of Evidence:
    Adult, Category B
- Bipolar disorder, maintenance; Adjunct
  - FDA Approval:
    Adult, yes
    Pediatric, yes 10 to 17 years, regular-release tablets
  - Efficacy:
    Adult, Evidence favors efficacy
    Pediatric, Evidence favors efficacy
  - Strength of Recommendation:
    Adult, Class IIa
    Pediatric, Class IIb
  - Strength of Evidence:
    Adult, Category B
    Pediatric, Category B
- Major depressive disorder; Adjunct
  - FDA Approval:
    Adult, yes extended-release tablets
    Pediatric, no
  - Efficacy:
    Adult, Evidence favors efficacy
  - Strength of Recommendation:
    Adult, Class IIb
  - Strength of Evidence:
    Adult, Category B
- Manic bipolar I disorder
  - FDA Approval:
    Adult, yes
    Pediatric, yes 10 to 17 years of age, regular-release tablets
  - Efficacy:
    Adult, Evidence favors efficacy

Pediatric, Evidence favors efficacy

- Strength of Recommendation:
  Adult, Class IIa
  Pediatric, Class IIb

- Strength of Evidence:
  Adult, Category B
  Pediatric, Category B

- Schizophrenia

  - FDA Approval:
    Adult, yes
    Pediatric, yes 13 to 17 years of age, regular-release tablets

  - Efficacy:
    Adult, Evidence favors efficacy
    Pediatric, Evidence favors efficacy

  - Strength of Recommendation:
    Adult, Class IIa
    Pediatric, Class IIb

  - Strength of Evidence:
    Adult, Category B
    Pediatric, Category B

- Schizophrenia, maintenance

  - FDA Approval:
    Adult, yes extended release only
    Pediatric, no

  - Efficacy:
    Adult, Evidence favors efficacy

  - Strength of Recommendation:
    Adult, Class IIa

  - Strength of Evidence:
    Adult, Category B

- **Non-FDA Labeled Indications**

  - Bipolar disorder, Maintenance Monotherapy

    - FDA Approval:
      Adult, no
      Pediatric, no

    - Efficacy:
      Adult, Evidence favors efficacy

    - Strength of Recommendation:
      Adult, Class IIb

- Strength of Evidence:
  Adult, Category B

- Major depressive disorder, Monotherapy

  - FDA Approval:
    Adult, no
    Pediatric, no

  - Efficacy:
    Adult, Evidence favors efficacy

  - Strength of Recommendation:
    Adult, Class IIb

  - Strength of Evidence:
    Adult, Category B

Black Box WARNING

Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo. Although the causes of death were varied in clinical trials, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. Not approved for the treatment of patients with dementia-related psychosis. Antidepressants increased the risk of suicidal thinking and behavior in children, adolescents, and young adults in short-term studies with major depressive disorder (MDD) and other psychiatric disorders. Short term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24, and there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older. This risk must be balanced with the clinical need. Monitor patients closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. Regular strength tablets not approved for use in patients under 10 years of age; extended-release tablets not approved for use in patients under 18 years of age.

Contraindications/Warnings

- **Contraindications**

  - specific contraindications have not been determined

- **Precautions**

  - elderly patients with dementia-related psychosis (unapproved use); increased risk of death reported when atypical antipsychotics were used to treat behavorial disorders associated with dementia
  - suicidal ideation and behavior or worsening depression; increased risk, particularly in children, adolescents, and young adults (ages 18 to 24), especially during the first few months of therapy or during changes in dosing (decreases or increases)
  - abrupt withdrawal may result in acute withdrawal symptoms; should be gradually withdrawn
  - agranulocytosis, including fatal cases, has been reported
  - alcohol use should be avoided
  - aspiration pneumonia, patients at risk for; may cause esophageal dysmotility and aspiration
  - cardiac arrhythmias including bradycardia, history of; increased risk of torsades de pointes and/or sudden death; avoid use
  - cardiovascular disease, known; risk of orthostatic hypotension and QT prolongation
  - cataracts or lens changes have been reported; monitoring recommended

- cerebrovascular disease; risk of orthostatic hypotension
- concomitant use of antihypertensive medications; risk of orthostatic hypotension
- concomitant use with drugs that prolong the QT interval should be avoided
- congenital long QT syndrome, history of; increased risk of torsades de pointes and/or sudden death; avoid use
- congestive heart failure and cardiac hypertrophy; may increase risk of QT prolongation
- dehydration; risk of orthostatic hypotension
- diabetes mellitus or at risk of diabetes mellitus; occurrence of hyperglycemia, some cases associated with ketoacidosis, hyperosmolar coma or death; monitoring recommended
- elderly patients; increased risk of tardive dyskinesia (especially elderly women) and QT prolongation
- elevated cholesterol and triglyceride levels have been reported; monitoring recommended
- elevated serum transaminases (asymptomatic, transient and reversible) have been reported
- hypokalemia or hypomagnesemia; increased risk of torsades de pointes and/or sudden death; avoid use
- hypertension has been reported in children and adolescents; monitoring recommended
- hypovolemia; risk of orthostatic hypotension
- leukopenia/neutropenia has been reported; increased risk with history of drug-induced leukopenia/neutropenia or preexisting low WBC; monitoring recommended; if develops, discontinue therapy
- neuroleptic malignant syndrome (NMS) has occurred; immediately discontinue therapy if NMS is suspected
- orthostatic hypotension, with or without syncope, may occur; increased risk during initial dose-titration period, if develops during titration, return to previous dose
- QT prolongation, family history of; may increase risk of QT prolongation
- seizures, history of or predisposing factors for developing
- tardive dyskinesia may occur; increased risk with increased duration of treatment and increased total cumulative dose; if develops, consider discontinuation
- report suspected adverse drug reactions to the US Food and Drug Administration (FDA) at 1-800-FDA-1088 or www.fda.gov/medwatch

- **Pregnancy Category**

  - Quetiapine: C (FDA)
  - Quetiapine: B3 (AUS)

- **Breast Feeding**

  - Quetiapine: Micromedex: Infant risk cannot be ruled out.

Drug Interactions

- **Contraindicated**

  - ◇ Bepridil (theoretical)
  - ◇ Cisapride (theoretical)
  - ◇ Dronedarone (theoretical)
  - ◇ Fluconazole (theoretical)
  - ◇ Mesoridazine (theoretical)
  - ◇ Metoclopramide (theoretical)
  - ◇ Pimozide (theoretical)
  - ◇ Posaconazole (theoretical)
  - ◇ Terfenadine (theoretical)
  - ◇ Thioridazine (theoretical)

- **Major**

  - ◇ Acecainide (theoretical)

- Ajmaline (probable)
- Alfuzosin (theoretical)
- Amiodarone (theoretical)
- Amitriptyline (theoretical)
- Amobarbital (probable)
- Amoxapine (theoretical)
- Apomorphine (theoretical)
- Aprindine (theoretical)
- Aprobarbital (probable)
- Arsenic Trioxide (theoretical)
- Artemether (theoretical)
- Asenapine (theoretical)
- Astemizole (theoretical)
- Azimilide (theoretical)
- Azithromycin (theoretical)
- Bedaquiline (theoretical)
- Betamethasone (probable)
- Bretylium (theoretical)
- Butabarbital (probable)
- Butalbital (probable)
- Chloral Hydrate (theoretical)
- Chloroquine (theoretical)
- Chlorpromazine (theoretical)
- Ciprofloxacin (theoretical)
- Citalopram (theoretical)
- Clarithromycin (theoretical)
- Clomipramine (theoretical)
- Clozapine (theoretical)
- Cobicistat (theoretical)
- Cortisone (probable)
- Crizotinib (theoretical)
- Dabrafenib (theoretical)
- Dasatinib (theoretical)
- Deflazacort (probable)
- Desipramine (theoretical)
- Dexamethasone (probable)
- Dibenzepin (theoretical)
- Disopyramide (probable)
- Dofetilide (theoretical)
- Dolasetron (theoretical)
- Domperidone (theoretical)
- Doxepin (theoretical)
- Droperidol (theoretical)
- Encainide (theoretical)
- Enflurane (theoretical)
- Erythromycin (theoretical)
- Eterobarb (probable)
- Fingolimod (theoretical)
- Flecainide (theoretical)
- Fluoxetine (theoretical)
- Formoterol (theoretical)
- Foscarnet (theoretical)
- Gatifloxacin (theoretical)
- Gemifloxacin (theoretical)
- Granisetron (theoretical)
- Halofantrine (theoretical)
- Haloperidol (probable)
- Halothane (theoretical)

- Hydrocortisone (probable)
- Hydromorphone (theoretical)
- Hydroquinidine (probable)
- Ibutilide (theoretical)
- Iloperidone (theoretical)
- Imipramine (theoretical)
- Isoflurane (theoretical)
- Isradipine (theoretical)
- Lapatinib (theoretical)
- Levofloxacin (theoretical)
- Lidoflazine (theoretical)
- Lorcainide (theoretical)
- Lumefantrine (theoretical)
- Mefloquine (theoretical)
- Mephobarbital (probable)
- Methadone (theoretical)
- Methohexital (probable)
- Methylprednisolone (probable)
- Mifepristone (theoretical)
- Milnacipran (theoretical)
- Moxifloxacin (theoretical)
- Nilotinib (theoretical)
- Norfloxacin (theoretical)
- Nortriptyline (theoretical)
- Octreotide (theoretical)
- Ofloxacin (theoretical)
- Ondansetron (theoretical)
- Paliperidone (theoretical)
- Paramethasone (probable)
- Pasireotide (theoretical)
- Pazopanib (theoretical)
- Pentamidine (theoretical)
- Pentobarbital (probable)
- Perflutren Lipid Microsphere (theoretical)
- Phenobarbital (probable)
- Pirmenol (probable)
- Prajmaline (probable)
- Prednisolone (probable)
- Prednisone (probable)
- Primidone (probable)
- Probucol (theoretical)
- Procainamide (probable)
- Prochlorperazine (theoretical)
- Promethazine (theoretical)
- Propafenone (theoretical)
- Protriptyline (theoretical)
- Quinidine (theoretical)
- Quinine (theoretical)
- Ranolazine (theoretical)
- Rifampin (probable)
- Risperidone (probable)
- Salmeterol (theoretical)
- Secobarbital (probable)
- Sematilide (theoretical)
- Sodium Phosphate (theoretical)
- Sodium Phosphate, Dibasic (theoretical)
- Sodium Phosphate, Monobasic (theoretical)
- Solifenacin (theoretical)

- Sorafenib (theoretical)
- Sotalol (theoretical)
- Sparfloxacin (theoretical)
- Spiramycin (theoretical)
- Sulfamethoxazole (theoretical)
- Sunitinib (theoretical)
- Tacrolimus (theoretical)
- Tedisamil (theoretical)
- Telavancin (theoretical)
- Telithromycin (theoretical)
- Tetrabenazine (theoretical)
- Thiopental (probable)
- Tizanidine (theoretical)
- Toremifene (theoretical)
- Trazodone (theoretical)
- Triamcinolone (probable)
- Trifluoperazine (theoretical)
- Trimethoprim (theoretical)
- Trimipramine (theoretical)
- Vandetanib (theoretical)
- Vardenafil (theoretical)
- Vasopressin (theoretical)
- Vemurafenib (theoretical)
- Vilanterol (theoretical)
- Voriconazole (theoretical)
- Ziprasidone (theoretical)
- Zolmitriptan (theoretical)

Moderate

- Aprepitant (probable)
- Armodafinil (established)
- Fosphenytoin (established)
- Ketoconazole (probable)
- Phenytoin (established)
- Warfarin (probable)

Adverse Effects

COMMON

- Cardiovascular: Hypertension (1% to 2% (adults); 15.2 to 40.6% (children and adolescents)), Orthostatic hypotension (4% to 7% (adults); less than 1% (children and adolescents)), Tachycardia (0.5% to 7%)
- Endocrine metabolic: Serum cholesterol raised (7% to 18%), Serum triglycerides raised (8% to 22%), Weight gain (3% to 23%)
- Gastrointestinal: Abdominal pain (4% to 7%), Constipation (2% to 11%), Increased appetite (2% to 12%), Indigestion (2% to 7%), Vomiting (1% to 11%), Xerostomia (4.1% to 44%)
- Hepatic: Increased liver enzymes (1% to 6%)
- Musculoskeletal: Backache (3% to 5%)
- Neurologic: Asthenia (2% to 10%), Dizziness (9% to 18%), Extrapyramidal disease (3% to 12.9%), Headache (7.4% to 21%), Insomnia (8% to 12%), Lethargy (1% to 5%), Somnolence (16% to 57%), Tremor (2% to 8%)
- Psychiatric: Agitation (6% to 20%)
- Respiratory: Nasal congestion (3% to 5%), Pharyngitis (4% to 6%)
- Other: Fatigue (3% to 14%), Pain (1% to 7%)

- **SERIOUS**
  - ◇ Cardiovascular: Prolonged QT interval, Sudden cardiac death, Syncope (0.3% to 1%)
  - ◇ Endocrine metabolic: Diabetic ketoacidosis
  - ◇ Gastrointestinal: Pancreatitis
  - ◇ Hematologic: Agranulocytosis, Leukopenia, Neutropenia (0.3%)
  - ◇ Immunologic: Anaphylaxis
  - ◇ Neurologic: Seizure (0.05% to 0.5%), Tardive dyskinesia (0.1% to less than 5%)
  - ◇ Psychiatric: Suicidal thoughts
  - ◇ Reproductive: Priapism
  - ◇ Other: Neuroleptic malignant syndrome (rare)

Name Info

- **US Trade Names**
  - Seroquel
  - Seroquel XR
- **Class**
  - Antipsychotic
  - Dibenzothiazepine
- **Regulatory Status**
  - RX
- **Generic Availability**
  - Yes

Mechanism of Action/Pharmacokinetics

- **Mechanism of Action**
  - Quetiapine fumarate is an antagonist at multiple neurotransmitter receptors in the brain. It antagonizes serotonin 5HT(1A) and 5HT(2), Dopamine D(1) and D(2), histamine H(1), adrenergic alpha(1) and alpha(2) receptors. It is believed that efficacy in the treatment of schizophrenia, bipolar depression and bipolar mania are due to the antagonism of a combination of D(2) and 5HT(2) receptors. Quetiapine fumarate also has no affinity at cholinergic muscarinic and benzodiazepine receptors.
- **Pharmacokinetics**
  - **Absorption**
    - ◇ Oral, regular-release tablets: time to peak concentration, 1.5 h
    - ◇ Oral, extended-release tablets: time to peak concentration, 6 h
    - ◇ Oral, bioavailability: 9%
    - ◇ Effect of food, regular-release tablets: bioavailability is marginally affected, increases Cmax by 25% and AUC by 15%
    - ◇ Effect of food, extended-release tablets: increases Cmax by 20% to 44% and AUC by 22% to 52% with a high-fat meal (approximately 800 to 1000 calories)
  - **Distribution**

- ◇ Vd: 10 L/kg +/- 4 L/kg
- ◇ Protein binding: 83%

- **Metabolism**

  - ◇ Hepatic: extensive via P450 CYP3A4, sulfoxidation and oxidation
  - ◇ Active metabolite: N-desalkyl quetiapine

- **Excretion**

  - ◇ Renal: approximately 73%
  - ◇ Fecal: approximately 20%

- **Elimination Half Life**

  - ◇ Quetiapine, regular-release tablet: approximately 6 h
  - ◇ Quetiapine, extended-release tablet: 7 h
  - ◇ N-desalkyl quetiapine, extended-release tablet: 9 to 12 h

Administration/Monitoring

- **Administration**

  - Oral

    - ◇ Oral: (extended-release tablets) do not chew, crush or split; swallow whole
    - ◇ Oral: (extended-release tablets) take without food or with a light meal (approximately 300 Calories)
    - ◇ Oral: (regular-release tablets) take with or without food

- **Monitoring**

  - improvement in signs and symptoms of schizophrenia, bipolar disorder (manic, depressed, or mixed episodes), or depression are indicative of efficacy
  - personal and family history of obesity, diabetes mellitus, and cardiovascular disease; prior to treatment, and updated annually
  - CBC with differential; frequently during the first few months of therapy in patients with preexisting low WBC or a history of drug-induced leukopenia/neutropenia
  - fasting blood glucose test; baseline, at week 12, and annually in all patients; more frequently for patients with risk factors for diabetes mellitus; diabetic patients should be closely monitored for worsening glucose control
  - fasting lipid profile; baseline, at week 12, and every 5 years thereafter
  - blood pressure; baseline, at week 12, and annually thereafter; more frequently in patients with risk factors for hypertension
  - waist circumference; baseline, and annually thereafter
  - weight and BMI; baseline, at week 4, at week 8, at week 12, following initiation or change in therapy, and quarterly thereafter
  - tardive dyskinesia; prior to treatment and annually thereafter; every 6 months in patients with higher risk (ie, elderly, patients who have experienced acute dystonic reactions, akathisia, or other clinically significant extrapyramidal side effects)
  - eye examination (eg, slit lamp exam); initiation of treatment or shortly thereafter, and every 6 months for long term use
  - suicide risk; patients at high-risk for suicide should be closely supervised during therapy

How Supplied

- Generic
  - ◇ Oral Tablet: 25 MG, 50 MG, 100 MG, 200 MG, 300 MG, 400 MG
- Seroquel
  - ◇ Oral Tablet: 25 MG, 50 MG, 100 MG, 200 MG, 300 MG, 400 MG
- Seroquel XR
  - ◇ Oral Tablet, Extended Release: 50 MG, 150 MG, 200 MG, 300 MG, 400 MG

Toxicology

- **Clinical Effects**
  - QUETIAPINE
    - ◇ USES: Quetiapine is an atypical antipsychotic drug and is used in schizophrenia and bipolar disorders. EPIDEMIOLOGY: Poisoning with quetiapine is common. Deaths are reported but are rare and usually due to a polypharmacy ingestion. PHARMACOLOGY: Quetiapine is mainly an antagonist at the serotonin receptor 2 (5-HT2) and has only minor antagonist effects on D2 dopamine receptors. In overdose, quetiapine exhibits antimuscarinergic, antihistamine (H1), and antiadrenergic (alpha 1) effects. TOXICOLOGY: Quetiapine overdose is mainly associated with CNS depression and anticholinergic effects. In most cases, sinus tachycardia is observed. Although quetiapine is associated with prolongation of the corrected QT interval (QTc), torsade de pointes (TdP) has not been documented. MILD TO MODERATE POISONING: Somnolence, dizziness, and mild sinus tachycardia may be observed. SEVERE POISONING: Marked CNS depression, signs of anticholinergic poisoning, such as pronounced sinus tachycardia and urinary retention. Seizures and/or myoclonic jerks may be observed. Mild hypotension occurs but usually responds promptly to fluid resuscitation. QTc prolongation is often observed, although ventricular dysrhythmias have not been documented. ADVERSE EFFECTS: Somnolence, dizziness, sinus tachycardia, palpitations, and orthostatic hypotension can develop. Dry mouth, constipation, and dyspepsia are also often reported.
- **Treatment of Exposure**
  - QUETIAPINE
    - ◇ Support: MANAGEMENT OF MILD TO MODERATE TOXICITY: Primarily supportive care; activated charcoal may prevent or shorten the duration of symptoms in patients presenting shortly after ingestion of a significant amount of the drug. MANAGEMENT OF SEVERE TOXICITY: Consider activated charcoal if a patient presents early after ingestion. If significant CNS depression occurs, perform orotracheal intubation for airway protection before giving charcoal. Administer benzodiazepines to treat seizures. Mild hypotension can be treated with normal saline. A foley catheter may be necessary in case of urinary retention.
    - ◇ Decontamination: PREHOSPITAL: Decontamination is not recommended because of the potential for somnolence and seizures. HOSPITAL: Consider activated charcoal after a recent substantial ingestion and if the patient is able to protect their airway. Quetiapine overdose is rarely life-threatening; gastric lavage is generally not indicated.
    - ◇ Airway management: Perform early orotracheal intubation in a patient with signs of severe intoxication (marked CNS depression, seizures).
    - ◇ Antidote: There is no antidote for quetiapine poisoning.
    - ◇ Monitoring of patient: Monitor vital signs and mental status. Quetiapine plasma levels are not rapidly available or clinically useful. No specific lab work is needed in most patients. Obtain an ECG and institute continuous cardiac monitoring in a patient with moderate to severe toxicity. Monitor creatinine phosphokinase levels in a patient with prolonged CNS depression, myoclonus or seizures.
    - ◇ Hypotensive episode: Mild hypotension can be treated with IV NS at 10 to 20 mL/kg. Consider norepinephrine or phenylephrine, if hypotension persists.

- Drug-induced dystonia: ADULT: Benztropine 1 to 2 mg IV or diphenhydramine 1 mg/kg/dose IV over 2 minutes. CHILD: Diphenhydramine 1 mg/kg/dose IV over 2 minutes (maximum 5 mg/kg/day or 50 mg/m(2)/day).
- Priapism: Priapism may result following a quetiapine overdose due to alpha-adrenergic blockade. An immediate urological consult is necessary. Clinical history should include the use of other agents (ie, antihypertensives, antidepressants, illegal agents) that may also be contributing to priapism. In a patient with ischemic priapism the corpora cavernosa are often completely rigid and the patient complains of pain, while nonischemic priapism the corpora are typically tumescent, but not completely rigid and pain is not typical. Aspirate blood from the corpus cavernosum with a fine needle. Blood gas testing of the aspirated blood may be used to distinguish ischemic (typically PO2 less than 30 mmHg, PCO2 greater than 60 mmHg, and pH less than 7.25) and nonischemic priapism. Color duplex ultrasonography may also be useful. If priapism persists after aspiration, inject a sympathomimetic. PHENYLEPHRINE: Dose: Adult: For intracavernous injection, dilute phenylephrine with normal saline for a concentration of 100 to 500 mcg/mL and give 1 mL injections every 3 to 5 minutes for approximately 1 hour (before deciding that treatment is not successful). For children and patients with cardiovascular disease: Use lower concentrations in smaller volumes. NOTE: Treatment is less likely to be effective if done more than 48 hours after the development of priapism. Distal shunting (NOT first-line therapy) should only be considered after a trial of intracavernous injection of sympathomimetics.
- Enhanced elimination procedure: There is no role for repeat-dose activated charcoal. Hemodialysis is not useful based on the large volume of distribution.
- Patient disposition: HOME CRITERIA: Children less than 12 years of age who are naive to quetiapine can be observed at home following an unintentional ingestion of 100 mg or less and are only experiencing mild sedation. All patients, 12 years of age or older, who are naive to quetiapine, can be observed at home following an unintentional ingestion of 125 mg or less and are experiencing only mild sedation. All patients who are taking quetiapine on a chronic basis can be observed at home if they have acutely ingested no more than 5 times their current single dose (not daily dose) of quetiapine. OBSERVATION CRITERIA: Any patient with a deliberate ingestion or more than minor symptoms should be referred to a healthcare facility. Children less than 12 years of age who are naive to quetiapine should be referred to a healthcare facility following an unintentional ingestion of more than 100 mg. All patients, 12 years of age or older, who are naive to quetiapine should be referred to a healthcare facility following an unintentional ingestion of more than 125 mg. All patients who are taking quetiapine on a chronic basis should be referred to a healthcare facility following an acute ingestion of more than 5 times their current single dose (not daily dose) of quetiapine. Patients should be observed for 6 hours (or at least 12 hours after ingestion of extended-release formulations) and should be admitted if they remain symptomatic. ADMISSION CRITERIA: Any patient with persistent hypotension, CNS depression, seizures, or myoclonus should be admitted to the hospital. CONSULT CRITERIA: Consult a poison center or medical toxicologist for assistance in decision making whether or not admission is advisable, managing patients with severe toxicity (CNS depression, seizures) or in whom the diagnosis is not clear.

- **Range of Toxicity**

- QUETIAPINE
  - TOXIC DOSE: SUMMARY: A dose of more than 100 mg is potentially toxic in a drug naive child less than 12 years old. A dose of more than 125 mg is potentially toxic in a drug naive child aged 12 years or greater. In children on chronic quetiapine therapy an acute ingestion of more than 5 times their current single dose (not daily dose) is potentially toxic. ADULT: An adult died after ingesting 10.8 g of quetiapine, but other patients have survived overdoses of up to 36 g. PEDIATRIC: An 11-year-old developed relatively minor symptoms following an overdose of 1300 mg. THERAPEUTIC DOSE: BIPOLAR: Initial dose: 50 mg orally once daily, increase the dosage up to 800 mg daily in 2 divided doses in bipolar maintenance therapy. MANIC BIPOLAR I DISORDER: Usual effective dosage range is 400 to 800 mg/day; maximum daily dose is 800 mg. PEDIATRIC: MANIC BIPOLAR I DISORDER: 10 to 17 years: Initial dose: 50 mg orally on day 1. Dosage adjustments should be done in increments of not more than 100 mg/day to the recommended dosage range of 400 to 600 mg/day. Maximum dose: 600 mg.

Clinical Teaching

- Advise patient to avoid activities requiring mental alertness or coordination until drug effects are realized, as drug may cause dizziness and somnolence.
- Counsel patient to use caution with activities leading to an increased core temperature (strenuous exercise, exposure to extreme heat, or dehydration), as drug may impair heat regulation.
- Instruct patient to rise from a sitting or lying down position slowly, as drug may cause orthostatic hypotension.
- Drug may cause weight gain, increased appetite, dry mouth, constipation, nausea, vomiting, dyspepsia, fatigue, dysarthria, and asthenia.
- Advise patient to report worsening depression, suicidal ideation, or unusual changes in behavior, especially at initiation of therapy or with dose changes. Children and adolescents are at higher risk during the first few months of therapy.
- Warn patient to report signs/symptoms of tardive dyskinesia (jerky muscle movements, tongue thrusting, facial grimacing/ticks, random movements of extremities) or neuroleptic malignant syndrome (sweating, fever, stupor, unstable blood pressure, muscular rigidity, autonomic dysfunction).
- Counsel diabetic patients to monitor for signs/symptoms of hyperglycemia and to report difficulties with glycemic control.
- Advise patient against sudden discontinuation of drug, as this may precipitate withdrawal symptoms.
- Instruct patient to avoid alcohol while taking this drug.

Last Modified: September 11, 2013

Images & Imprints

Ingredients: Quetiapine Fumarate (100 MG)
Color: Yellow
Shape: Circle
Pattern: Solid
Imprint: SEROQUEL 100
NDC: 00310-0271-10, 00310-0271-39, 12280-0020-15, 13411-0128-03, 16590-0520-30, 16590-0520-60, 16590-0520-90, 21695-0119-30, 23490-7089-01, 23490-7089-02, 49999-0602-00, 49999-0602-15, 54569-5691-01, 55289-0187-30, 63629-3291-01, 63629-3291-02, 68071-0413-30, 68115-0886-00, 68115-0886-15, 68258-7111-01

Ingredients: Quetiapine Fumarate (200 MG)
Color: White
Shape: Circle
Pattern: Solid
Imprint: SEROQUEL 200
NDC: 00310-0272-10, 00310-0272-39, 13411-0129-03, 16590-0679-30, 16590-0679-60, 16590-0679-90, 23490-7090-01, 49999-0951-30, 54569-5692-01, 54868-4272-00, 54868-4272-01, 55289-0447-30, 58864-0961-30, 63629-3378-01, 63629-3378-02, 63629-3378-03, 63629-3378-04, 63629-3378-05, 68071-0428-30, 68115-0912-00, 68115-0912-15, 68258-7112-01

Ingredients: Quetiapine Fumarate (300 MG)
Color: White
Shape: Capsule-shape
Pattern: Solid
Imprint: SEROQUEL; 300
NDC: 00310-0274-39, 00310-0274-60, 12280-0041-60, 13411-0130-03, 35356-0204-60, 54569-5693-01, 58864-0888-30, 63629-3379-01, 63629-3379-02, 63629-3379-03, 63629-3379-04, 68258-7113-01

Ingredients: Quetiapine Fumarate (25 MG)
Color: Light Orange
Shape: Circle
Pattern: Solid
Imprint: SEROQUEL 25
NDC: 00310-0275-10, 00310-0275-34, 00310-0275-39, 12280-0030-15, 12280-0030-30, 13411-0127-03, 16590-0521-30, 16590-0521-60, 16590-0521-90, 18837-0143-30, 18837-0143-60, 23490-7088-02, 23490-7088-03, 49999-0603-00, 49999-0603-15, 49999-0603-30, 54569-5707-00, 54868-4961-00, 54868-4961-01, 55048-0751-30, 55289-0872-30, 58864-0738-30, 63629-3319-01, 63629-3319-02, 63629-3319-03, 68071-0329-30, 68071-0329-60, 68115-0842-00, 68258-7110-01

Ingredients: Quetiapine Fumarate (50 MG)
Color: White
Shape: Circle
Pattern: Solid
Imprint: SEROQUEL 50
NDC: 00310-0278-10, 00310-0278-34, 00310-0278-39, 16590-0519-30, 16590-0519-60, 16590-0519-72, 16590-0519-90, 35356-0086-00, 35356-0086-30, 54868-5581-03, 55048-0752-60, 63629-3380-01, 63629-3380-02, 63629-3380-03, 63629-3380-04

Ingredients: Quetiapine Fumarate (400 MG)
Color: Yellow
Shape: Capsule-shape
Pattern: Solid
Imprint: SEROQUEL; 400
NDC: 00310-0279-10, 00310-0279-39, 12280-0396-30, 16590-0782-30

Ingredients: Quetiapine Fumarate (200 MG)

Color: Yellow
Shape: Capsule-shape
Pattern: Solid
Imprint: XR 200
NDC: 00310-0282-39, 00310-0282-55, 00310-0282-60, 35356-0440-30, 55048-0754-60

Ingredients: Quetiapine Fumarate (400 MG)
Color: White
Shape: Capsule-shape
Pattern: Solid
Imprint: SR 400
NDC: 00310-0284-39, 00310-0284-55, 00310-0284-60

Warranty and Disclaimer

The information above is for use only by healthcare professionals in conjunction with clinical data and their professional judgment.

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- Location In Title:
  - DRUGPOINTS® SYSTEM
    "Q" Monographs
    Quetiapine Fumarate

Overview[a] (see Users Guide). For additional information on this drug until a more detailed monograph is developed and published, the manufacturer's labeling should be consulted. It is *essential* that the manufacturer's labeling be consulted for more detailed information on usual cautions, precautions, contraindications, potential drug interactions, laboratory test interferences, and acute toxicity.

Preparations

Excipients in commercially available drug preparations may have clinically important effects in some individuals; consult specific product labeling for details.

Acamprosate Calcium

Oral

Tablets, delayed-release (enteric-coated)	333 mg	**Campral®**, Forest

Atomoxetine Hydrochloride

■ Atomoxetine is a selective norepinephrine-reuptake inhibitor.

Uses

Atomoxetine hydrochloride is used as an adjunct to psychological, educational, social, and other remedial measures in the treatment of attention-deficit hyperactivity disorder (ADHD).

■ **Attention Deficit Hyperactivity Disorder** Atomoxetine hydrochloride is used as an adjunct to psychological, educational, social, and other remedial measures in the treatment of ADHD (hyperkinetic disorder, hyperkinetic syndrome of childhood, minimal brain dysfunction) in adults and children 6 years of age and older. Efficacy of the drug for this indication was established in short-term (6–9 weeks) controlled clinical studies in children and adolescents 6–18 years of age and also in 10-week controlled clinical studies in adults who met DSM-IV criteria for ADHD. Efficacy of atomoxetine in the treatment of ADHD also was established in one longer-term (12 months) controlled clinical study in children and adolescents 6–15 years of age.

In controlled clinical studies in children 7–13 years of age with ADHD, therapy with atomoxetine (mean final dosage of 1.6 mg/kg daily, administered in 2 divided doses in the morning and late afternoon for 9 weeks) was more effective than placebo in decreasing inattention and hyperactive/impulsive symptoms, as measured by the ADHD Rating Scale-IV-Parent Version (ADHDRS), Clinical Global Impressions-ADHD-Severity (CGI-ADHD-S), and Conners Parent Rating Scale-Revised: Short Form (CPRS-R:S). In another controlled clinical study in children and adolescents 6–16 years of age with ADHD, therapy with atomoxetine (mean final dosage of 1.3 mg/kg once daily in the morning for 6 weeks) was more effective than placebo in decreasing inattention and hyperactive/impulsive symptoms, as measured by the ADHDRS, Conners Parent Rating Scale, and Conners Teacher Rating Scale.

In a randomized, placebo-controlled, dose-response study with atomoxetine (0.5, 1.2, or 1.8 mg/kg daily, administered in 2 divided doses in the morning and late afternoon for 8 weeks) in children and adolescents 8–18 years of age with ADHD, therapy with atomoxetine 1.2 or 1.8 mg/kg daily was more effective than placebo in decreasing inattention and hyperactive/impulsive symptoms, as measured by the ADHDRS, and improving social and family functioning, as measured by the Child Health Questionnaire (CHQ). Patients receiving atomoxetine 0.5 mg/kg daily exhibited responses intermediate to those observed in patients receiving placebo or atomoxetine at higher dosages (1.2 or 1.8 mg/kg daily), but no differences in response were observed between patients receiving dosages of 1.2 versus 1.8 mg/kg daily.

In an open-label, multicenter study in boys 7–15 years of age and girls 7–9 years of age with ADHD, therapy with atomoxetine (up to 2 mg/kg daily, administered in 2 divided doses in the morning and late afternoon) or methylphenidate (up to 60 mg daily, administered once daily or in 2 or 3 divided doses) for 10 weeks produced similar results in the reduction of ADHD symptoms; however, double-blind clinical studies are needed to establish the comparative efficacy and tolerance of these therapies.

In a randomized, double-blind, placebo-controlled maintenance study, 604 children and adolescents 6–15 years of age with ADHD initially received open-label atomoxetine (1.2–1.8 mg/kg daily in 2 divided doses) for 10 weeks. Patients who responded to therapy during the open-label phase were randomized at week 12 to receive either atomoxetine (at the same dosage) or placebo for an additional 9 months. At study end point, relapse (defined as an increase in ADHDRS total score to 90% of baseline score *and* an increase of 2 or more points on the CGI-S scale) occurred in fewer patients receiving atomoxetine compared with those receiving placebo (22 versus 38%). When the more sensitive secondary definition of relapse (an increase in ADHDRS total score to 50% of baseline score *and* an increase of 2 or more points on the CGI-S scale) was used, the relapse rate also was substantially lower in atomoxetine-treated patients (28%) than in placebo-treated patients (48%). In addition, patients who continued receiving atomoxetine experienced a longer time to relapse and achieved superior psychosocial functioning compared to those receiving placebo.

In controlled clinical studies in adults with ADHD, therapy with atomoxetine (mean final dosage of 95 mg daily, administered in 2 equally divided doses in the morning and late afternoon/early evening for 10 weeks) was more effective than placebo in decreasing inattention and hyperactive/impulsive symptoms, as measured by the Conners Adult ADHD Rating Scale (CAARS).

Dosage and Administration

■ **Administration** Atomoxetine hydrochloride may be administered orally once daily in the morning or in 2 equally divided doses in the morning and late afternoon/early evening. The drug may be administered without regard to meals.

The manufacturer states that atomoxetine is an ocular irritant; therefore, the capsules should be swallowed whole and should not be broken or opened, nor should the capsule contents be sprinkled on food.

■ **Dosage** Dosage of atomoxetine hydrochloride is expressed in terms of atomoxetine.

The usual initial dosage of atomoxetine in adults or in children and adolescents weighing more than 70 kg is 40 mg daily; dosage may be increased after a minimum of 3 days to a target dosage of approximately 80 mg daily. If an optimum response has not been achieved after 2–4 additional weeks of therapy, dosage may be increased to a maximum of 100 mg daily; dosages exceeding 100 mg daily have not been shown in clinical trials to result in additional therapeutic benefit. In adults or in children and adolescents weighing more than 70 kg, if atomoxetine is used concomitantly with potent inhibitors of the cytochrome P-450 2D6 (CYP2D6) isoenzyme (e.g., paroxetine, fluoxetine, quinidine) or in patients with poor metabolizer phenotypes of the CYP2D6 isoenzyme, the initial atomoxetine dosage should be 40 mg daily and dosage should be increased to the usual target dosage of 80 mg daily only if ADHD symptoms fail to improve after 4 weeks of therapy and the initial dosage is well tolerated. The maximum recommended dosage of atomoxetine in adults or in children and adolescents weighing more than 70 kg is 100 mg daily. The safety of single doses exceeding 120 mg and total daily dosages exceeding 150 mg has not been established.

The usual initial dosage of atomoxetine in children and adolescents weighing 70 kg or less is approximately 0.5 mg/kg daily; dosage may be increased after a minimum of 3 days to a target dosage of approximately 1.2 mg/kg daily. In children and adolescents weighing 70 kg or less, if atomoxetine is used concomitantly with potent CYP2D6 inhibitors (e.g., paroxetine, fluoxetine, quinidine) or in patients with poor metabolizer phenotypes of the CYP2D6 isoenzyme, the initial atomoxetine dosage should be 0.5 mg/kg daily and dosage should be increased to the usual target dosage of 1.2 mg/kg daily only if ADHD symptoms fail to improve after 4 weeks of therapy and the initial dosage is well tolerated. Daily dosage of atomoxetine in children and adolescents weighing 70 kg or less should not exceed 100 mg or 1.4 mg/kg, whichever is less; dosages exceeding 1.2 mg/kg daily have not been shown in clinical trials to result in additional therapeutic benefit.

Because the effectiveness of atomoxetine for long-term use (i.e., more than 12 months in children and adolescents 6–15 years of age, more than 9 weeks in those 16–18 years of age, and more than 10 weeks in adults) has not been established, patients receiving atomoxetine for extended periods should be periodically reevaluated to assess the long-term usefulness of the drug.

Atomoxetine may be discontinued without tapering the dosage.

■ **Special Populations** The manufacturer recommends that usual initial and target dosages of atomoxetine be reduced by 50% in patients with moderate hepatic impairment (Child-Pugh class B) and by 75% in those with severe hepatic impairment (Child-Pugh class C).

Cautions

■ **Contraindications** Known hypersensitivity to atomoxetine or any ingredient in the formulation.

The manufacturer states that atomoxetine is contraindicated in patients currently receiving or having recently received (i.e., within 2 weeks) monoamine oxidase (MAO) inhibitor therapy. In addition, at least 2 weeks should elapse after discontinuing atomoxetine before initiating MAO inhibitor therapy. Severe, potentially fatal, reactions (including hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma) have been reported in patients receiving other drugs that affect brain monoamine concentrations concomitantly with MAO inhibitor therapy.

The manufacturer also states that atomoxetine should not be used in patients with angle-closure glaucoma, since the drug was associated with an increased risk of mydriasis in some patients during controlled clinical trials.

■ **Warnings/Precautions** *Warnings* **Suicidality Risk.** Atomoxetine may increase the risk of suicidal ideation in children and adolescents with attention deficit hyperactivity disorder (ADHD). (See Pediatric Use under Warnings/Precautions: Specific Populations, in Cautions.) Pediatric patients should be closely monitored for clinical worsening, suicidality (suicidal ideation or behaviors), or unusual changes in behavior, particularly during the first few months after initiation of therapy and during periods of dosage adjustments.

Monitoring should include daily observation by family members and caregivers and frequent contact with the prescribing clinician, particularly if the patient's behavior changes or is a concern. The manufacturer recommends face-to-face contact between clinicians and patients or their family members or caregivers at least weekly during the first 4 weeks of therapy and then every other week for the next 4 weeks, with subsequent face-to-face contact at 12 weeks and as clinically indicated thereafter; additional contact via telephone may be appropriate between visits.

Discontinuance of therapy should be considered in patients with emergent suicidality or manifestations that may be precursors to emerging suicidality (e.g., anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia, hypomania, mania), particularly if such manifestations are severe or abrupt in onset or were not part of the patient's presenting symptoms.

Sensitivity Reactions Allergic reactions, including angioedema, urticaria, and rash, have been reported rarely in patients receiving atomoxetine.

Other Warnings and Precautions **Severe Hepatic Injury.** Severe hepatic injury was reported during postmarketing surveillance in 2 patients (an adolescent and an adult) who had received atomoxetine for several months. In one patient, hepatic injury was manifested by increased hepatic enzymes (up to 40 times the upper limit of normal [ULN]) and jaundice (bilirubin up to 12 times the ULN); manifestations recurred upon rechallenge with atomoxetine and resolved upon discontinuance of the drug, providing evidence that the hepatic injury was caused by atomoxetine. Both patients recovered and did not require liver transplantation. However, the manufacturer notes that severe drug-related hepatic injury may progress to acute hepatic failure resulting in death or requiring liver transplantation in a small percentage of patients. The actual incidence of hepatic injury in patients receiving atomoxetine is unknown because of possible underreporting of postmarketing adverse effects.

Adverse hepatic effects may occur several months after initiation of atomoxetine, and laboratory abnormalities may continue to worsen for several weeks after discontinuance of the drug. Hepatic enzyme concentrations should be determined after the first manifestation of hepatic dysfunction (e.g., pruritus, dark urine, jaundice, right upper quadrant tenderness, unexplained flu-like symptoms) in patients receiving atomoxetine. Atomoxetine should be discontinued in patients with jaundice or laboratory evidence of hepatic injury, and therapy with the drug should *not* be reinitiated in such patients.

Sudden Death and Serious Cardiovascular Events. Although a causal relationship to atomoxetine has not been established, sudden unexplained death, stroke, and myocardial infarction have been reported in adults receiving usual dosages of atomoxetine for the treatment of ADHD. Sudden unexplained death also has been reported in children and adolescents with structural cardiac abnormalities or other serious cardiac conditions receiving usual dosages of atomoxetine. Children, adolescents, and adults who are being considered for atomoxetine therapy should undergo a thorough medical history review (including evaluation for a family history of sudden death or ventricular arrhythmia) and physical examination to detect the presence of cardiac disease, and should receive further cardiac evaluation (e.g., ECG, echocardiogram) if initial findings suggest such disease. Although some serious cardiac conditions are independently associated with an increased risk of sudden death, atomoxetine generally should *not* be used in children, adolescents, or adults with known serious structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, coronary artery disease, or other serious cardiac conditions. Patients who develop exertional chest pain, unexplained syncope, or other manifestations suggestive of cardiac disease during atomoxetine therapy should undergo prompt cardiac evaluation.

For further information on screening for cardiac conditions, selecting appropriate candidates for stimulant therapy, and monitoring for treatment-emergent cardiac conditions, see Cardiovascular Precautions under Cautions: Precautions and Contraindications, in the Amphetamines General Statement 28:20.04.

Psychiatric Effects. Atomoxetine should be used with caution in the management of ADHD in patients with comorbid bipolar disorder because of the potential for precipitation of mixed or manic episodes in such patients. Prior to initiating atomoxetine therapy, patients with ADHD and comorbid depressive symptoms should be carefully screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history (e.g., family history of suicide, bipolar disorder, or depression).

Psychotic or manic symptoms (e.g., hallucinations, delusional thinking, mania) have been reported in children and adolescents without prior history of psychotic illness or mania who received usual dosages of atomoxetine. In a pooled analysis of multiple short-term, placebo-controlled studies, such symptoms occurred in about 0.2% of patients receiving usual dosages of atomoxetine compared with 0% of those receiving placebo. If psychotic or manic symptoms occur, a causal relationship to atomoxetine should be considered, and discontinuance of therapy may be appropriate.

Cardiovascular Effects. Increased blood pressure and heart rate were reported in children, adolescents, and adults receiving atomoxetine in controlled clinical studies. The drug should be used with caution in patients with hypertension, tachycardia, or cardiovascular or cerebrovascular disease that might be affected by increases in blood pressure or heart rate. Blood pressure and pulse rate should be measured before initiation of atomoxetine, following any increase in dosage, and periodically during therapy.

Orthostatic hypotension and syncope also were reported in patients receiving atomoxetine in controlled clinical studies. The drug should be used with caution in patients with conditions that would predispose them to hypotension.

Peripheral Vascular Effects. Exacerbation or precipitation of Raynaud's phenomenon was reported during postmarketing surveillance in patients receiving atomoxetine.

Genitourinary Effects. Urinary retention and urinary hesitation were reported in adults receiving atomoxetine in controlled clinical studies.

Growth Effects. Temporary suppression of normal weight and height patterns has been observed in pediatric patients receiving atomoxetine therapy. Gains in weight and height generally lag behind predicted population values for about the first 9–12 months of therapy; however, weight and height gains rebound with continued treatment. Similar growth patterns have been observed regardless of metabolizer phenotype (poor or extensive metabolizer of the drug) or pubertal status upon initiation of treatment. The manufacturer states that growth should be monitored in patients receiving therapy with atomoxetine.

Children and adolescents 6–18 years of age receiving atomoxetine for up to 9 weeks in controlled clinical studies had an average weight loss of 0.4 kg compared with an average weight gain of 1.5 kg in those receiving placebo for the same time period; similar rates of weight loss have been reported in other controlled clinical studies with the drug. In one clinical trial, decreases in body weight of at least 3.5% occurred in 7–29% of patients receiving atomoxetine at various dosages, compared with 1.3% of patients receiving placebo. However, in patients receiving atomoxetine for 3 years, weight increased by an average of 17.9 kg (0.5 kg more than predicted by baseline data) and height increased by an average of 19.4 cm (0.4 cm less than predicted by baseline data) at 3 years. Gain in height stabilized at about 12 months.

Behavioral Effects. Aggressive behavior and hostility frequently are observed in pediatric patients with ADHD and have been reported in patients receiving drug therapy (including atomoxetine) for the disorder. In controlled clinical studies in pediatric patients, aggressive behavior or hostility was reported slightly (overall risk ratio of 1.33), but not significantly, more frequently in those receiving atomoxetine compared with those receiving placebo. Patients beginning treatment for ADHD should be monitored for the onset or worsening of aggressive behavior or hostility.

Priapism. Priapism was reported rarely during postmarketing surveillance in pediatric and adult patients receiving atomoxetine; if priapism is suspected, prompt medical attention is required. (See Advice to Patients.)

Tics. In a controlled study, atomoxetine did not worsen tics in patients with ADHD and comorbid Tourette's disorder.

Specific Populations **Pregnancy.** Category C. (See Users Guide.)

Lactation. Atomoxetine and/or its metabolites are distributed into milk in rats; it is not known whether the drug is distributed into milk in humans. Therefore, atomoxetine should be used with caution in nursing women.

Pediatric Use. Safety and efficacy of atomoxetine have not been established in children younger than 6 years of age.

Atomoxetine may increase the risk of suicidal ideation in children and adolescents with ADHD. In a pooled analysis of 12 short-term controlled clinical studies in pediatric patients with ADHD (11 studies) or enuresis (1 study), the risk of suicidal ideation was about 0.4% in those receiving atomoxetine versus 0% in those receiving placebo. One child receiving the drug attempted suicide; no completed suicides were reported. All events representing suicidal behavior or thinking occurred in children 12 years of age or younger and occurred during the first month of therapy. It is not known whether the risk of suicidal ideation in pediatric patients extends to long-term use of the drug. A similar analysis of data from adults with ADHD or major depressive disorder found no increased risk of suicidal ideation or behavior in those receiving atomoxetine. The potential risks of suicidality should be weighed against the clinical need for the drug prior to initiating atomoxetine therapy in children or adolescents. (See Suicidality Risk under Warnings/Precautions: Warnings, in Cautions.)

Sudden death has been reported in children and adolescents with structural cardiac abnormalities or other serious cardiac conditions receiving usual dosages of stimulants. (See Sudden Death and Serious Cardiovascular Events under Warnings/Precautions: Other Warnings and Precautions, in Cautions.)

Temporary suppression of normal weight and/or height patterns has been reported during the first 9–12 months of atomoxetine therapy; however, weight and height gains have rebounded with continued treatment. (See Growth Effects under Warnings/Precautions: Other Warnings and Precautions, in Cautions.) The growth of pediatric patients receiving atomoxetine should be monitored.

Geriatric Use. Safety and efficacy of atomexetine have not been established in geriatric patients.

Hepatic Impairment. Systemic exposure to atomoxetine concentrations is increased twofold in patients with moderate hepatic impairment (Child-Pugh class B) and fourfold in those with severe hepatic impairment (Child-Pugh class C). (See Dosage and Administration: Special Populations.)

■ **Common Adverse Effects** Abdominal pain, decreased appetite, vomiting, somnolence, nausea, fatigue, irritability, and dizziness each occurred in 5% or more of children and adolescents receiving atomoxetine in controlled clinical studies and were at least twice as frequent in patients receiving the drug as in those receiving placebo. Dry mouth, nausea, insomnia, decreased appetite, constipation, fatigue, erectile dysfunction, hot flush, urinary disorders (urinary hesitation, urinary retention), and dysmenorrhea each occurred in 5% or more of adults receiving atomoxetine in controlled clinical studies and were

at least twice as frequent in patients receiving the drug as in those receiving placebo.

Drug Interactions

■ **Drugs Affecting Hepatic Microsomal Enzymes** Potential pharmacokinetic interaction (decreased metabolism of atomoxetine) when atomoxetine is used concomitantly with drugs that inhibit the activity of the cytochrome P-450 2D6 (CYP2D6) isoenzyme. Inhibitors of CYP2D6 may increase plasma concentrations of atomoxetine in patients with the extensive-metabolizer phenotype to such an extent that plasma concentrations of the drug are similar to those achieved in poor metabolizers. When atomoxetine is used concomitantly with potent CYP2D6 inhibitors (e.g., paroxetine, fluoxetine, quinidine), or in patients with poor-metabolizer phenotypes of the CYP2D6 isoenzyme, the manufacturer states that dosage adjustment of atomoxetine should be considered. (See Dosage and Administration: Dosage.) However, in vitro studies suggest that concomitant use of atomoxetine with CYP2D6 inhibitors will not increase plasma concentrations of atomoxetine in patients with the poor-metabolizer phenotype.

■ **Drugs Metabolized by Hepatic Microsomal Enzymes** Pharmacokinetic interaction unlikely; evidence to date suggests that atomoxetine does not cause clinically important inhibition or induction of cytochrome P-450 enzymes, including CYP1A2, CYP3A, CYP2D6, and CYP2C9.

■ **GI Drugs** No important pharmacokinetic interactions reported with drugs that increase gastric pH (e.g., antacids containing magnesium hydroxide and aluminum hydroxide, omeprazole).

■ **Protein-bound Drugs** Pharmacokinetic interaction unlikely. In vitro studies indicate that atomoxetine is not displaced from binding sites by, and does not displace from binding sites, other highly protein-bound drugs (e.g., warfarin, aspirin, phenytoin, diazepam) in therapeutic concentrations.

■ **Alcohol** No change in the intoxicating effects of alcohol when alcohol was ingested by individuals receiving atomoxetine.

■ **β-Adrenergic Agonists** Potential pharmacologic interaction (increased cardiovascular effects [e.g., increased heart rate and blood pressure]) when atomoxetine is used concomitantly with oral or parenteral β_2-adrenergic agonists (e.g., albuterol). Use with caution.

■ **Cardiovascular Agents** Potential pharmacologic interaction (increased hypertensive effects) with concomitant use of pressor agents (e.g., dopamine, dobutamine) and atomoxetine. Use with caution.

■ **Methylphenidate** No increase in cardiovascular effects with concomitant use of methylphenidate and atomoxetine relative to use of methylphenidate alone.

■ **Monoamine Oxidase Inhibitors** Potential pharmacologic interaction (inhibition of catecholamine metabolism). (See Cautions: Contraindications.)

Description

Atomoxetine is a selective norepinephrine-reuptake inhibitor. Atomoxetine is not considered a stimulant and also is structurally unrelated to other agents used for the treatment of attention deficit hyperactivity disorder (ADHD). The exact mechanism(s) of action of atomoxetine in the management of ADHD has not been fully elucidated but, based on in vitro studies, appears to be related to selective inhibition of the presynaptic norepinephrine transporter; the drug appears to have minimal affinity for other noradrenergic receptors or for other neurotransmitter transporters or receptors.

Atomoxetine is readily absorbed following oral administration. The drug is approximately 98% bound to plasma proteins, principally albumin, at therapeutic concentrations. Atomoxetine is metabolized principally via oxidation by the cytochrome P-450 2D6 (CYP2D6) isoenzyme and subsequent glucuronidation. Individuals who extensively metabolize atomoxetine via the CYP2D6 pathway exhibit the extensive-metabolizer phenotype, while those who have an impaired ability to metabolize the drug by this pathway exhibit the poor-metabolizer phenotype. In patients with the poor-metabolizer phenotype (about 7% of Caucasians and 2% of African-Americans), metabolic clearance of atomoxetine may be decreased; a fivefold increase in peak plasma concentrations of atomoxetine and a tenfold increase in area under the plasma concentration-time curve (AUC) have been reported in individuals with the poor-metabolizer phenotype relative to those with the extensive-metabolizer phenotype. The mean elimination half-life of atomoxetine is 5.2 or 21.6 hours in extensive or poor metabolizers, respectively. Atomoxetine does not inhibit or induce CYP2D6.

Advice to Patients

Importance of providing patient or caregiver with a copy of the manufacturer's patient information (medication guide); discuss and answer questions about its contents (e.g., benefits and risks of atomoxetine therapy, appropriate use) as needed. Importance of instructing the patient or caregiver to read and understand the contents of the medication guide before initiating therapy and each time the prescription is refilled.

Risk of suicidal thinking. Importance of patients, caregivers, and family members immediately informing clinician if clinical worsening, anxiety, agitation, panic attacks, insomnia, irritability, aggressive behaviors, hostility, impulsivity, restlessness, mania, depression, suicidal ideation or behaviors, or unusual changes in behavior occur, particularly during the first few months after initiation of therapy or following dosage adjustments.

Patients and/or caregivers should be advised that hepatic dysfunction may develop rarely. Importance of informing clinician immediately if symptoms of hepatic injury occur (e.g., pruritus, jaundice, dark urine, upper right-sided abdominal tenderness, unexplained flu-like symptoms).

Importance of informing clinician immediately if adverse cardiovascular effects (e.g., chest pain, shortness of breath, fainting) occur.

Importance of informing clinician immediately if precipitation of psychotic (e.g., hallucinations, delusional thinking) or manic symptoms occurs.

Importance of exercising caution when driving or operating machinery until the effects of the drug on the individual are known.

Risk of priapism. Importance of seeking immediate medical attention if an erection persists for more than 4 hours.

Importance of taking atomoxetine exactly as prescribed. If a patient misses a dose of the drug, the missed dose should be taken as soon as it is remembered, but the amount of atomoxetine taken within a 24-hour period should not exceed the prescribed total daily dosage of the drug.

Importance of advising patient and/or caregivers that atomoxetine capsules should not be opened because the drug is an ocular irritant; if eye contact occurs, flush the affected eye(s) with water immediately, obtain medical advice, and wash hands and potentially contaminated surfaces as soon as possible.

Importance of informing clinician of any history of physical or mental disorders (e.g., cardiovascular disease, liver disease, depression).

Importance of women informing clinicians if they are or plan to become pregnant or plan to breast-feed.

Importance of informing clinicians of existing or contemplated concomitant therapy, including prescription and OTC drugs, dietary supplements, and herbal products, as well as any concomitant illnesses/conditions (e.g., glaucoma, suicidal ideation or behaviors, cardiac/cardiovascular disease, mental/psychiatric disorder, hepatic disease).

Importance of informing patients and/or caregivers of other important precautionary information. (See Cautions.)

Overview® (see Users Guide). For additional information on this drug until a more detailed monograph is developed and published, the manufacturer's labeling should be consulted. It is *essential* that the manufacturer's labeling be consulted for more detailed information on usual cautions, precautions, contraindications, potential drug interactions, laboratory test interferences, and acute toxicity.

Preparations

Excipients in commercially available drug preparations may have clinically important effects in some individuals; consult specific product labeling for details.

Atomoxetine Hydrochloride

Oral		
Capsules	10 mg (of atomoxetine)	Strattera®, Lilly
	18 mg (of atomoxetine)	Strattera®, Lilly
	25 mg (of atomoxetine)	Strattera®, Lilly
	40 mg (of atomoxetine)	Strattera®, Lilly
	60 mg (of atomoxetine)	Strattera®, Lilly
	80 mg (of atomoxetine)	Strattera®, Lilly
	100 mg (of atomoxetine)	Strattera®, Lilly

Flumazenil

■ Flumazenil, a 1,4-imidazobenzodiazepine derivative, is a benzodiazepine antagonist.

Uses

Flumazenil is used in adults for the complete or partial reversal of benzodiazepine-induced sedation when benzodiazepines are used for induction or maintenance of general anesthesia or for diagnostic or therapeutic procedures (i.e., conscious sedation) and for the management of benzodiazepine intoxication. Flumazenil also is used in children 1–17 years of age for the reversal of benzodiazepine-induced sedation when benzodiazepines are used for diagnostic or therapeutic procedures. The manufacturer states that the safety and efficacy of flumazenil have *not* been established in pediatric patients for reversal of benzodiazepine-induced sedation when benzodiazepines are used for induction of general anesthesia, for the management of benzodiazepine intoxication, nor for the resuscitation of neonates. (See Special Populations: Pediatric Use.)

■ **Reversal of General Anesthesia** Flumazenil has been shown to be effective in reversing sedation and restoring psychomotor function in adults who received midazolam for induction or maintenance of general anesthesia. Efficacy was established in 4 clinical studies in adults who received 5–80 mg

Atomoxetine Hydrochloride

Dosing & Indications

- **Adult Dose**
  - Attention deficit hyperactivity disorder: 40 mg/day ORALLY; increase after a minimum of 3 days to a target dose of approximately 80 mg/day; MAX dosage of 100 mg/day may be considered after 2 to 4 additional weeks in patients who have not achieved adequate response on lower doses
- **Pediatric Dose**
  - safety and effectiveness not established in children less than 6 years of age
  - Attention deficit hyperactivity disorder: acute treatment: (weight of 70 kg or less) 0.5 mg/kg/day ORALLY; increase after a minimum of 3 days to a target dose of 1.2 mg/kg/day; MAX dosage is 1.4 mg/kg/day or 100 mg/day (whichever is less)
  - Attention deficit hyperactivity disorder: acute treatment: (weight greater than 70 kg) 40 mg/day ORALLY; increase after a minimum of 3 days to a target dose of approximately 80 mg/day; MAX dosage of 100 mg/day may be considered after 2 to 4 additional weeks in patients who have not achieved adequate response on lower doses
  - Attention deficit hyperactivity disorder: maintenance: 1.2 to 1.8 mg/kg/day ORALLY has been studied in 1 clinical trial; MAX dosage is 1.4 mg/kg/day or 100 mg/day, whichever is less (weight of 70 kg or less) OR 100 mg/day (weight greater than 70 kg)
- **Dose Adjustments**
  - concomitant strong CYP2D6 inhibitor therapy, adults and children/adolescents weighing over 70 kg: initial dose, 40 mg/day ORALLY; increase to 80 mg/day only if symptoms do not improve after 4 weeks and the initial dose is well tolerated
  - concomitant strong CYP2D6 inhibitor therapy, children/adolescents weighing 70 kg or less: initial dose, 0.5 mg/kg/day ORALLY; increase up to 1.2 mg/kg/day only if symptoms do not improve after 4 weeks and the initial dose is well tolerated
  - renal impairment: no dosage adjustment necessary for renal impairment
  - hepatic impairment, moderate hepatic insufficiency (Child-Pugh Class B): initial and target doses should be reduced to 50% of the normal dose
  - hepatic impairment, severe hepatic insufficiency (Child-Pugh Class C): initial and target doses should be reduced to 25% of the normal dose
  - CYP2D6 poor metabolizers, adults and children/adolescents weighing over 70 kg: initial dose, 40 mg/day ORALLY; increase up to 80 mg/day only if symptoms do not improve after 4 weeks and the initial dose is well tolerated
  - CYP2D6 poor metabolizers, children/adolescents weighing 70 kg or less: initial dose, 0.5 mg/kg/day ORALLY; increase up to 1.2 mg/kg/day only if symptoms do not improve after 4 weeks and the initial dose is well tolerated
- **FDA Labeled Indications**
  - Attention deficit hyperactivity disorder
    - ◇ FDA Approval:
      Adult, yes
      Pediatric, yes 6 years and older
    - ◇ Efficacy:
      Adult, Evidence favors efficacy
      Pediatric, Evidence favors efficacy

- Strength of Recommendation:
  Adult, Class IIb
  Pediatric, Class IIb

- Strength of Evidence:
  Adult, Category B
  Pediatric, Category B

- **Non-FDA Labeled Indications**

  - Attention deficit hyperactivity disorder - Social phobia

    - FDA Approval:
      Adult, no
      Pediatric, no

    - Efficacy:
      Adult, Evidence favors efficacy
      Pediatric, Evidence favors efficacy

    - Strength of Recommendation:
      Adult, Class IIb
      Pediatric, Class IIb

    - Strength of Evidence:
      Adult, Category B
      Pediatric, Category B

  - Nocturnal enuresis

    - FDA Approval:
      Adult, no
      Pediatric, no

    - Efficacy:
      Adult, Evidence favors efficacy

    - Strength of Recommendation:
      Adult, Class IIb

    - Strength of Evidence:
      Adult, Category B

Black Box WARNING

There is an increased risk of suicidal ideation in children and adolescents. No suicides occurred in clinical trials. Monitor patients closely for suicidal thinking and behavior, clinical worsening, or unusual changes in behavior.

Contraindications/Warnings

- **Contraindications**

  - cardiac or vascular disorders, severe; at risk for deterioration with clinically important increase of blood pressure (15 to 20 mm Hg) or heart rate (20 beats per minute); monitoring recommended
  - hypersensitivity to atomoxetine or to other components of the product

- MAO inhibitor use; do not administer atomoxetine during therapy with or within 2 weeks of discontinuing an MAO inhibitor; do not administer MAO inhibitor within 2 weeks of discontinuing atomoxetine
- narrow angle glaucoma; increased risk of mydriasis
- pheochromocytoma, current or history of; increased risk for serious reactions, including tachyarrhythmia and elevated blood pressure

- **Precautions**

  - suicidal ideation has occurred; increased risk in children and adolescents in short-term studies; monitoring recommended, especially during the first few months of therapy or following a dosage adjustment; discontinuation may be necessary
  - aggressive behavior or hostility, new onset or worsening, has been reported; monitoring recommended
  - allergic reactions, including anaphylactic reactions, angioneurotic edema, urticaria, and rash, have been reported
  - bipolar disorder; mixed/manic episode may be induced; screening recommended prior to therapy for patients with comorbid depressive symptoms
  - cardiac abnormalities, serious, including structural abnormalities, cardiomyopathy, serious heart rhythm abnormalities, and coronary artery disease; sudden death (children, adolescents, and adults), stroke (adults), and myocardial infarction (adults) have been reported with usual doses; do not use in children or adolescents and consider not using in adults with these conditions
  - cardiovascular or cerebrovascular disease; risk of increased blood pressure and heart rate; monitoring recommended
  - depressive symptoms, preexisting; possible induction of mixed/manic episode in patients at risk for bipolar disorder; screen for bipolar disorder
  - growth (height and weight gains) may be affected in pediatric patients; monitoring recommended
  - hypertension; risk of increased blood pressure and heart rate; monitoring recommended
  - liver injury, severe, has been reported; discontinue and do not restart if jaundice or laboratory evidence of liver injury develops
  - orthostatic hypotension and syncope have been reported; use cautiously in conditions predisposing to hypotension or associated with abrupt heart rate or blood pressure changes
  - priapism has been reported in children and adults; seek prompt medical attention
  - psychotic or manic symptoms (eg, hallucinations, delusional thinking, mania) may occur at usual doses in children and adolescents without a prior history of psychotic illness or mania; discontinuation may be necessary
  - tachycardia; risk of increased blood pressure and heart rate; monitoring recommended
  - urinary retention and hesitation have been reported
  - report suspected adverse reactions to the US Food and Drug Administration at 1-800-FDA-1088 or www.fda.gov/medwatch

- **Pregnancy Category**

  - Atomoxetine: C (FDA)

- **Breast Feeding**

  - Atomoxetine: Micromedex: Infant risk cannot be ruled out.

Drug Interactions

- **Contraindicated**

  - ◇ Brofaromine (theoretical)
  - ◇ Clorgyline (theoretical)
  - ◇ Furazolidone (theoretical)
  - ◇ Iproniazid (theoretical)

- ◇ Isocarboxazid (theoretical)
- ◇ Lazabemide (theoretical)
- ◇ Linezolid (theoretical)
- ◇ Moclobemide (theoretical)
- ◇ Nialamide (theoretical)
- ◇ Pargyline (theoretical)
- ◇ Phenelzine (theoretical)
- ◇ Procarbazine (theoretical)
- ◇ Rasagiline (theoretical)
- ◇ Selegiline (theoretical)
- ◇ Toloxatone (theoretical)
- ◇ Tranylcypromine (theoretical)

- **Major**
  - ◇ Albuterol (probable)

- **Moderate**
  - ◇ Amitriptyline (probable)
  - ◇ Amoxapine (probable)
  - ◇ Clomipramine (probable)
  - ◇ Desipramine (probable)
  - ◇ Dibenzepin (probable)
  - ◇ Dothiepin (probable)
  - ◇ Imipramine (probable)
  - ◇ Lofepramine (probable)
  - ◇ Nortriptyline (probable)
  - ◇ Opipramol (probable)
  - ◇ Protriptyline (probable)
  - ◇ Trimipramine (probable)

Adverse Effects

- **COMMON**
  - ◇ Cardiovascular: Increased diastolic arterial pressure (adult, 4.8% to 12.6%; pediatric, 9.3% to 21.5%), Increased systolic arterial pressure (adult, 4.2% to 12.4%; pediatric, 4.9% to 12.5%), Tachycardia (adult, 1.5% to 22.4%; pediatric, 0.3% to 23.4%)
  - ◇ Endocrine metabolic: Weight decreased (adults, 2%; pediatric, 7.1% to 29.1%)
  - ◇ Gastrointestinal: Abdominal pain (adult, 7%; pediatric, 17% to 18%), Constipation (adult, 8%; pediatric, 1% to 2%), Decrease in appetite (adult, 16%; pediatric, 16%), Nausea (adult, 26%; pediatric, 7% to 13%), Vomiting (adult, 4%; pediatric, 11%), Xerostomia (adult, 20%)
  - ◇ Neurologic: Headache (pediatric, 19%), Insomnia (adult, 15%; pediatric, at least 2%), Somnolence (adult, 8%; pediatric, 11%)
  - ◇ Renal: Delay when starting to pass urine (adult, 6%)
  - ◇ Reproductive: Dysmenorrhea (adult, 3%), Erectile dysfunction (adult, 9%)
  - ◇ Other: Menopausal flushing (adult, 3%)

- **SERIOUS**
  - ◇ Cardiovascular: Myocardial infarction, Prolonged QT interval, Sudden cardiac death
  - ◇ Hepatic: Injury of liver (Severe), Liver failure
  - ◇ Neurologic: Cerebrovascular accident, Dyskinesia, Seizure (adult, 0.1%; pediatric, 0.2%)
  - ◇ Psychiatric: Mania, Psychotic disorder, Suicidal thoughts (pediatric, 0.4%)
  - ◇ Reproductive: Priapism (rare)
  - ◇ Other: Angioedema

Name Info

- **US Trade Names**
  - Strattera
- **Class**
  - Central Nervous System Agent
  - Norepinephrine Reuptake Inhibitor
- **Regulatory Status**
  - RX
- **Generic Availability**
  - No

Mechanism of Action/Pharmacokinetics

- **Mechanism of Action**
  - Atomoxetine is a selective norepinephrine reuptake inhibitor that produces therapeutic effects in patients with Attention-Deficit/Hyperactivity Disorder (ADHD). The exact mechanism of how selective inhibition of pre-synaptic norepinephrine exerts effects in ADHD is yet to be determined.
- **Pharmacokinetics**
  - **Absorption**
    - Oral, tablets: rapid, time to peak concentration, 1 h to 2 h
    - Bioavailability: (Oral, normal metabolizers), 63%
    - Bioavailability: (Oral, poor metabolizers), 94%
    - Effect of food: (Oral), minimal effect on extent of absorption
  - **Distribution**
    - Vd: 0.85 L/kg
    - Protein binding: 98%
  - **Metabolism**
    - Hepatic; isoenzyme P450 CYP2D6; poor metabolizers have 5 fold higher plasma concentrations of atomoxetine
    - Active metabolite: 4-hydroxyatomoxetine; equipotent to atomoxetine but circulates in low concentrations, 1% in normal metabolizers, 0.1% in poor metabolizers
  - **Excretion**
    - Fecal: 17% as metabolite
    - Renal: 80% as metabolite
    - Dialyzable: no (hemodialysis)
  - **Elimination Half Life**

- ◇ Atomoxetine, Normal metabolizers: 5.2 h (mean)
- ◇ Atomoxetine, Poor metabolizers: 21.6 h (mean)
- ◇ 4-hydroxyatomoxetine, Normal metabolizers: 6 h to 8 h

Administration/Monitoring

- **Administration**

  - Oral

    - ◇ Oral: may be taken with or without food
    - ◇ Oral: swallow capsules whole; do not open

- **Monitoring**

  - improvement of mental and behavioral symptoms of ADHD is indicative of efficacy
  - blood pressure and heart rate; baseline, following dose increases, and during therapy with routine follow-up at 1 to 3 months, every 6 to 12 months thereafter
  - signs of clinical worsening, suicidality, or unusual changes in behavior; particularly at start of and during first few months of therapy or when dose is adjusted; including daily observation by families and caregivers
  - aggressive behavior or hostility, new onset or worsening; in pediatric patients at start of treatment
  - growth rate; in pediatric patients

How Supplied

- Strattera
  - ◇ Oral Capsule: 10 MG, 18 MG, 25 MG, 40 MG, 60 MG, 80 MG, 100 MG

Toxicology

- **Clinical Effects**

  - ATOMOXETINE
    - ◇ OVERDOSE: Overdose data are limited. Drowsiness, mild tachycardia and hypertension, nausea and vomiting, nystagmus, tremor, and rarely seizures have been reported after overdose. ADVERSE EFFECTS: Increases in blood pressure and heart rate, somnolence, skin rash, weight loss, nausea and vomiting, anorexia, dyspepsia, constipation, dry mouth, abdominal pain, decreased libido, ejaculatory failure or disorder, dysmenorrhea, urinary hesitation, urinary retention, and/or difficulty in micturition have been reported. Drug-induced hepatotoxicity has been reported with therapeutic use.

- **Treatment of Exposure**

  - ATOMOXETINE

    - ◇ Decontamination: Activated charcoal.
    - ◇ Support: Treatment is symptomatic and supportive.
    - ◇ Monitoring of patient: Vital signs, fluid and electrolytes status in symptomatic patients.
    - ◇ Enhanced elimination procedure: Atomoxetine is highly protein-bound and has a large volume of distribution, therefore it is unlikely that hemodialysis or hemoperfusion would be effective.

- **Range of Toxicity**

  - ATOMOXETINE
    - ◇ TOXICITY: A minimum toxic dose has not been established. Generalized seizures and prolonged

QTc interval developed in a 15-year-old who ingested 1200 mg atomoxetine. A 12-year-old developed mild transient tachycardia and no other effects after ingesting 180 mg. An adolescent developed a single seizure, tremors, nystagmus and hyperreflexia after ingesting 2840 mg. Mild to moderate effects have been reported with ingestions up to 750 mg in children and adolescents. THERAPEUTIC DOSE: ADULTS OR CHILDREN OVER 70 KG BODY WEIGHT - Initial, 40 mg/day and increased after a minimum of 3 days to a target total daily dose of approximately 80 mg. May increase to 100 mg after 2 to 4 additional weeks of therapy. PEDIATRIC DOSING: UP TO 70 KG BODY WEIGHT - Initial, approximately 0.5 mg/kg/day and increased after a minimum of 3 days to a target total daily dose of approximately 1.2 mg/kg. Max 1.4 mg/kg or 100 milligrams, whichever is less.

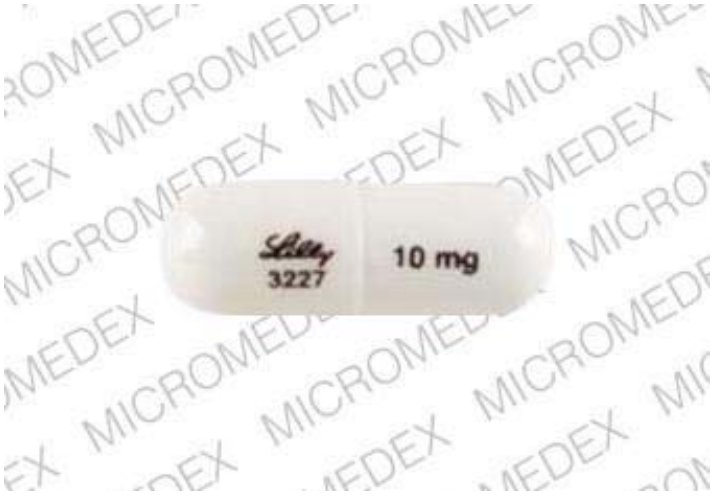
Clinical Teaching

- Instruct patient to report use of MAOI within the past 14 days.
- Advise patient to avoid activities requiring mental alertness or coordination until drug effects are realized.
- Counsel parents that growth rate and weight may need to be monitored more frequently for children using drug.
- This drug may cause anticholinergic effects, loss of appetite, nausea, insomnia, erectile dysfunction, or reduced libido.
- Instruct patient to report new or worsened psychiatric problems (eg, behavior and thought problems, bipolar illness, aggressive behavior or hostility). Children and adolescents may also experience new psychotic (eg, hearing voices) or manic symptoms.
- Patient should also report chest pain, palpitations, dyspnea, or signs/symptoms of cardiac dysrhythmia, myocardial infarction, or cerebrovascular accident.

Last Modified: September 03, 2013

Images & Imprints

Ingredients: Atomoxetine Hydrochloride (10 MG)
Color: White
Shape: Capsule-shape
Pattern: Solid
Imprint: LILLY 3227; 10 mg
NDC: 00002-3227-30



Ingredients: Atomoxetine Hydrochloride (25 MG)
Color: Blue; White
Shape: Capsule-shape
Pattern: Two-toned
Imprint: LILLY 3228; 25 mg
NDC: 00002-3228-30, 49999-0636-30, 49999-0636-90, 54868-4740-00

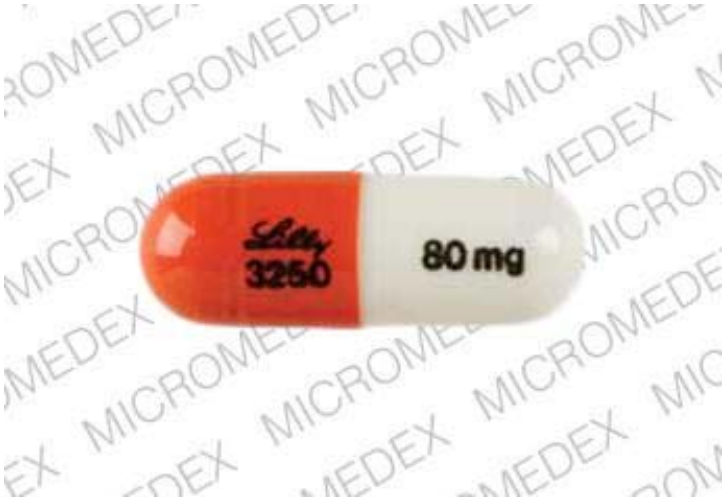
Ingredients: Atomoxetine Hydrochloride (40 MG)

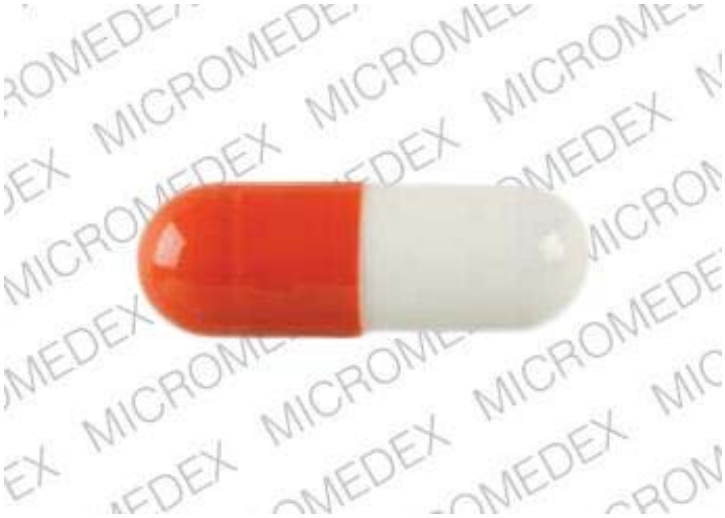
Color: Blue
Shape: Capsule-shape
Pattern: Solid
Imprint: LILLY 3229; 40 mg
NDC: 00002-3229-30, 35356-0142-30, 35356-0142-90, 54868-4741-00

Ingredients: Atomoxetine Hydrochloride (18 MG)
Color: Gold; White
Shape: Capsule-shape
Pattern: Two-toned
Imprint: LILLY 3238; 18 mg
NDC: 00002-3238-30, 35356-0141-30

Ingredients: Atomoxetine Hydrochloride (60 MG)
Color: Blue; Gold
Shape: Capsule-shape
Pattern: Two-toned
Imprint: LILLY 3239; 60 mg
NDC: 00002-3239-30, 49999-0637-30, 54868-4884-00

Ingredients: Atomoxetine Hydrochloride (80 MG)
Color: Brown; White
Shape: Capsule-shape
Pattern: Two-toned
Imprint: LILLY 3250; 80 mg
NDC: 00002-3250-30, 54868-1911-00





Ingredients: Atomoxetine Hydrochloride (100 MG)
Color: Brown
Shape: Capsule-shape
Pattern: Solid
Imprint: LILLY 3251; 100 mg
NDC: 00002-3251-30

Warranty and Disclaimer

The information above is for use only by healthcare professionals in conjunction with clinical data and their professional judgment.

of paroxetine kinetics observed with increasing dosage and duration of treatment. The role of the CYP2D6 enzyme in paroxetine metabolism also suggests potential drug-drug interactions. (See Drug Interactions: Drugs Undergoing Hepatic Metabolism or Affecting Hepatic Microsomal Enzymes.)

Following oral administration, paroxetine and its metabolites are excreted in both urine and feces. Following oral administration of a single, 30-mg dose of paroxetine (administered as paroxetine hydrochloride) as an oral solution (not commercially available), approximately 64% of the dose was excreted in the urine within 10 days; unchanged paroxetine accounted for 2% of the dose and metabolites accounted for the remaining 62% of the dose. During the same period, approximately 36% of the dose was eliminated in feces (probably via the bile), mostly as metabolites and less than 1% as the parent drug.

The effect of age on the elimination of paroxetine has not been fully elucidated. In healthy geriatric adults, hepatic clearance of paroxetine was mildly impaired leading to slower elimination and increased plasma concentrations of the drug. (See Pharmacokinetics: Absorption.) Studies in depressed, geriatric patients confirm these findings with higher steady-state concentrations and longer elimination half-lives reported compared with younger individuals. These results suggest that older patients may be more susceptible to saturation of hepatic metabolic activity resulting in nonlinear kinetics and higher plasma concentrations occurring at lower dosages of paroxetine. Therefore, the manufacturers and some clinicians recommend that paroxetine initially be administered in a reduced dosage in geriatric patients. (See Cautions: Geriatric Precautions and see Dosage and Administration: Dosage in Geriatric and Debilitated Patients.)

Because paroxetine is extensively metabolized by the liver, hepatic impairment can affect the elimination of the drug. In cirrhotic patients with moderate hepatic impairment who received a single 20-mg dose of paroxetine (administered as paroxetine hydrochloride), no significant difference in plasma paroxetine concentrations and pharmacokinetic parameters was observed when compared with corresponding data in healthy individuals. However, accumulation potentially may occur in patients receiving multiple daily doses of paroxetine. The manufacturers state that patients with impaired hepatic function have approximately twofold higher peak plasma concentrations and AUC values. Therefore, the manufacturers recommend that paroxetine be administered in a reduced dosage initially in patients with severe hepatic impairment; caution also should be exercised when increasing the dosage of paroxetine in such patients. (See Cautions: Precautions and Contraindications and see Dosage and Administration: Dosage in Renal and Hepatic Impairment.)

The effect of renal impairment on the pharmacokinetics of paroxetine has not been fully evaluated to date. Following oral administration of multiple daily doses of paroxetine as paroxetine hydrochloride in patients with creatinine clearances less than 30 mL/minute, mean plasma concentrations of paroxetine were approximately 4 times greater than those seen in healthy individuals. In patients with creatinine clearances of 30–60 mL/minute, peak plasma concentrations and AUC values were approximately twofold higher when compared with healthy individuals. The influence of renal impairment in patients receiving multiple daily doses of paroxetine has not been evaluated to date. Pending further accumulation of data, the manufacturers and some clinicians recommend that paroxetine be administered in a reduced dosage initially in patients with severe renal impairment. (See Cautions: Precautions and Contraindications and see Dosage and Administration: Dosage in Renal and Hepatic Impairment.)

Because of the large volume of distribution of paroxetine and its principal metabolite, peritoneal dialysis, forced diuresis, hemoperfusion, and/or exchange transfusion are unlikely to be effective in removing substantial amounts of paroxetine from the body.

Chemistry and Stability

■ **Chemistry** Paroxetine, a selective serotonin-reuptake inhibitor (SSRI) antidepressant agent, is a phenylpiperidine-derivative. Paroxetine differs structurally from other SSRIs (e.g., citalopram, fluoxetine, sertraline) and also differs structurally and pharmacologically from other currently available antidepressants (e.g., tricyclic antidepressants, monoamine oxidase inhibitors).

Paroxetine is commercially available in the US as the hydrochloride and mesylate salts. Paroxetine hydrochloride occurs as an odorless, off-white powder and has a solubility of 5.4 mg/mL in water. The drug has a pK_a of approximately 9.9. Paroxetine mesylate also occurs as an odorless, off-white powder but has a solubility of more than 1 g/mL in water.

The commercially available extended-release tablets of paroxetine hydrochloride contain the drug in a biodegradable polymeric delivery system, consisting of a hydrophilic core surrounded by a biodegradable barrier layer. This delivery system is designed to release the drug gradually over a period of 4–5 hours after ingestion; in addition, an enteric coating delays the release of drug until after the extended-release tablet has left the stomach.

■ **Stability** Paroxetine hydrochloride conventional tablets should be stored at 15–30°C. The oral suspension and extended-release tablets of paroxetine hydrochloride should be stored at or below 25°C. When stored as directed, paroxetine hydrochloride conventional tablets and oral suspension have an expiration date of 3 and 2 years following the date of manufacture, respectively.

Paroxetine mesylate conventional tablets should be stored at a temperature of 25°C but may be exposed to temperatures ranging from 15–30°C; the tablets should be protected from humidity.

Preparations

Excipients in commercially available drug preparations may have clinically important effects in some individuals; consult specific product labeling for details.

Paroxetine Hydrochloride

Oral		
Suspension	10 mg (of paroxetine) per 5 mL	**Paxil®**, GlaxoSmithKline
Tablets, extended-release, film-coated	12.5 mg (of paroxetine)	**Paxil CR®**, GlaxoSmithKline
	25 mg (of paroxetine)	**Paxil CR®**, GlaxoSmithKline
	37.5 mg (of paroxetine)	**Paxil CR®**, GlaxoSmithKline
Tablets, film-coated	10 mg (of paroxetine)*	**Paroxetine Hydrochloride Film-coated Tablets**
		Paxil® (scored), GlaxoSmithKline
	20 mg (of paroxetine)*	**Paroxetine Hydrochloride Film-coated Tablets**
		Paxil® (scored), GlaxoSmithKline
	30 mg (of paroxetine)*	**Paroxetine Hydrochloride Film-coated Tablets**
		Paxil®, GlaxoSmithKline
	40 mg (of paroxetine)*	**Paroxetine Hydrochloride Film-coated Tablets**
		Paxil®, GlaxoSmithKline

*available from one or more manufacturer, distributor, and/or repackager by generic (nonproprietary) name

Paroxetine Mesylate

Oral		
Tablets, film-coated	10 mg (of paroxetine)	**Pexeva®**, JDS Pharmaceuticals
	20 mg (of paroxetine)	**Pexeva®** (scored), JDS Pharmaceuticals
	30 mg (of paroxetine)	**Pexeva®**, JDS Pharmaceuticals
	40 mg (of paroxetine)	**Pexeva®**, JDS Pharmaceuticals

†Use is not currently included in the labeling approved by the US Food and Drug Administration

Sertraline Hydrochloride

■ Sertraline, a selective serotonin-reuptake inhibitor (SSRI), is an antidepressant agent.

Uses

■ **Major Depressive Disorder** Sertraline is used in the treatment of major depressive disorder. A major depressive episode implies a prominent and relatively persistent depressed or dysphoric mood that usually interferes with daily functioning (nearly every day for at least 2 weeks). According to DSM-IV criteria, a major depressive episode includes at least 5 of the following 9 symptoms (with at least one of the symptoms being either depressed mood or loss of interest or pleasure): depressed mood most of the day as indicated by subjective report (e.g., feels sad or empty) or observation made by others; markedly diminished interest or pleasure in all, or almost all, activities most of the day; significant weight loss (when not dieting) or weight gain (e.g., a change of more than 5% of body weight in a month), or decrease or increase in appetite; insomnia or hypersomnia; psychomotor agitation or retardation (observable by others, not merely subjective feelings of restlessness or being slowed down); fatigue or loss of energy; feelings of worthlessness or excessive or inappropriate guilt (not merely self-reproach or guilt about being sick); diminished ability to think or concentrate or indecisiveness (either by subjective account or as observed by others); and recurrent thoughts of death, recurrent suicidal ideation without a specific plan, or a suicide attempt or specific plan for committing suicide.

Treatment of major depressive disorder generally consists of an acute phase (to induce remission), a continuation phase (to preserve remission), and a maintenance phase (to prevent recurrence). Various interventions (e.g., psychotherapy, antidepressant drug therapy, electroconvulsive therapy [ECT]) are used alone or in combination to treat major depressive episodes. Treatment should be individualized and the most appropriate strategy for a particular patient is determined by clinical factors such as severity of depression (e.g., mild, moderate, severe), presence or absence of certain psychiatric features (e.g., suicide risk, catatonia, psychotic or atypical features, alcohol or substance abuse or dependence, panic or other anxiety disorder, cognitive dysfunction, dysthymia, personality disorder, seasonal affective disorder), and concurrent illness (e.g., asthma, cardiac disease, dementia, seizure disorder, glaucoma, hypertension). Demographic and psychosocial factors as well as patient preference also are used to determine the most effective treatment strategy.

While use of psychotherapy alone may be considered as an initial treatment strategy for patients with mild to moderate major depressive disorder (based on patient preference and presence of clinical features such as psychosocial stressors), combined use of antidepressant drug therapy and psychotherapy may be useful for initial treatment of patients with moderate to severe major depressive disorder with psychosocial issues, interpersonal problems, or a comorbid axis II disorder. In addition, combined use of antidepressant drug therapy and psychotherapy may be beneficial in patients who have a history of poor compliance or only partial response to adequate trials of either antidepressant drug therapy or psychotherapy alone.

Antidepressant drug therapy can be used alone for initial treatment of patients with mild major depressive disorder (if preferred by the patient) and usually is indicated alone or in combination with psychotherapy for initial treatment of patients with moderate to severe major depressive disorder (unless ECT is planned). ECT is not generally used for initial treatment of uncomplicated major depression, but is recommended as first-line treatment for severe major depressive disorder when it is coupled with psychotic features, catatonic stupor, severe suicidality, food refusal leading to nutritional compromise, or other situations when a rapid antidepressant response is required. ECT also is recommended for patients who have previously shown a positive response or a preference for this treatment modality and can be considered for patients with moderate or severe depression who have not responded to or cannot receive antidepressant drug therapy. In certain situations involving depressed patients unresponsive to adequate trials of several individual antidepressant agents, adjunctive therapy with another agent (e.g., buspirone, lithium) or concomitant use of a second antidepressant agent (e.g., bupropion) has been used; however, such combination therapy is associated with an increased risk of adverse reactions, may require dosage adjustments, and (if not contraindicated) should be undertaken only after careful consideration of the relative risks and benefits. (See Drug Interactions: Drugs Associated with Serotonin Syndrome and see Drug Interactions: Tricyclic and Other Antidepressants.)

The efficacy of sertraline for the acute treatment of major depression has been established by 2 placebo-controlled studies in adult outpatients who met DSM-III criteria for major depression. In the first study of 8 weeks' duration, sertraline was administered with flexible dosing in a range of 50–200 mg daily; the mean daily dosage for patients completing the study was 145 mg daily. In the second study of 6 weeks' duration, sertraline was administered in fixed doses of 50, 100, and 200 mg daily. Overall, these 2 studies demonstrated that sertraline was superior to placebo in improving scores on the Hamilton Depression Rating Scale and the Clinical Global Impression Severity and Improvement Scales. However, the second study was not readily interpretable regarding whether there was a dose-response relationship for the drug's efficacy.

In a third study, depressed outpatients who had responded by the end of an initial 8-week open treatment phase to sertraline 50–200 mg daily were randomized to continue sertraline in the same dosage range or placebo for 44 weeks in a double-blind manner. The mean daily dosage of sertraline in those who completed this long-term study was 70 mg daily, and the relapse rate in the sertraline-treated patients was substantially lower than in those who received placebo.

An analysis of these 3 controlled studies for possible gender-related effects on treatment outcome did not suggest any difference in efficacy based on the gender of the patient.

While the optimum duration of sertraline therapy has not been established, many experts state that acute depressive episodes require several months or longer of sustained antidepressant therapy. In addition, some clinicians recommend that long-term antidepressant therapy be considered in certain patients at risk for recurrence of depressive episodes (such as those with highly recurrent unipolar depression). The efficacy of sertraline in maintaining an antidepressant response for up to 1 year without increased toxicity has been demonstrated in a controlled setting. The manufacturers state that the usefulness of the drug in patients receiving prolonged therapy should be reevaluated periodically. (See Dosage and Administration: Dosage.)

The manufacturers state that the drug's antidepressant efficacy in hospital settings has not been adequately studied to date.

As with certain other antidepressants, the possibility that sertraline may precipitate hypomanic or manic attacks in patients with bipolar or other major affective disorder should be considered. Sertraline is *not* approved for use in treating bipolar depression in adults.

Considerations in Choosing an Antidepressant A variety of antidepressant drugs are available for the treatment of major depressive disorder, including selective serotonin-reuptake inhibitors (e.g., citalopram, escitalopram, fluoxetine, paroxetine, sertraline), tricyclic antidepressants (e.g., amitriptyline, amoxapine, desipramine, doxepin, imipramine, nortriptyline, protriptyline, trimipramine), monoamine oxidase (MAO) inhibitors (e.g., phenelzine, tranylcypromine), and other antidepressants (e.g., bupropion, duloxetine, maprotiline, nefazodone, trazodone, venlafaxine). Most clinical studies have shown that the antidepressant effect of usual dosages of sertraline in patients with depression is greater than that of placebo and comparable to that of usual dosages of tricyclic antidepressants (e.g., amitriptyline), other selective serotonin-reuptake inhibitors (e.g., fluoxetine), and other antidepressants (e.g., nefazodone). In geriatric patients with major depression, sertraline appears to be as effective as amitriptyline. The onset of action of sertraline appears to be comparable to that of tricyclic antidepressants.

In general, response rates in patients with major depression are similar for currently available antidepressants, and the choice of antidepressant agent for a given patient depends principally on other factors such as potential adverse effects, safety or tolerability of these adverse effects in the individual patient, psychiatric and medical history, patient or family history of response to specific therapies, patient preference, quantity and quality of available clinical data, cost, and relative acute overdose safety. No single antidepressant can be recommended as optimal for all patients because of substantial heterogeneity in individual responses and in the nature, likelihood, and severity of adverse effects. In addition, patients vary in the degree to which certain adverse effects and other inconveniences of drug therapy (e.g., cost, dietary restrictions) affect their preferences.

In the large-scale Sequenced Treatment Alternatives to Relieve Depression (STAR*D) effectiveness trial, patients with major depressive disorder who did not respond to or could not tolerate therapy with one SSRI (citalopram) were randomized to switch to extended-release ("sustained-release") bupropion, sertraline, or extended-release venlafaxine as a second step of treatment (level 2). Remission rates as assessed by the 17-item Hamilton Rating Scale for Depression (HRSD-17) and the Quick Inventory of Depressive Symptomology—Self Report (QIDS-SR-16) were approximately 21 and 26% for extended-release bupropion, 18 and 27% for sertraline, and 25 and 25% for extended-release venlafaxine therapy, respectively; response rates as assessed by the QIDS-SR-16 were 26, 27, and 28% for extended-release bupropion, sertraline, and extended-release venlafaxine therapy, respectively. These results suggest that after unsuccessful initial treatment of depressed patients with an SSRI, approximately 25% of patients will achieve remission after therapy is switched to another antidepressant and that either another SSRI (e.g., sertraline) or an agent from another class (e.g., bupropion, venlafaxine) may be reasonable alternative antidepressants in patients not responding to initial SSRI therapy.

Patient Tolerance Considerations. Because of differences in the adverse effect profile between selective serotonin-reuptake inhibitors and tricyclic antidepressants, particularly less frequent anticholinergic effects, cardiovascular effects, and weight gain with selective serotonin-reuptake inhibitors, these drugs may be preferred in patients in whom such effects are not tolerated or are of potential concern. The decreased incidence of anticholinergic effects associated with sertraline and other selective serotonin-reuptake inhibitors compared with tricyclic antidepressants is a potential advantage, since such effects may result in discontinuance of the drug early during therapy in unusually sensitive patients. In addition, some anticholinergic effects may become troublesome during long-term tricyclic antidepressant therapy (e.g., persistent dry mouth may result in tooth decay). Although selective serotonin-reuptake inhibitors share the same overall tolerability profile, certain patients may tolerate one drug in this class better than another. In an open study, most patients who had discontinued fluoxetine therapy because of adverse effects subsequently tolerated sertraline therapy. Antidepressants other than selective serotonin-reuptake inhibitors may be preferred in patients in whom certain adverse GI effects (e.g., nausea, anorexia), nervous system effects (e.g., anxiety, nervousness, insomnia), and/or weight loss are not tolerated or are of concern, since such effects appear to occur more frequently with this class of drugs.

Pediatric Considerations. The clinical presentation of depression in children and adolescents can differ from that in adults and generally varies with the age and developmental stages of the child. Younger children may exhibit behavioral problems such as social withdrawal, aggressive behavior, apathy, sleep disruption, and weight loss; adolescents may present with somatic complaints, self esteem problems, rebelliousness, poor performance in school, or a pattern of engaging in risky or aggressive behavior.

Only limited data are available to date from controlled clinical studies evaluating various antidepressant agents in children and adolescents, and many of these studies have methodologic limitations (e.g., nonrandomized or uncontrolled, small sample size, short duration, nonspecific inclusion criteria). However, there is some evidence that the response to antidepressants in pediatric patients may differ from that seen in adults, and caution should be used in extrapolating data from adult studies when making treatment decisions for pediatric patients. Results of several studies evaluating tricyclic antidepressants (e.g., amitriptyline, desipramine, imipramine, nortriptyline) in preadolescent and adolescent patients with major depression indicate a lack of overall efficacy in this age group. Based on the lack of efficacy data regarding use of tricyclic antidepressants and MAO inhibitors in pediatric patients and because of the potential for life-threatening adverse effects associated with the use of these drugs, many experts consider selective serotonin-reuptake inhibitors, including sertraline, the drugs of choice when antidepressant therapy is indicated for the treatment of major depressive disorder in children and adolescents. However, the US Food and Drug Administration (FDA) states that, while efficacy of fluoxetine has been established in pediatric patients, efficacy of other newer antidepressants (i.e., sertraline, citalopram, duloxetine, escitalopram, fluvoxamine, mirtazapine, nefazodone, paroxetine, venlafaxine) was not conclusively established in clinical trials in pediatric patients with major depressive disorder. In addition, FDA now warns that antidepressants increase the risk of suicidal thinking and behavior (suicidality) in children and adolescents with major depressive disorder and other psychiatric disorders. (See Cautions: Pediatric Precautions.) FDA currently states that anyone considering using an antidepressant in a child or adolescent for any clinical use must balance the potential risk of therapy with the clinical need. (See Cautions: Precautions and Contraindications.)

Geriatric Considerations. The response to antidepressants in geriatric patients is similar to that reported in younger adults, but depression in geriatric patients often is not recognized and is not treated. In geriatric patients with major depressive disorder, selective serotonin-reuptake inhibitors appear to be as effective as tricyclic antidepressants (e.g., amitriptyline) but generally are associated with fewer overall adverse effects than these other agents. Geriatric patients appear to be especially sensitive to anticholinergic (e.g., dry mouth, constipation, vision disturbance), cardiovascular, orthostatic hypotensive, and sedative effects of tricyclic antidepressants. The low incidence of anticholinergic effects associated with sertraline compared with tricyclic antidepressants also is a potential advantage in geriatric patients, since such effects (e.g., constipation, dry mouth, confusion, memory impairment) may be particularly troublesome in these patients. Some clinicians state that selective serotonin-reuptake inhibitors such as sertraline may be preferred for treating depression in geriatric patients in whom the orthostatic hypotension associated with many antidepressants including tricyclics potentially may result in injuries (such as severe falls). However, despite the fewer cardiovascular and anticholinergic effects associated with selective serotonin-reuptake inhibitors, these drugs did not show any advantage over tricyclic antidepressants with regard to hip fracture in a case-control study. In addition, there was little difference in the rates of falls between nursing home residents receiving selective serotonin-reuptake inhibitors and those receiving tricyclic antidepressants in a retrospective study. Therefore, all geriatric individuals receiving either type of antidepressant should be considered at increased risk of falls and appropriate measures should be taken.

Patients with dementia of the Alzheimer's type (Alzheimer's disease, presenile or senile dementia) often present with depressive symptoms, such as depressed mood, appetite loss, insomnia, fatigue, irritability, and agitation. Most experts recommend that patients with dementia of the Alzheimer's type and depressive symptoms be considered as candidates for pharmacotherapy even if they fail to meet the criteria for a major depressive syndrome. The goals of such therapy are to improve mood, functional status (e.g., cognition), and quality of life. Although patients may present with depressed mood alone, the possibility of more extensive depressive symptomatology should be considered. Therefore, patients should be monitored carefully for indices of major depression, suicidal ideation, and neurovegetative signs since safety measures (e.g., hospitalization for suicidality) and more vigorous and aggressive therapy (e.g., relatively high dosages, multiple drug trials) may be needed in some patients.

If pharmacotherapy is initiated for depressive symptoms in Alzheimer's patients, most experts recommend selective serotonin-reuptake inhibitors such as sertraline, citalopram, escitalopram, fluoxetine, or paroxetine as first-line therapy because of their favorable adverse effect profile in this population compared with other currently available antidepressants (e.g., tricyclic antidepressants, MAO inhibitors). Although evidence of efficacy from controlled studies currently is limited, the available evidence and experience with the use of antidepressants in patients with dementia of the Alzheimer's type and associated depressive manifestations indicate that depressive symptoms (including depressive mood alone and with neurovegetative changes) in such patients are responsive to antidepressant therapy. In some patients, cognitive deficits may partially or fully resolve during antidepressant therapy, but the extent of response will be limited to the degree of cognitive impairment that is directly related to depression.

Cardiovascular Considerations. The relatively low incidence of adverse cardiovascular effects, including orthostatic hypotension and conduction disturbances, associated with sertraline and other selective serotonin-reuptake inhibitors may be advantageous in patients in whom the cardiovascular effects associated with tricyclic antidepressants may be hazardous. Patients with a recent history of myocardial infarction or unstable cardiovascular disease were excluded from premarketing clinical studies with sertraline. However, the cardiovascular safety of sertraline (50–200 mg daily for 24 weeks; mean dosage of 89 mg daily) was evaluated in a postmarketing, double-blind, placebo-controlled study in adult outpatients with major depressive disorder and a recent history of myocardial infarction or unstable angina pectoris requiring hospitalization but who were otherwise free of life-threatening medical conditions. When therapy was initiated during the acute phase of recovery (within 30 days after a myocardial infarction or hospitalization for unstable angina), sertraline therapy did not differ from placebo on the following cardiovascular end points at week 16: left ventricular ejection fraction and total cardiovascular events (angina, chest pain, edema, palpitations, syncope, postural dizziness, chronic heart failure, myocardial infarction, tachycardia, bradycardia, blood pressure changes). Although not statistically significant, approximately 20% fewer major cardiovascular events involving death or requiring hospitalization (e.g., for myocardial infarction, chronic heart failure, stroke, angina) occurred in the sertraline-treated patients compared with those receiving placebo. (See Cautions: Cardiovascular Effects and see also Cautions: Precautions and Contraindications.)

Sedative Considerations. Because sertraline and other selective serotonin-reuptake inhibitors are generally less sedating than some other antidepressants (e.g., tricyclics), some clinicians state that these drugs may be preferable in patients who do not require the sedative effects associated with many antidepressant agents; however, an antidepressant with more prominent sedative effects may be preferable in certain patients (e.g., those with insomnia).

Suicidal Risk Considerations. Suicide is a known risk of depression and certain other psychiatric disorders, and these disorders themselves are the strongest predictors of suicide. However, there has been a long-standing concern that antidepressants may have a role in inducing worsening of depression and the emergence of suicidal thinking and behavior (suicidality) in certain patients during the early phases of treatment. FDA states that antidepressants increased the risk of suicidality in short-term studies in children, adolescents, and young adults (18–24 years of age) with major depressive disorder and other psychiatric disorders. (See Cautions: Pediatric Precautions.) An increased suicidality risk was not demonstrated with antidepressants compared with placebo in adults older than 24 years of age and a reduced risk was observed in adults 65 years of age or older. It currently is unknown whether the suicidality risk extends to longer-term antidepressant use (i.e., beyond several months); however, there is substantial evidence from placebo-controlled maintenance trials in adults with major depressive disorder that antidepressants can delay the recurrence of depression. Because the risk of suicidality in depressed patients may persist until substantial remission of depression occurs, appropriate monitoring and close observation of all patients who are receiving antidepressant therapy is recommended. (See Cautions: Precautions and Contraindications.)

Other Considerations. Sertraline has been effective in patients with moderate to severe depression.

In the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) level 2 trial, patients with major depressive disorder who did not respond to or could not tolerate therapy with citalopram (another SSRI) were randomized to receive either extended-release ("sustained-release") bupropion or buspirone therapy in addition to citalopram. Although both extended-release bupropion and buspirone were found to produce similar remission rates, extended-release bupropion produced a greater reduction in the number and severity of symptoms and a lower rate of drug discontinuance than buspirone in this large-scale, effectiveness trial. These results suggest that augmentation of SSRI therapy with extended-release bupropion may be useful in some patients with refractory depression.

Sertraline has been effective in patients with depression and concurrent human immunodeficiency virus (HIV) infection and depression with anxiety.

In a double-blind, placebo-controlled study, both sertraline or imipramine were found to be more effective than placebo in reducing the depressive symptoms and improving psychosocial functioning in patients with dysthymia† without concurrent major depression; moreover, fewer patients treated with sertraline than those treated with imipramine or placebo discontinued therapy because of adverse effects. The results of several other studies, both controlled and uncontrolled, also suggest that sertraline may be effective in patients with dysthymia. Because dysthymia is a chronic condition and requires prolonged antidepressant therapy, the good tolerability demonstrated in clinical studies to date may be advantageous. Sertraline also has been used in the treatment of anger attacks associated with atypical depression and dysthymia† in a limited number of patients.

■ **Obsessive-Compulsive Disorder** Sertraline is used in the treatment of obsessive-compulsive disorder when the obsessions or compulsions cause marked distress, are time consuming (take longer than 1 hour daily), or interfere substantially with the patient's normal routine, occupational or academic functioning, or usual social activities or relationships. Obsessions are recurrent and persistent ideas, thoughts, impulses, or images that, at some time during the disturbance, are experienced as intrusive and inappropriate (i.e., "ego dystonic") and that cause marked anxiety or distress but that are not simply excessive worries about real-life problems. Compulsions are repetitive, intentional behaviors (e.g., hand washing, ordering, checking) or mental acts (e.g., praying, counting, repeating words silently) performed in response to an obsession or according to rules that must be applied rigidly (e.g., in a stereotyped fashion). Although the behaviors or acts are aimed at preventing or reducing distress or preventing some dreaded event or situation, they either are not connected in a realistic manner with what they are designed to neutralize or prevent or are clearly excessive. At some time during the course of the disturbance, the patient, if an adult, recognizes that the obsessions or compulsions are excessive or unreasonable; children may not make such a recognition.

The efficacy of sertraline for the management of obsessive-compulsive disorder has been established in several multicenter, placebo-controlled studies, including one study of 8 weeks' duration and 2 studies of 12 weeks' duration in adults and one study of 12 weeks' duration in children and adolescents 6–17 years of age. Patients in these studies had moderate to severe obsessive-compulsive disorder with mean baseline total scores on the Yale-Brown Obsessive-Compulsive Scale (YBOCS) of 23–25 in adults and 22 in children and adolescents (measured in the Children's Yale-Brown Obsessive-Compulsive Scale [CY-BOCS]). In the 8-week study with flexible dosing, adult patients received sertraline in dosages ranging from 50–200 mg daily; the mean dosage for those completing the study was 186 mg daily. Total scores on the YBOCS decreased by an average of approximately 4 points in sertraline-treated patients and 2 points in patients receiving placebo; this difference was statistically significant.

In a fixed-dose study of 12 weeks' duration involving sertraline dosages of 50, 100, and 200 mg daily, adult patients receiving 50 and 200 mg of the drug daily experienced substantially greater reductions in the YBOCS total score than those receiving placebo (approximately 6 to approximately 3 points, respectively). In a 12-week study with flexible dosing in the range of 50–200 mg daily, the mean sertraline dosage in adult patients completing the study was 185 mg daily. YBOCS total scores in the sertraline-treated patients were reduced by a mean of approximately 7 points, which was better than the mean reduction of approximately 4 points reported in the placebo-treated patients.

In a 12-week study with flexible dosing, sertraline therapy was initiated at dosages of 25 or 50 mg daily in children 6–12 years of age or adolescents 13–17 years of age, respectively. Subsequent dosage was titrated according to individual tolerance over the first 4 weeks to a maximum dosage of 200 mg daily; the mean dosage for those completing the study was 178 mg daily. The drug produced substantially greater reductions in scores in the Children's Yale-Brown Obsessive-Compulsive Scale (CY-BOCS), the National Institute of Mental Health Global Obsessive-Compulsive Scale (NIMH-OC), and the Clinical Global Impressions (CGI) Improvement Scale; total scores on the CY-BOCS decreased by an average of approximately 7 units in sertraline-treated patients and 3 units in patients receiving placebo. An analysis of these controlled studies for possible age- and gender-related effects on treatment outcome did not suggest any difference in efficacy based on either the age or gender of the patient.

In addition, in an uncontrolled 6-week study with flexible dosing (50–200 mg daily) in children or adolescents 6–17 years of age with obsessive-compulsive disorder or major depression†, those with a diagnosis of obsessive-compulsive disorder had mean baseline total scores on the CY-BOCS, NIMH-OC, and CGI of about 24.9, 10.2, and 5.2, respectively. Sertraline produced substantial reductions in all 3 of the scales; total scores on CY-BOCS, NIMH-OC, and CGI decreased to 12.9, 6.7, and 3.4, respectively. In another uncontrolled, 6-week study employing a sertraline dosage that was escalated from 25 to 200 mg daily over 3 weeks, the drug combined with behavioral therapy was effective in a limited number of adolescents 13–17 years of age with obsessive-compulsive disorder refractory to other therapies; total scores on the CY-BOCS at the end of the study decreased by 11 points (from 25.4 to 14.4).

Results from comparative studies to date suggest sertraline and other selective serotonin-reuptake inhibitors (e.g., fluoxetine, fluvoxamine, paroxetine) are as effective or somewhat less effective than clomipramine and more effective than tricyclic antidepressants (e.g., amitriptyline, desipramine, imipramine, nortriptyline) in the management of obsessive-compulsive disorder. In a pooled analysis of separate short-term (10–13 weeks) studies comparing clomipramine, fluoxetine, fluvoxamine, or sertraline with placebo, clomipramine was calculated as being more effective (as determined by measures on the YBOC scale) than selective serotonin-reuptake inhibitors, although all drugs were superior to placebo. Like clomipramine, selective serotonin-reuptake inhibitors reduce but do not completely eliminate obsessions and compulsions.

Many clinicians consider a selective serotonin-reuptake inhibitor (e.g., sertraline, paroxetine, fluoxetine, fluvoxamine) or clomipramine to be the drugs of choice for the pharmacologic treatment of obsessive-compulsive disorder. The decision whether to initiate therapy with a selective serotonin-reuptake inhibitor or clomipramine often is made based on the adverse effect profile of these drugs. For example, some clinicians prefer clomipramine in patients who may not tolerate the adverse effect profile of selective serotonin-reuptake inhibitors (nausea, headache, overstimulation, sleep disturbances) while selective serotonin-reuptake inhibitors may be useful alternatives in patients unable to tolerate the adverse effects (anticholinergic effects, cardiovascular effects, sedation) associated with clomipramine therapy. Consideration of individual patient characteristics (age, concurrent medical conditions), pharmacokinetics of the drug, potential drug interactions, and cost of therapy may also influence clinicians when selecting between selective serotonin-reuptake inhibitors and clomipramine as first-line therapy in patients with obsessive-compulsive disorder. Although not clearly established, it has been suggested that the mechanism of action of sertraline and other potent serotonin-reuptake inhibitors (e.g., clomipramine, fluoxetine, fluvoxamine, paroxetine) used in the management of obsessive-compulsive disorder may be related to their serotonergic activity.

■ **Panic Disorder** Sertraline is used in the treatment of panic disorder with or without agoraphobia. Panic disorder is characterized by the occurrence of unexpected panic attacks and associated concern about having additional attacks, worry about the implications or consequences of the attacks, and/or a clinically important change in behavior related to the attacks.

According to DSM-IV, panic disorder is characterized by recurrent unexpected panic attacks, which consist of a discrete period of intense fear or discomfort in which 4 (or more) of the following symptoms develop abruptly and reach a peak within 10 minutes: palpitations, pounding heart, or accelerated heart rate; sweating; trembling or shaking; sensations of shortness of breath or smothering; feeling of choking; chest pain or discomfort; nausea or abdominal distress; feeling dizzy, unsteady, lightheaded, or faint; derealization (feelings of unreality) or depersonalization (being detached from oneself); fear of losing control; fear of dying; paresthesias (numbness or tingling sensations); and chills or hot flushes.

The efficacy of sertraline for the management of panic disorder has been established by 3 double-blind, placebo-controlled studies in adult outpatients who met DSM-III-R criteria for panic disorder with or without agoraphobia. The first 2 studies were of 10 weeks' duration and used a flexible dosing schedule. Sertraline therapy was initiated in a dosage of 25 mg daily for the first week and then dosage was escalated to 50–200 mg daily depending on clinical response and tolerability. The mean sertraline dosages for completers were 131 and 144 mg daily for the first 2 studies. Overall, these 2 studies demonstrated that sertraline was superior to placebo in decreasing the frequency of panic attacks and in improving scores on the Clinical Global Impression Severity of Illness and Global Improvement Scales. The difference between sertraline and placebo in reduction in the number of full panic attacks per week compared with baseline was approximately 2 in both studies.

The third study was a fixed-dose study of 12 weeks' duration. Sertraline was given in dosages of 50, 100, and 200 mg daily. The patients receiving sertraline demonstrated a substantially greater reduction in panic attack frequency than patients receiving placebo. However, the results of this study were not readily interpretable regarding a dose-response relationship for efficacy in this condition.

An analysis of these 3 controlled studies for possible age-, race-, or gender-related effects on treatment outcome did not suggest any difference in efficacy based on these patient characteristics.

Panic disorder can be treated with cognitive and behavioral psychotherapy and/or pharmacologic therapy. There are several classes of drugs that appear to be effective in the pharmacologic management of panic disorder, including tricyclic antidepressants, MAO inhibitors (e.g., phenelzine), selective serotonin-reuptake inhibitors (e.g., citalopram, fluoxetine, paroxetine, sertraline), and benzodiazepines (e.g., alprazolam, clonazepam). When choosing among the available drugs, clinicians should consider their acceptance and tolerability by patients; their ability to reduce or eliminate panic attacks, reduce clinically important anxiety and disability secondary to phobic avoidance, and ameliorate other common comorbid conditions (such as depression); and their ability to prevent relapse during long-term therapy. Because of their better tolerability when compared with other agents (such as the tricyclic antidepressants and benzodiazepines), the lack of physical dependence problems commonly associated with benzodiazepines, and efficacy in panic disorder with comorbid conditions (e.g., depression, other anxiety disorders such as obsessive-compulsive disorder, alcoholism), many clinicians prefer selective serotonin-reuptake inhibitors as first-line therapy in the management of panic disorder. If selective serotonin-reuptake inhibitor therapy is ineffective or not tolerated, use of a tricyclic antidepressant or a benzodiazepine is recommended.

Sertraline has improved chronic idiopathic urticaria† associated with panic disorder in at least one patient, but further study is needed to determine whether serotonin is involved in the pathogenesis of urticaria and whether selective serotonin-reuptake inhibitors are effective in this condition.

■ **Posttraumatic Stress Disorder** Sertraline is used in the treatment of posttraumatic stress disorder (PTSD). PTSD is an anxiety disorder that involves the development of certain characteristic symptoms following personal exposure to an extreme traumatic stressor. According to DSM-IV, PTSD requires exposure to a traumatic event(s) that involved actual or threatened death or serious injury, or threat to the physical integrity of self or others, and the response to the event must involve intense fear, helplessness, or horror (in children the response may be expressed by disorganized or agitated behavior). PTSD is characterized by persistent symptoms of *reexperiencing* the trauma (e.g., intrusive distressing recollections of the event; recurrent distressing dreams of the event; acting or feeling as if the event were recurring including illusions, hallucinations, or flashbacks; intense distress at exposure to internal or external cues that symbolize or resemble an aspect of the event; physiologic reactivity on exposure to internal or external cues that symbolize or resemble an aspect of the event), persistent *avoidance* of stimuli associated with the trauma and numbing of general responsiveness (e.g., efforts to avoid thoughts, feelings, or conversations related to the event; efforts to avoid activities, places, or people that arouse recollections of the event; inability to recall an important aspect of the event; markedly diminished interest or participation in significant activities; feeling of detachment or estrangement from others; restricted emotions and/or range of affect not present before the event; sense of a foreshortened future), and persistent symptoms of *increased arousal* (e.g., difficulty sleeping; irritability/outbursts of anger; difficulty concentrating; hypervigilance; exaggerated startle response). According to DSM-IV, a PTSD diagnosis requires the presence of 1 or more symptoms of *reexperiencing*, 3 or more symptoms of *avoidance*, and 2 or more symptoms of *increased arousal*, all of which must be present for at least one month and cause clinically important distress or impairment in social, occupational, or other important areas of functioning. PTSD, like other anxiety disorders, rarely occurs alone, and patients with PTSD often present with comorbid disorders (e.g., major depressive disorder, substance abuse disorders, panic disorder, generalized anxiety disorders, obsessive-compulsive disorder, social phobia); it is unknown whether these comorbid disorders precede or follow the onset of PTSD.

Psychotherapy alone or in combination with pharmacotherapy generally is considered the treatment of choice for PTSD. Pharmacologic therapy may be indicated in addition to psychotherapy for initial treatment of PTSD in patients who have comorbid disorders (e.g., major depressive disorder, bipolar disorder, other anxiety disorders) and also may be indicated in those who do not respond to initial treatment with psychotherapy alone. If pharmacotherapy is indicated in patients with PTSD, selective serotonin-reuptake inhibitors (e.g., sertraline, fluoxetine, paroxetine) usually are considered the drugs of choice (except in patients with bipolar disorder who require treatment with mood stabilizing agents).

The efficacy of sertraline for the management of PTSD has been established in 2 placebo-controlled studies of 12 weeks' duration in adult outpatients (76% women) who met DSM-III-R criteria for chronic PTSD (duration of symptoms 3 months or longer). The mean duration of PTSD for these patients was approximately 12 years and 44% of patients had secondary depressive disorders. Sertraline therapy was initiated at a dosage of 25 mg daily for the first week and then dosage was escalated (using a flexible dosage schedule) to 50–200 mg daily based on clinical response and tolerability. The mean sertraline dosage for patients who completed studies 1 and 2 was 146 mg and 151 mg daily, respectively. Overall, these 2 studies showed that sertraline was superior to placebo in improving scores on the Clinician-Administered PTSD Scale Part 2

total severity scale (a measure of the intensity and frequency of all 3 PTSD diagnostic symptom clusters [reexperiencing/intrusion, avoidance/numbing, and hyperarousal]), Impact of Event Scale (a patient rated measurement of the intrusion and avoidance symptoms), and the Clinical Global Impressions Severity of Illness and Global Improvement Scales.

However, in 2 additional placebo-controlled studies of similar design and duration, the difference in response to treatment on key assessment scales between patients receiving sertraline and those receiving placebo was not statistically significant. In one study of mostly female patients who met the DSM-III-R criteria for PTSD related to sexual/physical trauma, those receiving placebo experienced substantially greater improvement on the Impact of Event Scale than those receiving sertraline therapy. Although this study enrolled a higher proportion of patients with comorbid anxiety disorders and a higher proportion of patients receiving placebo with a successful response to previous psychotropic therapies than the studies demonstrating efficacy of the drug, it is unknown whether these factors alone account for the high placebo response in the study.

Efficacy of sertraline for the management of PTSD related to war or combat was evaluated in a study involving primarily white men in a VA medical center outpatient setting (mean duration of PTSD approximately 18 years). At the end of this study, patients receiving sertraline did not differ from those receiving placebo on any of the key efficacy assessment scales (e.g., Clinician-Administered PTSD scale, Davidson Self-Rating Trauma scale, Impact of Event Scale). In addition, the mean change from baseline for both treatment groups in this study was of a lesser magnitude than those of patients receiving placebo in the other reported studies. The lack of response to sertraline treatment in these combat veterans is consistent with controlled studies evaluating other selective serotonin-reuptake inhibitors (e.g., fluoxetine, brofaromine [not commercially available in the US]) in Vietnam veterans with PTSD. Some experts suggest that patients with combat- or war-related PTSD may be less responsive to treatment than patients with PTSD related to other traumatic events (e.g., sexual assault, accidents, natural disasters) because of some factor inherent in combat- or war-related trauma. However, other experts suggest that the poor treatment response in studies evaluating use in veterans may be the result of sampling error since veterans receiving treatment at VA hospitals may constitute a self-selected group of patients with chronic PTSD who have multiple impairments (comorbid disorders, substance abuse) that make them less responsive to treatment.

Since PTSD is a more common disorder in women than men, the majority (76%) of patients in reported studies were women. A retrospective analysis of pooled data has shown a substantial difference between sertraline and placebo on key efficacy assessment scales (e.g., Clinician-Administered PTSD scale, Impact of Event Scale, Clinical Global Impressions Severity of Illness Scale) in women (regardless of a baseline diagnosis of comorbid depression), but essentially no effect in the limited number of men studied. The clinical importance of this apparent gender effect is unknown; however, only limited data are available to date regarding use of selective serotonin-reuptake inhibitors in men who have PTSD related to noncombat-related trauma (e.g., sexual assault, accidents, natural disasters). There are insufficient data to date to determine whether race or age has any effect on the efficacy of sertraline in the management of PTSD.

■ **Premenstrual Dysphoric Disorder** Sertraline is used in the treatment of premenstrual dysphoric disorder (previously late luteal phase dysphoric disorder). DSM-IV criteria for premenstrual dysphoric disorder (PMDD) requires that in most menstrual cycles of the previous year at least 5 of the following 11 symptoms must have been present for most of the time during the last week of the luteal phase (with at least one of the symptoms being one of the first 4 listed): marked depressed mood, feelings of hopelessness, or self-deprecating thoughts; marked anxiety, tension, feelings of being "keyed up" or on "edge"; marked affective lability (e.g., feeling suddenly sad or tearful or increased sensitivity to rejection); persistent and marked anger or irritability or increased interpersonal conflicts; decreased interest in usual activities (e.g., work, school, friends, hobbies); a subjective sense of difficulty in concentrating; lethargy, easy fatigability, or marked lack of energy; marked change in appetite, overeating, or specific food cravings; hypersomnia or insomnia; a subjective sense of being overwhelmed or out of control; and other physical symptoms, such as breast tenderness or swelling, headaches, joint or muscle pain, or a sensation of "bloating" or weight gain. Such symptoms should begin to remit within a few days of the onset of menses (follicular phase) and are always absent in the week following menses. The presence of this cyclical pattern of symptoms must be confirmed by at least 2 consecutive months of prospective daily symptom ratings. PMDD should be distinguished from the more common premenstrual syndrome (PMS) by prospective daily ratings and the strict criteria listed above.

The efficacy of sertraline for the management of PMDD has been established in 2 randomized, placebo-controlled studies over 3 menstrual cycles in adult women who met DSM-III-R or DSM-IV criteria for PMDD. In these studies, flexible dosages (range: 50–150 mg daily) of sertraline administered continuously throughout the menstrual cycle or during the luteal phase only (i.e., for 2 weeks prior to the onset of menses) were shown to be substantially more effective than placebo in improving scores from baseline on the Daily Record of Severity of Problems (DRSP), the Clinical Global Impression of Severity of Illness (CGI-S) and Improvement (CGI-I), and/or the Hamilton Depression Rating Scales (HAMD-17). The mean dosage of sertraline in patients completing these trials was 102 or 74 mg daily for those receiving continuous or luteal-phase dosing of the drug, respectively.

When given in a flexible dosage of 50–150 mg daily in a separate double-blind, placebo-controlled study, sertraline was substantially better than placebo in improving symptoms (depressive symptoms, physical symptoms, anger/irritability) and functional impairment associated with this disorder. The beneficial effect of the drug was apparent by the first treatment cycle. In an open study comparing sertraline and desipramine in the treatment of premenstrual dysphoric disorder, sertraline and possibly desipramine were found to be effective; however, sertraline was better tolerated than desipramine. Additional controlled studies are needed to determine whether the efficacy of the drug is sustained during longer-term, maintenance therapy in women with this condition. In addition, efficacy of sertraline used in conjunction with oral contraceptives for the treatment of PMDD has not been determined since patients receiving oral contraceptives were excluded from most clinical studies to date.

■ **Social Phobia** Sertraline is used in the treatment of social phobia (social anxiety disorder). According to DSM-IV, social phobia is characterized by a marked and persistent fear of one or more social or performance situations in which the person is exposed to unfamiliar people or to possible scrutiny by others. Exposure to the feared situation almost invariably provokes anxiety, which may approach the intensity of a panic attack. The feared situations are avoided or endured with intense anxiety or distress. The avoidance, fear, or anxious anticipation of encountering the social or performance situation interferes significantly with the person's daily routine, occupational or academic functioning, or social activities or relationships, or there is marked distress about having the phobias. Lesser degrees of performance anxiety or shyness generally do not require psychotherapy or pharmacologic treatment.

The efficacy of sertraline in the treatment of social phobia has been established in 2 multicenter, placebo-controlled studies in adult outpatients who met DSM-IV criteria for social phobia. In one study of 12 weeks' duration, 47% of patients receiving flexible dosages of sertraline (50–200 mg daily; mean dosage of 144 mg daily) were characterized as responders (defined as a score of 1 or 2 on the Clinical Global Impressions [CGI] Global Improvement Scale) compared with 26% of those receiving placebo (intent-to-treat analysis). Sertraline also was found to be superior to placebo on the Liebowitz Social Anxiety Scale (LSAS), a 24-item clinician administered measure of fear, anxiety, and avoidance of social and performance situation, and on most secondary efficacy measures, including the Duke Brief Social Phobia Scale (BSPS) total score, fear and avoidance subscales of BSPS, and fear/anxiety and avoidance subscales of LSAS. These results were similar to those seen in a flexible-dose study of 20 weeks' duration, in which a score of 1 ("very much improved") or 2 ("much improved") on the CGI Global Improvement Scale was attained by the end of the treatment period by 53 or 29% of patients receiving sertraline (50–200 mg daily; mean dosage of 147 mg daily) or placebo, respectively (intent-to-treat analysis). Sixty-five patients in this study subsequently were enrolled in a separate controlled study, including 50 patients who had responded to sertraline in the initial study and then were randomized to receive either continued treatment with sertraline or placebo in the subsequent study and 15 patients who had responded to placebo in the initial study and continued to receive placebo in the subsequent study. Based on an intent-to-treat analysis, 4% of patients who continued treatment with sertraline, 36% of patients randomized to receive placebo, and 27% of those who continued treatment with placebo relapsed (defined as an increase of 2 or more points from baseline in the CGI Severity of Illness score or discontinuance of the study drug because of lack of efficacy) at the end of the 24-week treatment period. Similar to results of pivotal, short-term clinical studies, sertraline also was shown to be substantially more effective than placebo on the CGI Severity of Illness Scale, Marks Fear Questionnaire (MFQ) Social Phobia subscale, and BSPS total score.

Subgroup analysis of short-term, controlled studies in adult outpatients with social anxiety disorder did not reveal any evidence of gender-related differences in treatment outcome. There was insufficient information to determine the effect of race or age on treatment outcome. Safety and efficacy of sertraline for the treatment of social phobia in children or adolescents have not been established to date.

■ **Premature Ejaculation** Like some other serotonin-reuptake inhibitors, sertraline has been used with some success in the treatment of premature ejaculation†. In a placebo-controlled study, sertraline produced substantial improvements compared with placebo in time to ejaculation, number of successful attempts at intercourse, and incidence of ejaculation during foreplay, as well as overall clinical judgment of improvement. In addition, the drug was well tolerated in most patients. A trial with drug therapy may be particularly useful in patients who fail or refuse behavioral or psychotherapeutic treatment or when partners are unwilling to cooperate with such therapy.

■ **Other Uses** Sertraline has been used in a limited number of patients with various types of headache† with variable results; however, its use in this condition may be limited by frequent adverse effects.

Dosage and Administration

■ **Administration** Sertraline is administered orally. The drug usually is administered once daily in the morning or evening. The extent of GI absorption of sertraline reportedly may be increased slightly, the peak concentration increased by about 25%, and the time to peak concentration after a dose decreased from about 8 to 5.5 hours when the drug is administered with food, but such changes do not appear to be clinically important.

When sertraline hydrochloride concentrate for oral solution (Zoloft®) is used, doses of the drug should be measured carefully using the calibrated dropper provided by the manufacturer. The appropriate dose of the oral solution should be diluted in 120 mL of water, ginger ale, lemon/lime soda, lemonade, or orange juice before administration. The diluted solution containing sertraline hydrochloride should be mixed and administered immediately and should not be allowed to stand before administration. A slight haze may occasionally appear in the diluted oral solution, but the manufacturer states that this is normal.

■ **Dosage** Dosage of sertraline hydrochloride is expressed in terms of sertraline.

Abrupt discontinuance of sertraline therapy should be avoided because of the potential for withdrawal reactions. (See Chronic Toxicity.) In addition, patients may experience a worsening of psychiatric status when the drug is discontinued abruptly. Therefore, it is recommended that dosage be tapered gradually (e.g., over a period of several weeks) and the patient monitored carefully when sertraline therapy is discontinued.

Clinical experience regarding the optimal timing of switching from other antidepressants to sertraline therapy is limited. Therefore, the manufacturers recommend that care and prudent medical judgment be exercised when switching from other antidepressants to sertraline, particularly from long-acting agents (such as fluoxetine). Because some adverse reactions resembling serotonin syndrome have developed when fluoxetine therapy was discontinued abruptly and sertraline therapy was initiated immediately afterward, a washout period appears to be advisable when transferring a patient from fluoxetine to sertraline therapy. However, the appropriate duration of the washout period when switching from one selective serotonin-reuptake blocker to another has not been clearly established. Pending further experience in patients being transferred from therapy with another antidepressant to sertraline, it generally is recommended that the previous antidepressant be discontinued according to the recommended guidelines for the specific antidepressant prior to initiation of sertraline therapy. (See Drug Interactions: Drugs Associated with Serotonin Syndrome and see Drug Interactions: Tricyclic and Other Antidepressants.)

Patients receiving sertraline should be monitored for possible worsening of depression, suicidality, or unusual changes in behavior, especially at the beginning of therapy or during periods of dosage adjustment. (See Cautions: Precautions and Contraindications.)

The manufacturers recommend that an interval of at least 2 weeks elapse when switching a patient from a monoamine oxidase (MAO) inhibitor to sertraline or when switching from sertraline to an MAO inhibitor. (See Drug Interactions: Drugs Associated with Serotonin Syndrome.)

Major Depressive Disorder For the management of major depressive disorder in adults, the recommended initial dosage of sertraline is 50–100 mg once daily. If no clinical improvement is apparent, dosage may be increased at intervals of not less than 1 week up to a maximum of 200 mg daily. Clinical experience with the drug to date suggests that many patients will respond to 50–100 mg of the drug once daily. While a relationship between dose and antidepressant effect has not been established, efficacy of the drug was demonstrated in clinical trials employing 50–200 mg daily.

While the optimum duration of sertraline therapy has not been established, many experts state that acute depressive episodes require several months or longer of sustained antidepressant therapy. In addition, some clinicians recommend that long-term antidepressant therapy be considered in certain patients at risk for recurrence of depressive episodes (such as those with highly recurrent unipolar depression). Whether the dose of sertraline required to induce remission is identical to the dose needed to maintain and/or sustain euthymia is unknown. Systematic evaluation of sertraline has shown that its antidepressant efficacy is maintained for periods of up to 1 year in patients receiving 50–200 mg daily (mean dose of 70 mg daily). The usefulness of the drug in patients receiving prolonged therapy should be reevaluated periodically.

Obsessive-Compulsive Disorder For the management of obsessive-compulsive disorder in adults and adolescents 13–17 years of age, the recommended initial dosage of sertraline is 50 mg once daily. In children 6–12 years of age, the recommended initial dosage of sertraline is 25 mg once daily. If no clinical improvement is apparent, dosage may be increased at intervals of not less than 1 week up to a maximum of 200 mg daily. However, it should be considered that children usually have a lower body weight than adults and particular care should be taken to avoid excessive dosage in children. While a relationship between dose and efficacy in obsessive-compulsive disorder has not been established, efficacy of the drug was demonstrated in clinical trials employing 50–200 mg daily in adults and 25–200 mg daily in children and adolescents.

While the optimum duration of sertraline therapy required to prevent recurrence of obsessive-compulsive symptoms has not been established to date, the manufacturer and many experts state that this disorder is chronic and requires several months or longer of sustained therapy. Whether the dose of sertraline required to induce remission is identical to the dose needed to maintain and/or sustain remission in patients with this disorder is unknown. Systematic evaluation of sertraline has shown that its efficacy in the management of obsessive-compulsive disorder is maintained for periods of up to 28 weeks in patients receiving 50–200 mg daily. The usefulness of the drug in patients receiving prolonged therapy should be reevaluated periodically.

Panic Disorder For the management of panic disorder in adults, the recommended initial dosage of sertraline is 25 mg once daily. After 1 week, the dosage should be increased to 50 mg once daily. If no clinical improvement is apparent, dosage may then be increased at intervals of not less than 1 week up to a maximum of 200 mg daily.

While the optimum duration of sertraline therapy required to prevent recurrence of panic disorder has not been established to date, the manufacturer and many experts state that this disorder is chronic and requires several months or longer of sustained therapy. Whether the dose of sertraline required to induce remission is identical to the dose needed to maintain and/or sustain remission in patients with this disorder is unknown. Systematic evaluation of sertraline has shown that its efficacy in the management of panic disorder is maintained for periods of up to 28 weeks in patients receiving 50–200 mg daily. The usefulness of the drug in patients receiving prolonged therapy should be reevaluated periodically.

Posttraumatic Stress Disorder For the management of posttraumatic stress disorder (PTSD) in adults, the recommended initial dosage of sertraline is 25 mg once daily. After 1 week, dosage should be increased to 50 mg once daily. If no clinical improvement is apparent, dosage may then be increased at intervals of not less than 1 week up to a maximum of 200 mg daily.

While the optimum duration of sertraline therapy required to prevent recurrence of PTSD has not been established to date, this disorder is chronic and it is reasonable to continue therapy in responding patients. Whether the dose of sertraline required to induce remission is identical to the dose needed to maintain and/or sustain remission in patients with this disorder is unknown. Systematic evaluation of sertraline has shown that its efficacy in the management of posttraumatic stress disorder is maintained for periods of up to 28 weeks in patients receiving 50–200 mg daily. The usefulness of the drug in patients receiving prolonged therapy should be reevaluated periodically.

Premenstrual Dysphoric Disorder For the treatment of premenstrual dysphoric disorder (previously late luteal-phase dysphoric disorder), the recommended initial dosage of sertraline is 50 mg daily given continuously throughout the menstrual cycle or given during the luteal-phase only (i.e., starting 2 weeks prior to the anticipated onset of menstruation and continuing through the first full day of menses). If no clinical improvement is apparent, dosage may be increased in 50-mg increments at the onset of each new menstrual cycle up to a maximum of 150 mg daily when administered continuously or 100 mg daily when administered during the luteal-phase only. If a dosage of 100 mg daily has been established with luteal phase dosing, dosages should be increased gradually over the first 3 days of each luteal phase dosing period. While a relationship between dose and effect in premenstrual dysphoric disorder (PMDD) has not been established, efficacy of the drug was demonstrated in clinical trials employing 50–150 mg daily.

The optimum duration of sertraline therapy required to treat PMDD has not been established to date. The manufacturer states that the efficacy of sertraline therapy beyond 3 menstrual cycles has not been demonstrated in controlled studies. However, because women commonly report that symptoms of PMDD worsen with age until relieved by the onset of menopause, the manufacturer recommends that long-term sertraline therapy be considered in responding women. Dosage adjustments, which may include transfers between dosing regimens (e.g., continuous versus luteal phase dosing), may be needed to maintain the patient on the lowest effective dosage, and patients should be periodically reassessed to determine the need for continued treatment.

Social Phobia For the management of social phobia in adults, the recommended initial dosage of sertraline is 25 mg once daily. After 1 week, the dosage should be increased to 50 mg once daily. If no clinical improvement is apparent, dosage may then be increased at intervals of not less than 1 week up to a maximum of 200 mg daily.

While the optimum duration of sertraline therapy required to prevent recurrence of social phobia symptoms has not been established to date, the manufacturer states that this disorder is chronic and requires several months or longer of sustained therapy. Whether the dose of sertraline required to induce remission is identical to the dose needed to maintain and/or sustain remission in patients with this disorder is unknown. Systematic evaluation of sertraline has shown that its efficacy in the management of social phobia is maintained for periods of up to 24 weeks following 20 weeks of therapy at dosages of 50–200 mg daily. Dosages should be adjusted so that the patient is maintained on the lowest effective dosage, and patients should be reassessed periodically to determine the need for continued therapy.

Premature Ejaculation For the management of premature ejaculation†, sertraline has been given in a dosage of 25–50 mg daily. Alternatively, patients have taken sertraline on an "as needed" basis using doses of 25–50 mg daily.

■ **Dosage in Renal and Hepatic Impairment** The manufacturers state that, based on the pharmacokinetics of sertraline, there is no need for dosage adjustment in patients with renal impairment. Because sertraline does not appear to be removed substantially by dialysis, supplemental doses of the drug probably are unnecessary after dialysis.

Because sertraline is metabolized extensively by the liver, hepatic impairment can affect the elimination of the drug. (See Pharmacokinetics: Elimination.) Therefore, the manufacturers recommend that sertraline be administered with caution and in a reduced dosage or less frequently in patients with hepatic impairment.

■ **Treatment of Pregnant Women during the Third Trimester** Because some neonates exposed to sertraline and other selective serotonin-

reuptake inhibitors or selective serotonin- and norepinephrine-reuptake inhibitors (SNRIs) late in the third trimester of pregnancy have developed severe complications, consideration may be given to cautiously tapering sertraline therapy in the third trimester prior to delivery if the drug is administered during pregnancy. (See Pregnancy, under Cautions: Pregnancy, Fertility, and Lactation.)

Cautions

The adverse effect profile of sertraline is similar to that of other selective serotonin-reuptake inhibitors (e.g., citalopram, escitalopram, fluoxetine, paroxetine). Because sertraline is a highly selective serotonin-reuptake inhibitor with little or no effect on other neurotransmitters, the incidence of some adverse effects commonly associated with tricyclic antidepressants, such as anticholinergic effects (dry mouth, constipation), adverse cardiovascular effects, drowsiness, and weight gain, is lower in patients receiving sertraline. However, certain adverse GI (e.g., nausea, diarrhea, anorexia) and nervous system (e.g., tremor, insomnia) effects appear to occur more frequently with sertraline and other selective serotonin-reuptake inhibitors than with tricyclic antidepressants.

Overall, the adverse effect profile of sertraline in adults with depression, obsessive-compulsive disorder, or panic disorder appears to be similar. In controlled studies, the most common adverse effects occurring more frequently in adults receiving sertraline than in those receiving placebo included GI effects such as nausea, diarrhea or loose stools, dyspepsia, and dry mouth; nervous system effects such as somnolence, dizziness, insomnia, and tremor; sexual dysfunction in males (principally ejaculatory delay); and sweating. Discontinuance of sertraline therapy was required in about 15% of adults in clinical trials, principally because of adverse psychiatric (e.g., somnolence, insomnia, agitation, tremor), other nervous system (e.g., dizziness, headache), GI (e.g., nausea, diarrhea or loose stools, anorexia), or male sexual dysfunction (e.g., ejaculatory delay) effects or because of fatigue.

■ **Nervous System Effects** Headache is the most common adverse nervous system effect of sertraline, occurring in approximately 26% of patients receiving the drug in controlled clinical trials; headache occurred in 23% of those receiving placebo in these trials. Somnolence or drowsiness occurred in about 14% of patients receiving sertraline in controlled clinical trials. Headache or somnolence each required discontinuance of therapy in about 2% of patients. Fatigue has been reported in approximately 12% of patients receiving the drug in clinical trials and required discontinuance of therapy in about 1% of patients; this effect was reported in 8% of those receiving placebo in these trials.

Dizziness occurred in about 13% of patients receiving sertraline in controlled clinical trials and required discontinuance of therapy in less than 1% of patients. Insomnia occurred in about 22% of patients receiving the drug in controlled clinical trials. However, because insomnia is a symptom also associated with depression, relief of insomnia and improvement in sleep patterns may occur when clinical improvement in depression becomes apparent during antidepressant therapy. In clinical trials, about 2% of patients discontinued sertraline because of insomnia.

Tremor occurred in about 9%, nervousness in about 6%, anxiety (which occasionally may be severe [e.g., panic]) in about 4%, paresthesia in about 3%, and agitation in about 6% of patients receiving sertraline in controlled clinical trials. Tremor, agitation, and nervousness resulted in discontinuance of sertraline in about 1% of patients while anxiety resulted in discontinuance in less than 1% of patients in clinical trials. Agitation and anxiety may subside with continued therapy. Hypoesthesia, hypertonia, or malaise occurred in at least 1% of patients receiving sertraline in clinical trials. Impaired concentration, dystonia, or twitching occurred in approximately 0.1–1% of patients receiving sertraline, although these adverse effects have not been definitely attributed to the drug.

The incidence of seizures during sertraline therapy appears to be similar to or less than that observed during therapy with most other currently available antidepressants. Seizures occurred in less than 0.1% of patients receiving sertraline in clinical trials. (See Cautions: Precautions and Contraindications.)

Hypomania and mania have been reported in approximately 0.4% of patients receiving sertraline in controlled clinical trials, which is similar to the incidence reported in patients receiving active control agents (i.e., other antidepressants). In at least 2 patients, hypomanic symptoms occurred after they were receiving sertraline 200 mg daily for approximately 9 weeks. In both patients, the adverse reaction was obviated by a reduction in sertraline dosage. (See Cautions: Precautions and Contraindications.) Such reactions have occurred in patients receiving other antidepressant agents and may be caused by antidepressant-induced functional increases in catecholamine activity within the CNS, resulting in a "switch" from depressive to manic behavior. There is some evidence that patients with bipolar disorder may be more likely to experience antidepressant-induced hypomanic or manic reactions than patients without evidence of this disorder. In addition, limited evidence suggests that such reactions may occur more frequently in bipolar depressed patients receiving tricyclics and tetracyclics (e.g., maprotiline, mianserin [not commercially available in the US]) than in those receiving selective serotonin-reuptake inhibitors (e.g., citalopram, escitalopram, fluoxetine, paroxetine, sertraline). However, further studies are needed to confirm these findings.

Asthenia has been reported in at least 1% of patients receiving sertraline; however, a causal relationship to the drug has not been established. Confusion, migraine, abnormal coordination, abnormal gait, hyperesthesia, ataxia, depersonalization, hallucinations, hyperkinesia, hypokinesia, nystagmus, vertigo, abnormal dreams, aggressive reaction, amnesia, apathy, paroniria, delusion, depression or aggravated depression, emotional lability, euphoria, abnormal thinking, or paranoid reaction have been reported in 0.1–1% of patients receiving the drug, although these adverse effects have not been definitely attributed to sertraline.

Adverse nervous system effects reported in less than 0.1% of patients receiving sertraline include dysphoria, choreoathetosis, dyskinesia, coma, dysphonia, hyporeflexia, hypotonia, ptosis, somnambulism, and illusion; these effects have not been definitely attributed to the drug. Although a causal relationship has not been established, psychosis, extrapyramidal symptoms, oculogyric crisis, serotonin syndrome, and neuroleptic malignant syndrome (NMS)-like events also have been reported during postmarketing surveillance of sertraline. In some cases, features of serotonin syndrome have resembled those associated with NMS, which may occur in patients receiving phenothiazines or other antipsychotic agents. (See Drug Interactions: Drugs Associated with Serotonin Syndrome.)

A withdrawal syndrome, which also has not been definitely attributed to the drug, has been reported in less than 0.1% of sertraline-treated patients. Fatigue, severe abdominal cramping, memory impairment, and influenza-like symptoms were reported 2 days following the abrupt discontinuance of sertraline in one patient; when sertraline was restarted, the symptoms remitted. Electric shock-like sensations occurred in another patient 1 day after the last administered dose of sertraline; these sensations became less intense and eventually disappeared 13 weeks after sertraline therapy was discontinued. (See Chronic Toxicity.) Forgetfulness, panic attacks, and unspecified pain also have been reported rarely, although a causal relationship to sertraline has not been established. Sertraline also has been reported to precipitate or exacerbate "flashbacks" in patients who previously had used lysergic acid diethylamide (LSD).

Extrapyramidal reactions, including akathisia, stuttering (which may be a speech manifestation of akathisia), bilateral jaw stiffness, and torticollis, have been reported rarely with sertraline use, and such reactions appear to be a class effect of selective serotonin-reuptake inhibitors and dose related. Reactions occurring *early* during therapy with these drugs may be secondary to preexisting parkinsonian syndrome and/or concomitant therapy.

Suicidality Suicidal ideation has been reported in less than 0.1% of adults receiving sertraline. The US Food and Drug Administration (FDA) has determined that antidepressants increase the risk of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults (18–24 years of age) with major depressive disorder and other psychiatric disorders. (See Suicidality, under Cautions: Nervous System Effects, in Paroxetine 28:16.04.20.) Patients, therefore, should be appropriately monitored and closely observed for clinical worsening, suicidality, and unusual changes in behavior, particularly during initiation of sertraline therapy (i.e., the first few months) and during periods of dosage adjustments. (See Cautions: Precautions and Contraindications and Cautions: Pediatric Precautions.)

■ **GI Effects** Like other selective serotonin-reuptake inhibitors (e.g., citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine), sertraline therapy is associated with a relatively high incidence of GI disturbances, principally nausea, dry mouth, and diarrhea/loose stools. The most frequent adverse effect associated with sertraline therapy is nausea, which occurred in about 28% of patients receiving the drug in controlled clinical trials. In clinical trials, nausea required discontinuance of sertraline in about 4% of patients. In general, the incidence of nausea associated with selective serotonin-reuptake inhibitors appears to be higher when therapy is initiated with high doses but decreases as therapy with these drugs is continued. While the mechanism(s) of sertraline-induced GI effects has not been fully elucidated, they appear to arise at least in part because of increased serotonergic activity in the GI tract (which may result in stimulation of small intestine motility and inhibition of gastric and large intestine motility) and possibly because of the drug's effect on central serotonergic type 3 (5-HT_3) receptors.

Diarrhea or loose stools occurred in about 20%, dry mouth in about 15%, constipation in about 7%, dyspepsia in about 8%, or anorexia in about 6% of patients receiving sertraline in controlled clinical trials. Other adverse GI effects associated with sertraline therapy include vomiting which occurred in about 4% and flatulence which occurred in about 3% of patients receiving the drug in controlled clinical trials. Abdominal pain was reported in approximately 2% and taste perversion in about 1% of patients receiving sertraline. In clinical trials, diarrhea or loose stools required discontinuance of sertraline in about 3% of patients and dry mouth required discontinuance of therapy in about 1% of patients.

Epidemiologic case-control and cohort design studies have suggested that selective serotonin-reuptake inhibitors may increase the risk of upper GI bleeding. Although the precise mechanism for this increased risk remains to be clearly established, serotonin release by platelets is known to play an important role in hemostasis, and selective serotonin-reuptake inhibitors decrease serotonin uptake from the blood by platelets thereby decreasing the amount of serotonin in platelets. In addition, concurrent use of aspirin or other nonsteroidal anti-inflammatory drugs was found to substantially increase the risk of GI bleeding in patients receiving selective serotonin-reuptake inhibitors in 2 of these studies. Although these studies focused on upper GI bleeding, there is some evidence suggesting that bleeding at other sites may be similarly potentiated. Further clinical studies are needed to determine the clinical importance of these findings. (See Cautions: Hematologic Effects, and see also Drug Interactions: Drugs Affecting Hemostasis.)

Although a causal relationship to sertraline has not been established, dysphagia, esophagitis, aggravation of dental caries, gastroenteritis, eructation, and increased salivation have been reported in 0.1–1% of patients receiving the drug. Aphthous stomatitis, ulcerative stomatitis, stomatitis, tongue ulceration or edema, glossitis, diverticulitis, gastritis, hemorrhagic peptic ulcer, rectal hemorrhage, colitis, proctitis, fecal incontinence, melena, or tenesmus has been reported in less than 0.1% of patients receiving sertraline; however, these adverse effects have not been definitely attributed to the drug. Pancreatitis also has been reported rarely in association with sertraline; however, a causal relationship to the drug has not been clearly established.

Although a causal relationship has not been established, nocturnal bruxism (clenching and/or grinding of the teeth during sleep) has developed within 2–4 weeks following initiation of sertraline or fluoxetine therapy in several patients. The bruxism remitted upon reduction in dosage of the serotonin-reuptake inhibitor and/or the addition of buspirone therapy.

Speech blockage also has been reported in at least one sertraline-treated patient.

■ **Dermatologic and Sensitivity Reactions** Sweating occurred in about 7% of patients receiving sertraline in controlled clinical trials.

Rash, which may be erythematous, follicular, maculopapular, or pustular, has been reported in about 3% of patients receiving sertraline in controlled clinical trials. Adverse dermatologic effects reported in 0.1–1% of patients receiving sertraline in controlled clinical trials include acne, alopecia, dry skin, urticaria, pruritus, and photosensitivity reaction (which may be severe); however, these adverse effects have not been definitely attributed to sertraline. Bullous eruption, eczema, contact dermatitis, skin discoloration, and hypertrichosis have been reported in less than 0.1% of patients receiving the drug, although a causal relationship to sertraline has not been established. Allergy, allergic reaction, and angioedema also have been reported rarely.

Other dermatologic and sensitivity events, which can be severe and potentially may be fatal, reported during the postmarketing surveillance of sertraline have included anaphylactoid reaction, angioedema, Stevens-Johnson syndrome, erythema multiforme, and vasculitis.

■ **Metabolic Effects** Thirst has been reported in 0.1–1% of patients receiving sertraline in controlled clinical trials.

Weight loss occurred in 0.1–1% of patients receiving sertraline. In controlled clinical trials, patients lost an average of about 0.45–0.9 kg while receiving sertraline. Rarely, weight loss has required discontinuance of therapy. Like fluoxetine, sertraline exhibits anorexigenic activity and can cause anorexia, which may be more pronounced in overweight patients and those with carbohydrate craving. Anorexia occurred in about 3% of patients receiving sertraline in controlled clinical trials and required discontinuance in at least 1% of patients. Increased appetite and weight gain have been reported in at least 1% of patients receiving sertraline in controlled clinical trials, although a causal relationship to the drug has not been established. (See Cautions: Pediatric Precautions.)

Sertraline use has been associated with small mean decreases (approximately 7%) in serum uric acid concentration as a result of a weak uricosuric effect; the clinical importance is not known and there have been no cases of acute renal failure associated with the drug. Small mean increases in serum total cholesterol (about 3%) and triglyceride (about 5%) concentrations also have been reported in patients receiving sertraline. Hypercholesterolemia has been reported in less than 0.1% of patients. Other adverse effects reported in less than 0.1% of patients receiving the drug include dehydration and hypoglycemia. These adverse effects have not been definitely attributed to sertraline.

■ **Ocular and Otic Effects** Abnormal vision (including blurred vision) occurred in about 4% of patients receiving sertraline in controlled clinical trials. Adverse ocular effects reported in 0.1–1% of patients receiving sertraline include abnormality of accommodation, conjunctivitis, mydriasis, and ocular pain. Although a causal relationship to sertraline has not been established, anisocoria, abnormal lacrimation, xerophthalmia, diplopia, scotoma, visual field defect, exophthalmos, hemorrhage of the anterior chamber of the eye, glaucoma, or photophobia has been reported in less than 0.1% of patients receiving the drug. Other adverse ocular effects reported during postmarketing surveillance of sertraline have included blindness, optic neuritis, and cataract; however, a causal relationship to the drug has not been established.

Tinnitus occurred in at least 1% of patients receiving sertraline in controlled clinical trials. Earache has been reported in 0.1–1% of patients, and hyperacusis and labyrinthine disorder have been reported in less than 0.1% of patients.

■ **Cardiovascular Effects** Sertraline does not exhibit clinically important anticholinergic activity, and current evidence suggests that sertraline is less cardiotoxic than many antidepressant agents (e.g., tricyclic antidepressants, monoamine oxidase inhibitors). (See Cardiovascular Considerations in Uses: Major Depressive Disorder and see also Pharmacology: Cardiovascular Effects.) However, bradycardia, AV block, atrial arrhythmias, QT-interval prolongation, and ventricular tachycardia (including torsades de pointes-type arrhythmias) have been reported during postmarketing surveillance evaluations of the drug.

Hot flushes occurred in about 2% of patients receiving sertraline in controlled clinical trials. Palpitation and chest pain have been reported in at least 1% of patients receiving sertraline in controlled clinical trials. In one patient with underlying coronary artery disease, chest pain developed suddenly and was relieved with sublingual nitroglycerin but was not associated with ECG changes; the mechanism of this effect, particularly regarding any potential cardiovascular effect, is unclear and alternative mechanisms (e.g., GI) for the chest pain have been proposed.

Unlike tricyclic antidepressants, sertraline has been associated with hypotension (e.g., orthostatic) infrequently; in controlled clinical trials, postural effects (e.g., dizziness, hypotension [which can also be nonpostural]) occurred in 0.1–1% of patients receiving sertraline. Syncope also occurred in at least 0.1% of patients.

Hypertension, peripheral ischemia, and tachycardia have been reported in 0.1–1% of patients receiving the drug, although a definite causal relationship to sertraline has not been established. Precordial or substernal chest pain, aggravated hypertension, myocardial infarction, pallor, vasodilation, and cerebrovascular disorder have been reported in less than 0.1% of patients receiving sertraline; these adverse effects have not been definitely attributed to the drug.

Generalized, dependent, periorbital, or peripheral edema has been reported in at least 0.1% of patients receiving sertraline, and facial edema has been reported rarely. However, a causal relationship to the drug has not been established.

■ **Musculoskeletal Effects** Myalgia or back pain occurred in at least 1% of patients receiving sertraline in controlled clinical trials. Arthralgia, arthrosis, leg or other muscle cramps, or muscle weakness has been reported in 0.1–1% of patients receiving sertraline; these adverse effects have not been definitely attributed to the drug.

■ **Hematologic Effects** Purpura, aplastic anemia, pancytopenia, leukopenia, thrombocytopenia, and abnormal bleeding have been reported occasionally in patients receiving sertraline; however, these adverse effects have not been definitely attributed to the drug.

Altered platelet function and/or abnormal platelet laboratory results have been reported rarely, but a causal relationship to sertraline remains to be established. In addition, in at least one patient with idiopathic thrombocytopenic purpura, sertraline therapy was associated with an increase in platelet counts. Anemia has been reported in less than 0.1% of patients receiving sertraline, although a causal relationship to the drug has not been established. Neutropenia also has been reported rarely with sertraline use and has been a reason for drug discontinuance. Agranulocytosis and septic shock developed in a geriatric woman who had been receiving sertraline for about 1 month in addition to atenolol, bendroflumethiazide, and thioridazine; the patient responded to antiinfective and granulocyte colony-stimulating factor therapy and made a full recovery within 10 days.

Bleeding complications (e.g., ecchymosis, purpura, menorrhagia, rectal bleeding) have been reported infrequently in patients receiving selective serotonin-reuptake inhibitors. Although the precise mechanism for these reactions has not been established, it has been suggested that impaired platelet aggregation and prolonged bleeding time may be due at least in part to inhibition of serotonin reuptake into platelets and/or that increased capillary fragility and vascular tone may contribute to these cases. (See Cautions: GI Effects and see also Drug Interactions: Drugs Affecting Hemostasis.)

■ **Respiratory Effects** Rhinitis or yawning has been reported in at least 1% of patients receiving sertraline in controlled clinical trials. Adverse respiratory effects reported in 0.1–1% of patients receiving the drug include bronchospasm, dyspnea, epistaxis, upper respiratory tract infection, sinusitis, and coughing; however, a definite causal relationship to sertraline has not been established. Adverse respiratory effects reported in less than 0.1% of patients receiving sertraline include bradypnea, hypoventilation, hyperventilation, apnea, stridor, hiccups, hemoptysis, bronchitis, laryngismus, and laryngitis. Pulmonary hypertension also has been reported during postmarketing surveillance evaluations of the drug. However, these adverse effects have not been definitely attributed to the drug.

■ **Renal, Electrolyte, and Genitourinary Effects** ***Sexual Dysfunction*** Like other selective serotonin-reuptake inhibitors, adverse effects on sexual function have been reported in both men and women receiving sertraline. Although changes in sexual desire, sexual performance, and sexual satisfaction often occur as manifestations of a psychiatric disorder, they also may occur as the result of pharmacologic therapy. It is difficult to determine the true incidence and severity of adverse effects on sexual function during sertraline therapy, in part because patients and clinicians may be reluctant to discuss these effects. Therefore, incidence data reported in product labeling and earlier studies are most likely underestimates of the true incidence of adverse sexual effects. Recent reports indicate that up to 50% of patients receiving selective serotonin-reuptake inhibitors describe some form of sexual dysfunction during treatment and the actual incidence may be even higher.

Sexual dysfunction (principally ejaculatory delay) is the most common adverse urogenital effect of sertraline in males, occurring in about 14% of male patients receiving the drug in controlled clinical trials. In some cases, this effect has been used for therapeutic benefit in the treatment of premature ejaculation. (See Uses: Premature Ejaculation.) Impotence has occurred in at least 1% of male patients receiving sertraline in controlled trials, and priapism has been reported rarely. Female sexual dysfunction (e.g., anorgasmia) has been reported in at least 1% of female patients receiving the drug in controlled clinical trials. Decreased libido has been reported in males and females, occurring in 6% of patients in controlled clinical studies. Sexual dysfunction (principally ejaculatory delay) required discontinuance of therapy in at least 1% of patients in controlled clinical trials. Increased libido has been reported in less than 1% of patients receiving the drug.

Results of some (but not all) studies in men and women suggest that paroxetine may be associated with a higher incidence of sexual dysfunction than some other currently available selective serotonin-reuptake inhibitors, including sertraline and citalopram. Since it is difficult to know the precise risk of sexual dysfunction associated with serotonin-reuptake inhibitors, clinicians should routinely inquire about such possible adverse effects in patients receiving these drugs.

The long-term effects of selective serotonin-reuptake inhibitors on sexual function have not been fully determined to date. In a double-blind study evaluating 6 months of sertraline or citalopram therapy in depressed patients, sexual desire and overall sexual functioning (as measured on the UKU Side Effect Scale) substantially improved in women and sexual desire improved in men. In men, no change in orgasmic dysfunction, erectile dysfunction, or overall sexual functioning was reported after 6 months of therapy with sertraline or citalopram, although there was a trend toward worsening of ejaculatory dysfunction. However, in the subgroups of women and men reporting no sexual problems at baseline, approximately 12% of women reported decreased sexual desire and 14% reported orgasmic dysfunction after 6 months of citalopram therapy; the corresponding figures in the same subgroup of men were approximately 17 and 19%, respectively, and as many as 25% experienced ejaculatory dysfunction after 6 months. No substantial differences between sertraline and citalopram were reported in this study.

Management of sexual dysfunction caused by selective serotonin-reuptake inhibitor therapy includes waiting for tolerance to develop; using a lower dosage of the drug; using drug holidays; delaying administration of the drug until after coitus; or changing to another antidepressant. Although further study is needed, there is some evidence that adverse sexual effects of the selective serotonin-reuptake inhibitors may be reversed by concomitant use of certain drugs, including buspirone, 5-hydroxytryptamine-2 (5-HT_2) receptor antagonists (e.g., nefazodone), 5-HT_3 receptor inhibitors (e.g., granisetron), or α_2-adrenergic receptor antagonists (e.g., yohimbine), selective phosphodiesterase (PDE) inhibitors (e.g., sildenafil), or dopamine receptor agonists (e.g., amantadine, dextroamphetamine, pemoline [no longer commercially available in the US], methylphenidate). In most patients, sexual dysfunction is fully reversed 1–3 days after discontinuance of the antidepressant.

Other Renal, Electrolyte, and Genitourinary Effects Although a definite causal relationship to sertraline has not been established, menstrual disorders, dysmenorrhea, intermenstrual bleeding, amenorrhea, vaginal hemorrhage, and leukorrhea have been reported in 0.1–1% of patients receiving sertraline. In addition, menorrhagia, breast enlargement, female breast pain or tenderness, acute mastitis in females, gynecomastia, and atrophic vaginitis have been reported in less than 0.1% of patients receiving sertraline; however, a causal relationship to the drug has not been clearly established.

Hyponatremia and transient syndrome of inappropriate secretion of antidiuretic hormone [SIADH]) have been reported in some patients receiving sertraline. Similar effects have been reported with other selective serotonin-reuptake inhibitors (e.g., citalopram, fluoxetine, fluvoxamine, paroxetine) and appear to develop an average of 2 weeks after initiating therapy (range: 3–120 days). (See Cautions: Renal, Electrolyte, and Genitourinary Effects in Fluoxetine Hydrochloride 28:16.04.20.) Most cases of hyponatremia reported to date have occurred in geriatric patients and/or in patients concurrently receiving diuretics or who were otherwise volume depleted. (See Cautions: Geriatric Precautions.) Hyponatremia associated with sertraline therapy appears to be reversible following discontinuance of the drug and/or fluid restriction. Because geriatric patients may be at increased risk for hyponatremia associated with selective serotonin-reuptake inhibitor therapy, clinicians prescribing sertraline in such patients should be aware of the possibility that such reactions may occur. Periodic monitoring of serum sodium concentrations in geriatric patients receiving the drug has been recommended by some clinicians.

A variety of urinary disorders, including urinary frequency, polyuria, urinary hesitancy and/or retention, dysuria, nocturia, and urinary incontinence, has been reported in 0.1–1% of patients receiving sertraline; however, these effects have not been definitely attributed to the drug. In addition, cystitis, oliguria, pyelonephritis, hematuria, renal pain, strangury, and balanoposthitis have been reported in less than 0.1% of patients receiving sertraline, although a causal relationship to the drug has not been clearly established.

■ **Hepatic Effects** Impaired hepatic function has been reported in less than 1% of patients receiving sertraline in controlled clinical trials; in most cases, such reactions appeared to be reversible upon discontinuance of sertraline therapy. Asymptomatic elevations in serum AST (SGOT) and ALT (SGPT) concentrations have been reported in approximately 0.8% of patients receiving the drug and occasionally have been a reason for drug discontinuance. Elevations in aminotransferase concentrations usually occurred within the first 1–9 weeks of sertraline therapy and were rapidly reversible following discontinuance of the drug. In addition, in at least 2 patients, elevated liver enzymes returned to normal levels with continued therapy.

Increased serum alkaline phosphatase and bilirubin concentrations occurred rarely in patients receiving sertraline in clinical trials and required discontinuance of therapy in some cases. Other clinical features associated with adverse hepatic reactions that have been reported in at least one patient include hepatitis, hepatomegaly, jaundice, abdominal pain, vomiting, hepatic failure, and death. However, these effects have not been definitely attributed to the drug.

■ **Endocrine Effects** Low levels of total thyroxine developed in a depressed adolescent who had been receiving sertraline therapy; however, it appears that sertraline only displaced the bound fraction of total thyroxine but was not associated with true hypothyroidism. In a limited number of hypothyroid patients receiving thyroxine therapy, elevated serum thyrotropin and reduced serum thyroxine concentrations have been observed following the initiation of sertraline therapy. Hypothyroidism also has been reported. (See Cautions: Precautions and Contraindications.)

Hyperprolactinemia and galactorrhea also have been reported rarely; however, a causal relationship to the drug has not been established.

■ **Other Adverse Effects** Cold clammy skin, flushing, fever, or rigors has been reported in 0.1–1% of patients receiving the drug, although a causal relationship to sertraline has not been established. In addition, lupus-like syndrome and serum sickness have been reported during postmarketing surveillance evaluations of the drug; however, a causal relationship has not been definitively established.

■ **Precautions and Contraindications** Worsening of depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior may occur in both adult and pediatric (see Cautions: Pediatric Precautions) patients with major depressive disorder or other psychiatric disorders, whether or not they are taking antidepressants. This risk may persist until clinically important remission occurs. Suicide is a known risk of depression and certain other psychiatric disorders, and these disorders themselves are the strongest predictors of suicide. However, there has been a long-standing concern that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients during the early phases of treatment. Pooled analyses of short-term, placebo-controlled studies of antidepressants (i.e., selective serotonin-reuptake inhibitors and other antidepressants) have shown an increased risk of suicidality in children, adolescents, and young adults (18–24 years of age) with major depressive disorder and other psychiatric disorders. An increased suicidality risk was not demonstrated with antidepressants compared to placebo in adults older than 24 years of age and a reduced risk was observed in adults 65 years of age or older. It currently is unknown whether the suicidality risk extends to longer-term use (i.e., beyond several months); however, there is substantial evidence from placebo-controlled maintenance trials in adults with major depressive disorder that antidepressants can delay the recurrence of depression.

The US Food and Drug Administration (FDA) recommends that all patients being treated with antidepressants for any indication be appropriately monitored and closely observed for clinical worsening, suicidality, and unusual changes in behavior, particularly during initiation of therapy (i.e., the first few months) and during periods of dosage adjustments. Families and caregivers of patients being treated with antidepressants for major depressive disorder or other indications, both psychiatric and nonpsychiatric, also should be advised to monitor patients on a daily basis for the emergence of agitation, irritability, or unusual changes in behavior as well as the emergence of suicidality, and to report such symptoms immediately to a health-care provider. (See Suicidality, under Cautions: Nervous System Effects, in Paroxetine 28:16.04.20.)

Although a causal relationship between the emergence of symptoms such as anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia, hypomania, and/or mania and either the worsening of depression and/or the emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality. Consequently, consideration should be given to changing the therapeutic regimen or discontinuing therapy in patients whose depression is persistently worse or in patients experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidality, particularly if such manifestations are severe, abrupt in onset, or were not part of the patient's presenting symptoms. If a decision is made to discontinue therapy, sertraline dosage should be tapered as rapidly as is feasible but with recognition of the risks of abrupt discontinuance. (See Dosage and Administration: Dosage.) FDA also recommends that the drugs be prescribed in the smallest quantity consistent with good patient management, in order to reduce the risk of overdosage.

It is generally believed (though not established in controlled trials) that treating a major depressive episode with an antidepressant alone may increase the likelihood of precipitating a mixed or manic episode in patients at risk for bipolar disorder. Therefore, patients should be adequately screened for bipolar disorder prior to initiating treatment with an antidepressant; such screening should include a detailed psychiatric history (e.g., family history of suicide, bipolar disorder, and depression).

The dropper dispenser provided with Zoloft® oral solution contains natural latex proteins in the form of dry natural rubber which may cause sensitivity reactions in susceptible individuals.

Because clinical experience with sertraline in patients with certain concurrent systemic disease, including cardiovascular disease and renal impairment, is limited, caution should be exercised when sertraline is administered to patients with any systemic disease or condition that may alter metabolism of the drug or adversely affect hemodynamic function. (See Dosage and Administration: Dosage.)

Sertraline should be used with caution in patients with hepatic impairment, since prolonged elimination of the drug has been reported to occur in patients with liver cirrhosis. (See Pharmacokinetics: Elimination and see Dosage and Administration: Dosage in Renal and Hepatic Impairment.)

The manufacturers recommend that patients receiving sertraline be advised to notify their clinician if they are taking or plan to take nonprescription (over-the-counter) or prescription medications or alcohol-containing beverages or

preparations. Although no interactions with nonprescription medications have been reported to date, the potential for such adverse drug interactions exists. Therefore, the use of any nonprescription medication should be initiated cautiously according to the directions of use provided on the nonprescription medication. Although sertraline has not been shown to potentiate the impairment of mental and motor skills caused by alcohol, the manufacturers recommend that patients be advised to avoid alcohol while receiving the drug.

Sertraline generally is less sedating than most other currently available antidepressants and does not appear to produce substantial impairment of cognitive or psychomotor function. However, patients should be cautioned that sertraline may impair their ability to perform activities requiring mental alertness or physical coordination (e.g., operating machinery, driving a motor vehicle) and to avoid such activities until they experience how the drug affects them. Because the risk of using sertraline concomitantly with other CNS active drugs has not been evaluated systematically to date, the manufacturers recommend that such therapy be employed cautiously.

Seizures have been reported in patients receiving therapeutic dosages of sertraline. Because of limited experience with sertraline in patients with a history of seizures, the drug should be used with caution in such patients.

Activation of mania and hypomania has occurred in patients receiving therapeutic dosages of sertraline. The drug should be used with caution in patients with a history of mania or hypomania.

Altered platelet function has been reported rarely in patients receiving sertraline. In addition, use of the drug has been associated with several reports of abnormal bleeding or purpura. While a causal relationship to sertraline remains to be established, pending such establishment, the drug should be used with caution in patients with an underlying coagulation defect since the possible effects on hemostasis may be exaggerated in such patients. (See Cautions: Hematologic Effects.)

Hyponatremia has been reported in several patients receiving sertraline, principally in geriatric patients but also in those concurrently receiving diuretics or who were otherwise volume depleted. Hyponatremia associated with sertraline therapy appears to be reversible following discontinuance of the drug.

Sertraline has a weak uricosuric effect. (See Cautions: Metabolic Effects.) Pending further elucidation of the clinical importance, if any, of this effect, the drug should be used with caution in patients who may be adversely affected (e.g., those at risk for acute renal failure).

Because sertraline therapy has been associated with anorexia and weight loss (see Cautions: Metabolic Effects), the drug should be used with caution in patients who may be adversely affected by these effects (e.g., underweight patients).

Like many other antidepressant drugs, sertraline has been associated with hypothyroidism, elevated serum thyrotropin, and/or reduced serum thyroxine concentrations in a limited number of patients. Because of reports with other antidepressant agents and the complex interrelationship between the hypothalamic-pituitary-thyroid axis and affective (mood) disorders, at least one manufacturer recommends that thyroid function be reassessed periodically in patients with thyroid disease who are receiving sertraline.

Potentially life-threatening serotonin syndrome may occur during therapy with selective serotonin-reuptake inhibitors (SSRIs), including sertaline, or selective serotonin- and norepinephrine-reuptake inhibitors (SNRIs), particularly with concurrent administration of other serotonergic drugs (e.g., serotonin [5-hydroxytryptamine; 5-HT] type 1 agonists ["triptans"]) or drugs that impair serotonin metabolism (e.g., monoamine oxidase [MAO] inhibitors). Symptoms of serotonin syndrome may include mental status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g., hyperreflexia, incoordination), and/or GI symptoms (e.g., nausea, vomiting, diarrhea). Patients should be cautioned about the risk of serotonin syndrome with the concomitant use of sertraline and 5-HT_1 receptor agonists (triptans), tramadol, or other serotonergic agents. Because of the risk of serotonin syndrome, caution also is advised when sertraline is concurrently administered with drugs affecting serotonergic neurotransmission, including linezolid, lithium, tramadol, and St. John's wort (*Hypericum perforatum*). If concurrent therapy with sertraline and a 5-HT_1 receptor agonist is clinically warranted, the patient should be observed carefully, particularly during initiation of therapy, when the dosage is increased, or when another serotonergic agent is initiated. Concomitant use of sertraline and serotonin precursors (e.g., tryptophan) is not recommended. (See Drug Interactions: Drugs Associated with Serotonin Syndrome.)

Sertraline is contraindicated in patients receiving pimozide or MAO inhibitor therapy; at least 2 weeks should elapse between discontinuance of MAO inhibitor therapy and initiation of sertraline therapy and vice versa. (See Drug Interactions: Pimozide, and also see Monamine Oxidase Inhibitors under Drug Interactions: Drugs Associated with Serotonin Syndrome.)

Commercially available sertraline hydrochloride oral solution (Zoloft®) contains alcohol. Therefore, concomitant use of sertraline hydrochloride oral solution and disulfiram is contraindicated.

Sertraline also is contraindicated in patients who are hypersensitive to the drug or any ingredient in the formulation.

■ **Pediatric Precautions** The manufacturer states that safety and efficacy of sertraline in children with obsessive-compulsive disorder (OCD) younger than 6 years of age have not been established. Safety and efficacy of sertraline in children with other disorders (e.g., major depressive disorder, panic disorder, posttraumatic stress disorder, premenstrual dysphoric disorder, social phobia) have not been established. The overall adverse effect profile of sertaline in over 600 pediatric patients who received sertaline in controlled clinical trials was generally similar to that seen in the adult clinical studies. However, adverse effects reported in at least 2% of the sertraline-treated pediatric patients in these trials and that occurred at least twice as frequently as in pediatric patients receiving placebo included fever, hyperkinesia, urinary incontinence, aggressive reaction, sinusitis, epistaxis, and purpura.

Efficacy of sertraline in pediatric patients with major depressive disorder was evaluated in 2 randomized, 10-week, double-blind, placebo-controlled, flexible-dose (50–200 mg daily) trials in 373 children and adolescents with major depressive disorder, but data from these studies were not sufficient to establish efficacy in pediatric patients. In a safety analysis of the pooled data from these 2 studies, a difference in weight change between the sertraline and placebo groups was noted of approximately 1 kg for both pediatric patients (6–11 years of age) and adolescents (12–17 years of age) representing a slight weight loss for those receiving sertraline and a slight weight gain for those receiving placebo. In addition, a larger difference was noted in children than in adolescents between the sertraline and placebo groups in the proportion of outliers for clinically important weight loss; about 7% of the children and about 2% of the adolescents receiving sertraline in these studies experienced a weight loss of more than 7% of their body weight compared with none of those receiving placebo.

A subset of patients who completed these controlled trials was continued into a 24-week, flexible-dose, open-label, extension study. A mean weight loss of approximately 0.5 kg was observed during the initial 8 weeks of treatment for those pediatric patients first exposed to sertraline during the extension study, which was similar to the weight loss observed among sertraline-treated patients during the first 8 weeks of the randomized controlled trials. The patients continuing in the extension study began gaining weight relative to their baseline weight by week 12 of sertraline therapy, and patients who completed the entire 34 weeks of therapy with the drug had a weight gain that was similar to that expected using data from age-adjusted peers. The manufacturers state that periodic monitoring of weight and growth is recommended in pediatric patients receiving long-term therapy with sertraline or other selective serotonin-reuptake inhibitors (SSRIs).

FDA warns that antidepressants increase the risk of suicidal thinking and behavior (suicidality) in children and adolescents with major depressive disorder and other psychiatric disorders. The risk of suicidality for these drugs was identified in a pooled analysis of data from a total of 24 short-term (4–16 weeks), placebo-controlled studies of 9 antidepressants (i.e., sertraline, bupropion, citalopram, fluoxetine, fluvoxamine, mirtazapine, nefazodone, paroxetine, venlafaxine) in over 4400 children and adolescents with major depressive disorder, OCD, or other psychiatric disorders. The analysis revealed a greater risk of adverse events representing suicidal behavior or thinking (suicidality) during the first few months of treatment in pediatric patients receiving antidepressants than in those receiving placebo. The average risk of such events was 4% among children and adolescents receiving these drugs, twice the risk (2%) that was observed among those receiving placebo. However, a more recent meta-analysis of 27 placebo-controlled trials of 9 antidepressants (SSRIs and others) in patients younger than 19 years of age with major depressive disorder, OCD, or non-OCD anxiety disorders suggests that the benefits of antidepressant therapy in treating these conditions may outweigh the risks of suicidal behavior or suicidal ideation. No suicides occurred in these pediatric trials.

The risk of suicidality in FDA's pooled analysis differed across the different psychiatric indications, with the highest incidence observed in the major depressive disorder studies. In addition, although there was considerable variation in risk among the antidepressants, a tendency toward an increase in suicidality risk in younger patients was found for almost all drugs studied. It is currently unknown whether the suicidality risk in pediatric patients extends to longer-term use (i.e., beyond several months). (See Suicidality, under Cautions: Nervous System Effects, in Paroxetine 28:16.04.20.)

As a result of this analysis and public discussion of the issue, FDA has directed manufacturers of all antidepressants to add a boxed warning to the labeling of their products to alert clinicians of this suicidality risk in children and adolescents and to recommend appropriate monitoring and close observation of patients receiving these agents. (See Cautions: Precautions and Contraindications.) The drugs that are the focus of the revised labeling are all drugs included in the general class of antidepressants, including those that have not been studied in controlled clinical trials in pediatric patients, since the available data are not adequate to exclude any single antidepressant from an increased risk. In addition to the boxed warning and other information in professional labeling on antidepressants, FDA currently recommends that a patient medication guide explaining the risks associated with the drugs be provided to the patient each time the drugs are dispensed. Caregivers of pediatric patients whose depression is persistently worse or who are experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidality during antidepressant therapy should consult their clinician regarding the best course of action (e.g., whether the therapeutic regimen should be changed or the drugs discontinued). *Patients should not discontinue use of selective serotonin-reuptake inhibitors without first consulting their clinician; it is very important that the drugs not be abruptly discontinued (see Dosage and Administration: Dosage), as withdrawal effects may occur.*

Anyone considering the use of sertraline in a child or adolescent for any clinical use must balance the potential risk of therapy with the clinical need.

■ **Geriatric Precautions** In clinical studies in geriatric patients, 660 patients receiving sertraline for the treatment of depression were 65 years of age or older, and 180 were 75 years of age or older. No overall differences in efficacy or adverse effects were observed for geriatric patients in these studies relative to younger patients, and other clinical experience has revealed no evidence of age-related differences in safety. In addition, no adverse effects on psychomotor performance were observed in geriatric individuals who received the drug in one controlled study. However, the possibility that older patients may exhibit increased sensitivity to the drug cannot be excluded. Limited evidence suggests that geriatric patients may be more likely than younger patients to develop sertraline-induced hyponatremia and transient syndrome of inappropriate secretion of antidiuretic hormone (SIADH). Therefore, clinicians prescribing sertraline in geriatric patients should be aware of the possibility that such reactions may occur. Periodic monitoring (especially during the first several months) of serum sodium concentrations in geriatric patients receiving the drug has been recommended by some clinicians.

In pooled data analyses, a *reduced* risk of suicidality was observed in adults 65 years of age or older with antidepressant therapy compared with placebo. (See Cautions: Precautions and Contraindications.)

Plasma clearance of sertraline may be decreased in geriatric patients; plasma clearance of the less active metabolite, *N*-desmethylsertraline, also may be decreased in older males.

■ **Mutagenicity and Carcinogenicity** Sertraline was not mutagenic, with or without metabolic activation, in several in vitro tests including the bacterial mutation assay and the mouse lymphoma mutation assay. Sertraline also was not mutagenic in tests for cytogenetic aberrations in vivo in mouse bone marrow and in vitro in human lymphocytes.

Lifetime studies to determine the carcinogenic potential of sertraline were performed in CD-1 mice and Long-Evans rats receiving dosages up to 40 mg/kg daily. This dosage corresponded to 1 and 2 times the maximum recommended human dose on a mg/m^2 basis in mice and rats, respectively. There was a dose-related increase in the incidence of hepatic adenomas in male mice receiving sertraline dosages of 10–40 mg/kg (0.25–1 times the maximum recommended human dose on a mg/m^2 basis). No increase was seen in female mice or in rats of either gender receiving the same dosages, nor was there an increase in hepatocellular carcinomas. Hepatic adenomas have a variable rate of spontaneous occurrence in this strain of mice, and the relevance of this finding to humans is not known. There was an increase in follicular adenomas of the thyroid, not accompanied by thyroid hyperplasia, in female rats receiving a sertraline dosage of 40 mg/kg (2 times the maximum recommended human dose on a mg/m^2 basis). There also was an increase in uterine adenocarcinomas in rats receiving sertraline dosages of 10–40 mg/kg (0.5–2 times the maximum recommended human dose on a mg/m^2 basis); however, this effect could not be directly attributed to the drug.

■ **Pregnancy, Fertility, and Lactation** ***Pregnancy*** Some neonates exposed to sertraline and other SSRIs or SNRIs late in the third trimester of pregnancy have developed complications that have sometimes been severe and required prolonged hospitalization, respiratory support, enteral nutrition, and other forms of supportive care in special-care nurseries. Such complications can arise immediately upon delivery and usually last several days or up to 2–4 weeks. Clinical findings reported to date in the neonates have included respiratory distress, cyanosis, apnea, seizures, temperature instability or fever, feeding difficulty, dehydration, excessive weight loss, vomiting, hypoglycemia, hypotonia, hyperreflexia, tremor, jitteriness, irritability, lethargy, reduced or lack of reaction to pain stimuli, and constant crying. These clinical features appear to be consistent with either a direct toxic effect of the SSRI or SNRI or, possibly, a drug withdrawal syndrome. It should be noted that in some cases the clinical picture was consistent with serotonin syndrome (see Drug Interactions: Drugs Associated with Serotonin Syndrome). When treating a pregnant woman with sertraline during the third trimester of pregnancy, the clinician should carefully consider the potential risks and benefits of such therapy. Consideration may be given to cautiously tapering sertraline therapy in the third trimester prior to delivery if the drug is administered during pregnancy. (See Treatment of Pregnant Women during the Third Trimester under Dosage and Administration: Dosage.)

FDA states that decisions about management of depression in pregnant women are challenging and that the patient and her clinician must carefully consider and discuss the potential benefits and risks of SSRI therapy during pregnancy for the individual woman. Two recent studies provide important information on risks associated with discontinuing or continuing antidepressant therapy during pregnancy.

The first study, which was prospective, naturalistic, and longitudinal in design, evaluated the potential risk of relapsed depression in pregnant women with a history of major depressive disorder who discontinued or attempted to discontinue antidepressant (SSRIs, tricyclic antidepressants, or others) therapy during pregnancy compared with that in women who continued antidepressant therapy throughout their pregnancy; all women were euthymic while receiving antidepressant therapy at the beginning of pregnancy. In this study, women who discontinued antidepressant therapy were found to be 5 times more likely to have a relapse of depression during their pregnancy than were women who continued to receive their antidepressant while pregnant, suggesting that pregnancy does not protect against a relapse of depression.

The second study suggests that infants exposed to SSRIs in late pregnancy may have an increased risk of persistent pulmonary hypertension of the newborn (PPHN), which is associated with substantial neonatal morbidity and mortality. PPHN occurs at a rate of 1–2 neonates per 1000 live births in the general population in the US. In this retrospective case-control study of 377 women whose infants were born with PPHN and 836 women whose infants were born healthy, the risk for developing persistent pulmonary hypertension of the newborn was approximately sixfold higher for infants exposed to SSRIs after the twentieth week of gestation compared with infants who had not been exposed to SSRIs during this period. The study was too small to compare the risk of PPHN associated with individual SSRIs, and the findings have not been confirmed. Although the risk of PPHN identified in this study still is low (6–12 cases per 1000) and further study is needed, the findings add to concerns from previous reports that infants exposed to SSRIs late in pregnancy may experience adverse effects.

Most epidemiologic studies of pregnancy outcome following first-trimester exposure to SSRIs, including sertraline, conducted to date have not revealed evidence of an increased risk of major congenital malformations. In a prospective, controlled, multicenter study, maternal use of several SSRIs (sertraline, fluvoxamine, paroxetine) in a limited number of pregnant women did not appear to increase the risk of congenital malformation, miscarriage, stillbirth, or premature delivery when used during pregnancy at recommended dosages. Birth weight and gestational age in neonates exposed to the drugs were similar to those in the control group. In another small study based on medical records review, the incidence of congenital anomalies reported in infants born to women who were treated with sertraline and other SSRIs during pregnancy was comparable to that observed in the general population. However, the results of epidemiologic studies indicate that exposure to paroxetine during the first trimester of pregnancy may increase the risk for congenital malformations, particularly cardiovascular malformations. (See Cautions: Pregnancy, Fertility, and Lactation, in Paroxetine 28:16.04.20.) Additional epidemiologic studies are needed to more thoroughly evaluate the relative safety of sertraline and other SSRIs during pregnancy, including their potential teratogenic risks and possible effects on neurobehavioral development.

The manufacturers state that there are no adequate and controlled studies to date using sertraline in pregnant women, and the drug should be used during pregnancy only when the potential benefits justify the possible risks to the fetus. Women should be advised to notify their physician if they become pregnant or plan to become pregnant during therapy with the drug. FDA states that women who are pregnant or thinking about becoming pregnant should not discontinue any antidepressant, including sertraline, without first consulting their clinician. The decision whether or not to continue antidepressant therapy should be made only after careful consideration of the potential benefits and risks of antidepressant therapy for each individual pregnant patient. If a decision is made to discontinue treatment with sertraline or other SSRIs before or during pregnancy, discontinuance of therapy should be done in consultation with the clinician in accordance with the prescribing information for the antidepressant and the patient should be closely monitored for possible relapse of depression.

Reproduction studies in rats using sertraline dosages up to 80 mg/kg daily and in rabbits using dosages up to 40 mg/kg daily have not revealed evidence of teratogenicity; these dosages correspond to approximately 4 times the maximum recommended human dosage on a mg/m^2 basis. No evidence of teratogenicity was observed at any dosage studied. When pregnant rats and rabbits were given sertraline during the period of organogenesis, delayed ossification was observed in fetuses at doses of 10 mg/kg (0.5 times the maximum recommended human dose on a mg/m^2 basis) in rats and 40 mg/kg (4 times the maximum recommended human dose on a mg/m^2 basis) in rabbits. When female rats received sertraline during the last third of gestation and throughout lactation, there was an increase in the number of stillborn pups and in the number of pups dying during the first 4 days after birth. The body weights of the pups also were decreased during the first 4 days after birth. These effects occurred at a dose of 20 mg/kg (approximately the same as the maximum recommended human dose on a mg/m^2 basis). At 10 mg/kg (0.5 times the maximum recommended human dose on a mg/m^2 basis), no effect on rat pup mortality was observed. The decrease in pup survival was shown to result from in utero exposure to the drug. The clinical importance of these effects is not known.

The effect of sertraline on labor and delivery is not known.

Fertility A decrease in fertility was observed in 1 of 2 reproduction studies in rats using sertraline dosages of 80 mg/kg (4 times the maximum recommended human dose on a mg/m^2 basis).

Lactation Sertraline and its principal metabolite, *N*-desmethylsertraline, are distributed into milk. Sertraline should be used with caution in nursing women, and women should be advised to notify their physician if they plan to breast-feed.

Drug Interactions

■ **Drugs Associated with Serotonin Syndrome** Use of selective serotonin-reuptake-inhibitors (SSRIs) such as sertraline concurrently or in close succession with other serotonergic drugs may result in serotonin syndrome. Symptoms of serotonin syndrome may include mental status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g., hyperreflexia, incoordination), and/or GI symptoms (e.g., nausea, vomiting, diarrhea). Although the syndrome appears to be relatively uncommon and usually mild in

severity, serious and potentially life-threatening complications, including seizures, disseminated intravascular coagulation, respiratory failure, and severe hyperthermia as well as death occasionally have been reported. The precise mechanism of the syndrome is not fully understood; however, it appears to result from excessive serotonergic activity in the CNS, probably mediated by activation of serotonin 5-HT_{1A} receptors. The possible involvement of dopamine and 5-HT_2 receptors also has been suggested, although their roles remain unclear.

Serotonin syndrome most commonly occurs when 2 or more serotonergic agents with different mechanisms of action are administered either concurrently or in close succession. Serotonergic agents include those that increase serotonin synthesis (e.g., the serotonin precursor tryptophan), stimulate synaptic serotonin release (e.g., some amphetamines, dexfenfluramine [no longer commercially available in the US], fenfluramine [no longer commercially available in the US]), inhibit the reuptake of serotonin after release (e.g., SSRIs, selective serotonin- and norepinephrine-reuptake inhibitors [SNRIs], tricyclic antidepressants, trazodone, dextromethorphan, meperidine, tramadol), decrease the metabolism of serotonin (e.g., MAO inhibitors), have direct serotonin postsynaptic receptor activity (e.g., buspirone), or nonspecifically induce increases in serotonergic neuronal activity (e.g., lithium salts). Selective agonists of serotonin (5-hydroxytryptamine; 5-HT) type 1 receptors ("triptans") and dihydroergotamine, agents with serotonergic activity used in the management of migraine headache, and St. John's wort also have been implicated in serotonin syndrome.

The combination of SSRIs and MAO inhibitors appears to be responsible for many of the reported cases of serotonin syndrome. The syndrome also has been reported in patients receiving SSRIs concomitantly with tryptophan, lithium, dextromethorphan, sumatriptan, or dihydroergotamine. In rare cases, serotonin syndrome reportedly has occurred in patients receiving the recommended dosage of a single serotonergic agent (e.g., clomipramine) or during accidental overdosage (e.g., sertraline intoxication in a child). Some other drugs that have been implicated in certain circumstances include buspirone, bromocriptine, dextropropoxyphene, methylenedioxymethamphetamine (MDMA; "ecstasy"), selegiline (a selective MAO-B inhibitor), and sibutramine (an SNRI used for the management of obesity). Other drugs that have been associated with the syndrome but for which less convincing data are available include carbamazepine, fentanyl, and pentazocine.

Clinicians should be aware of the potential for serious, possibly fatal reactions associated with serotonin syndrome in patients receiving 2 or more drugs that increase the availability of serotonin in the CNS, even if no such interactions with the specific drugs have been reported to date in the medical literature. Pending further accumulation of data, drugs with serotonergic activity should be used cautiously in combination and such combinations avoided whenever clinically possible. Serotonin syndrome may be more likely to occur when initiating therapy, increasing the dosage, or following the addition of another serotonergic drug. Some clinicians state that patients who have experienced serotonin syndrome may be at higher risk for recurrence of the syndrome upon reinitiation of serotonergic drugs. Pending further experience in such cases, some clinicians recommend that therapy with serotonergic agents be limited following recovery. In cases in which the potential benefit of the drug is thought to outweigh the risk of serotonin syndrome, lower potency agents and reduced dosages should be used, combination serotonergic therapy should be avoided, and patients should be monitored carefully for manifestations of serotonin syndrome.

For further information on serotonin syndrome, including manifestations and treatment, see Serotonin Syndrome under Drug Interactions: Drugs Associated with Serotonin Syndrome, in Fluoxetine Hydrochloride 28:16.04.20.

Monoamine Oxidase Inhibitors Concurrent use of selective serotonin-reuptake inhibitors and monoamine oxidase (MAO) inhibitors potentially is hazardous and may result in serotonin syndrome.

Serious, sometimes fatal, reactions have been reported in patients receiving sertraline in combination with an MAO inhibitor. Severe serotonin syndrome reaction developed several hours after initiating sertraline in a woman already receiving phenelzine, lithium, thioridazine, and doxepin. Such reactions also have been reported in patients who recently have discontinued a selective serotonin-reuptake inhibitor and have been started on an MAO inhibitor.

Because of the potential risk of serotonin syndrome, sertraline should not be used concomitantly with MAO inhibitors and at least 2 weeks should elapse between discontinuance of MAO inhibitor therapy and initiation of sertraline therapy and vice versa.

Linezolid Linezolid, an anti-infective agent that is a nonselective and reversible MAO inhibitor, has been associated with drug interactions resulting in serotonin syndrome and should therefore be used with caution in patients receiving sertraline.

Moclobemide Moclobemide (not commercially available in the US), a selective and reversible MAO-A inhibitor, has been associated with serotonin syndrome, and such reactions have been fatal in several cases in which the drug was given in combination with the selective serotonin-reuptake inhibitor citalopram or with clomipramine. Pending further experience with such combinations, some clinicians recommend that concurrent therapy with moclobemide and selective serotonin-reuptake inhibitors be used only with extreme caution and serotonin-reuptake inhibitors should have been discontinued for some time (depending on the elimination half-lives of the drug and its active metabolites) before initiating moclobemide therapy.

Selegiline Selegiline, a selective MAO-B inhibitor used in the management of parkinsonian syndrome, has been reported to cause serotonin syndrome when given concurrently with selective serotonin-reuptake inhibitors (e.g., fluoxetine, paroxetine, sertraline). Although selegiline is a selective MAO-B inhibitor at therapeutic dosages, the drug appears to lose its selectivity for the MAO-B enzyme at higher dosages (e.g., those exceeding 10 mg/kg), thereby increasing the risk of serotonin syndrome in patients receiving higher dosages of the drug either alone or in combination with other serotonergic agents. The manufacturer of selegiline recommends avoiding concurrent selegiline and selective serotonin-reuptake inhibitor therapy. In addition, the manufacturer of selegiline recommends that at least 2 weeks elapse between discontinuance of selegiline and initiation of selective serotonin-reuptake inhibitor therapy.

Isoniazid Isoniazid, an antituberculosis agent, appears to have some MAO-inhibiting activity. In addition, iproniazid (not commercially available in the US), another antituberculosis agent structurally related to isoniazid that also possesses MAO-inhibiting activity, reportedly has resulted in serotonin syndrome in at least 2 patients when given in combination with meperidine. Pending further experience, clinicians should be aware of the potential for serotonin syndrome when isoniazid is given in combination with selective serotonin-reuptake inhibitor therapy (such as sertraline) or other serotonergic agents.

5-HT_1 Receptor Agonists ("Triptans") Weakness, hyperreflexia, and incoordination have been reported rarely during postmarketing surveillance in patients receiving sumatriptan concomitantly with an SSRI (e.g., fluoxetine, fluvoxamine, paroxetine, sertraline). Oral or subcutaneous sumatriptan and SSRIs were used concomitantly in some clinical studies without unusual adverse effects. However, an increase in the frequency of migraine attacks and a decrease in the effectiveness of sumatriptan in relieving migraine headache have been reported in a patient receiving subcutaneous injections of sumatriptan intermittently while undergoing fluoxetine therapy.

Serotonin syndrome has been reported rarely during postmarketing surveillance in patients concurrently receiving 5-HT_1 receptor agonists (e.g., almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan, zolmitriptan) and SSRIs or selective serotonin- and norepinephrine-reuptake inhibitors (SNRIs). Clinicians prescribing 5-HT_1 receptor agonists, SSRIs, and SNRIs should consider that 5-HT_1 receptor agonists often are used intermittently and that either the 5-HT_1 receptor agonist, SSRI, or SNRI may be prescribed by a different clinician. Clinicians also should weigh the potential risk of serotonin syndrome with the expected benefit of using a 5-HT_1 receptor agonist concurrently with SSRI or SNRI therapy. If concomitant treatment with sumatriptan or another 5-HT_1 receptor agonist and citalopram is clinically warranted, the patient should be observed carefully, particularly during treatment initiation, dosage increases, and following the addition of other serotonergic agents. Patients receiving concomitant 5-HT_1 receptor agonist and SSRI or SNRI therapy should be informed of the possibility of serotonin syndrome and advised to immediately seek medical attention if they experience symptoms of this syndrome.

Selective Serotonin-reuptake Inhibitors and Selective Serotonin- and Norepinephrine-reuptake Inhibitors Because of the potential risk of serotonin syndrome, concurrent use of other SSRIs and SNRIs should be avoided in patients receiving sertraline.

Tryptophan and Other Serotonin Precursors Because of the potential risk of serotonin syndrome, concurrent use of tryptophan or other serotonin precursors should be avoided in patients receiving sertraline.

Other Serotonergic Drugs Because of the potential risk of serotonin syndrome, caution is advised whenever SSRIs, including sertraline, and SNRIs are concurrently administered with other drugs that may affect serotonergic neurotransmitter systems, including tramadol and St. John's wort.

■ **Drugs Undergoing Hepatic Metabolism or Affecting Hepatic Microsomal Enzymes** Animal studies have demonstrated that sertraline induces hepatic microsomal enzymes. In humans, microsomal enzyme induction by sertraline was minimal as determined by a small (5%) but statistically significant decrease in antipyrine half-life following sertraline administration (200 mg daily) for 21 days. The manufacturers state that this small change in antipyrine half-life reflects a clinically unimportant change in hepatic metabolism. Nonetheless, caution should be exercised when sertraline is given to patients receiving drugs that are hepatically metabolized and that have a low therapeutic ratio, such as warfarin. (See Anticoagulants under Drug Interactions: Protein-bound Drugs.)

Drugs Metabolized by Cytochrome P-450 (CYP) 2D6 Sertraline, like many other antidepressants (e.g., other selective serotonin-reuptake inhibitors, many tricyclic antidepressants) is metabolized by the drug-metabolizing cytochrome P-450 (CYP) 2D6 isoenzyme (debrisoquine hydroxylase). In addition, like many other drugs metabolized by CYP2D6, sertraline inhibits the activity of CYP2D6 and potentially may increase plasma concentrations of concomitantly administered drugs that also are metabolized by this isoenzyme. Although similar interactions are possible with other selective serotonin-reuptake inhibitors, there is considerable variability among the drugs in the extent to which they inhibit CYP2D6. At lower doses, sertraline has demonstrated a less prominent inhibitory effect on CYP2D6 than some other selective serotonin-reuptake inhibitors. Nevertheless, even sertraline has the potential for clinically important CYP2D6 inhibition.

Concomitant use of sertraline with other drugs metabolized by CYP2D6 has not been systematically studied. The extent to which this potential interaction may become clinically important depends on the extent of inhibition of CYP2D6 by the antidepressant and the therapeutic index of the concomitantly administered drug. The drugs for which this potential interaction is of greatest concern are those that are metabolized principally by CYP2D6 and have a narrow therapeutic index, such as tricyclic antidepressants, class IC antiarrhythmics (e.g., propafenone, flecainide, encainide), and some phenothiazines (e.g., thioridazine).

Caution should be used whenever concurrent therapy with sertraline and other drugs metabolized by CYP2D6 is considered. Because concomitant use of sertraline and thioridazine may result in increased plasma concentrations of the phenothiazine and increase the risk of serious, potentially fatal, adverse cardiac effects (e.g., cardiac arrhythmias), the manufacturer of thioridazine states that the drug should not be used concomitantly with any drug that inhibits the CYP2D6 isozyme. The manufacturers of sertraline state that concurrent use of a drug metabolized by CYP2D6 may necessitate the administration of dosages of the other drug that are lower than those usually prescribed. Furthermore, whenever sertraline therapy is discontinued (and plasma concentrations of sertraline are decreased) during concurrent therapy with another drug metabolized by CYP2D6, an increased dosage of the concurrently administered drug may be necessary.

Drugs Metabolized by Cytochrome P-450 (CYP) 3A4 Although sertraline can inhibit the cytochrome P-450 (CYP) 3A4 isoenzyme, results of in vitro and in vivo studies indicate that the drug is a much less potent inhibitor of this enzyme than many other drugs. In an in vivo drug interaction study, concomitant use of sertraline and the CYP3A4 substrate, carbamazepine, under steady-state conditions had no effect on plasma concentrations of carbamazepine. The manufacturers of sertraline state that these data suggest that the extent of sertraline's inhibition of CYP3A4 activity is unlikely to be of clinical importance. However, a marked increase in plasma concentrations (ranging from 80–250%) and bone marrow suppression developed within 1–2 months of initiating sertraline in a patient previously stabilized on carbamazepine and flecainide therapy. Although the precise mechanism for this possible interaction and the role of the cytochrome P-450 enzyme system are unclear, some clinicians recommend that carbamazepine concentrations be monitored during concomitant sertraline therapy.

Results of an in vivo drug interaction study with cisapride indicate that concomitant use of sertraline (200 mg daily) induces the metabolism of cisapride; peak plasma concentrations and area under the plasma concentration-time curve (AUC) of cisapride were decreased by about 35% in the study. However, the manufacturers of sertraline state that the extent of sertraline's inhibition of CYP3A4 activity is unlikely to be of clinical importance.

Results of another drug interaction study in which sertraline was used concomitantly with terfenadine (no longer commercially available in the US), a drug metabolized principally by the cytochrome P-450 microsomal enzyme system (mainly by the CYP3A4 isoenzyme), indicate that concurrent use of sertraline did not increase plasma concentrations of terfenadine and, therefore, the manufacturers state that these data suggest that the extent of sertraline's inhibition of CYP3A4 activity is unlikely to be of clinical importance. However, the manufacturer of astemizole (no longer commercially available in the US) and some clinicians state that until the clinical importance of these findings is established, concomitant use of sertraline with astemizole or terfenadine is not recommended since substantially increased plasma concentrations of unchanged astemizole or terfenadine could occur resulting in an increased risk of serious adverse cardiac effects.

■ **Tricyclic and Other Antidepressants** The extent to which selective serotonin-reuptake inhibitor interactions with tricyclic antidepressants may pose clinical problems depends on the degree of inhibition and the pharmacokinetics of the serotonin-reuptake inhibitor involved. In healthy individuals, sertraline has been shown to substantially reduce the clearance of two tricyclic antidepressants, desipramine and imipramine. This interaction appears to result from sertraline-induced inhibition of CYP2D6. Thus, the manufacturers and some clinicians recommend that caution be exercised during concurrent use of tricyclics with sertraline since sertraline may inhibit the metabolism of the tricyclic antidepressant. In addition, plasma tricyclic concentrations may need to be monitored and the dosage of the tricyclic reduced during concomitant administration. (See Drugs Metabolized by Cytochrome P-450 [CYP] 2D6 under Drug Interactions: Drugs Undergoing Hepatic Metabolism or Affecting Hepatic Microsomal Enzymes.)

Clinical experience regarding the optimal timing of switching from other antidepressants to sertraline therapy is limited. Therefore, the manufacturers recommend that care and prudent medical judgment be exercised when switching from other antidepressants to sertraline, particularly from long-acting agents (e.g., fluoxetine). Because some adverse reactions resembling serotonin syndrome have developed when fluoxetine therapy has been abruptly discontinued and sertraline therapy initiated immediately afterward, a washout period appears to be advisable when transferring a patient from fluoxetine to sertraline therapy. However, the appropriate duration of the washout period when switching from one selective serotonin-reuptake blocker to another has not been clearly established. Pending further experience in patients being transferred from therapy with another antidepressant to sertraline and as the clinical situation permits, it generally is recommended that the previous antidepressant be discontinued according to the recommended guidelines for the specific antidepressant prior to initiation of sertraline therapy. (See Drug Interactions: Drugs Associated with Serotonin Syndrome.)

■ **Protein-bound Drugs** Because sertraline is highly protein bound, the drug theoretically could be displaced from binding sites by, or it could displace from binding sites, other protein-bound drugs such as oral anticoagulants or digitoxin. In vitro studies to date have shown that sertraline has no effect on the protein binding of 2 other highly protein-bound drugs, propranolol or warfarin; these findings also have been confirmed in clinical studies. However, pending further accumulation of data, patients receiving sertraline concomitantly with any highly protein-bound drug should be observed for potential adverse effects associated with combined therapy.

■ **Drugs Affecting Hemostasis** ***Anticoagulants*** In a study comparing prothrombin time AUC (0–120 hour) following a dose of warfarin (0.75 mg/kg) or placebo prior to and after 21 days of either sertraline (50–200 mg daily) or placebo, prothrombin time increased by an average of 8% compared with baseline in the sertraline group and decreased by an average of 1% in those receiving placebo. In addition, the normalization of prothrombin time was slightly delayed in those receiving sertraline when compared with those receiving placebo. Because the clinical importance of these findings is not known, prothrombin time should be monitored carefully whenever sertraline therapy is initiated or discontinued in patients receiving anticoagulants.

Other Drugs That Interfere with Hemostasis Epidemiologic case-control and cohort design studies that have demonstrated an association between selective serotonin-reuptake inhibitor therapy and an increased risk of upper GI bleeding also have shown that concurrent use of aspirin or other nonsteroidal anti-inflammatory agents substantially increases the risk of GI bleeding. Although these studies focused on upper GI bleeding, there is some evidence suggesting that bleeding at other sites may be similarly potentiated. The precise mechanism for this increased risk remains to be clearly established; however, serotonin release by platelets is known to play an important role in hemostasis, and selective serotonin-reuptake inhibitors decrease serotonin uptake from the blood by platelets, thereby decreasing the amount of serotonin in platelets. Patients receiving sertraline should be cautioned about the concomitant use of drugs that interfere with hemostasis, including aspirin and other nonsteroidal anti-inflammatory agents.

■ **Alcohol** Sertraline administration did not potentiate the cognitive and psychomotor effects induced by alcohol in healthy individuals. In addition, no apparent additive CNS depressant effects were observed in geriatric patients receiving sertraline together with moderate amounts of alcohol. Nonetheless, the manufacturers state that concurrent use of sertraline and alcohol is not recommended.

■ **Electroconvulsive Therapy** The effects of sertraline in conjunction with electroconvulsive therapy (ECT) have not been evaluated to date in clinical studies.

■ **Cimetidine** In a study evaluating the effect of the addition of a single dose of sertraline (100 mg) on the second of 8 days of cimetidine administration (800 mg daily), the mean AUC, peak concentration, and elimination half-life of sertraline increased substantially (by 50, 24, and 26%, respectively) compared with the placebo group. The clinical importance of these changes is unknown.

■ **Benzodiazepines** In a study comparing the disposition of diazepam administered IV before and after 21 days of sertraline therapy (dosage titrated from 50–200 mg daily) or placebo, there was a 32% decrease in diazepam clearance in the sertraline recipients and a 19% decrease in those receiving placebo when compared with baseline. There was a 23% increase in the time to maximal plasma concentration for desmethyldiazepam in the sertraline group compared with a 20% decrease in the placebo group. The clinical importance of these findings is unknown; however, they suggest that sertraline and *N*-desmethylsertraline are not likely to inhibit substantially the CYP2C19 and CYP3A3/4 hepatic isoenzymes involved in the metabolism of diazepam.

■ **Clozapine** Concomitant use of selective serotonin-reuptake inhibitors such as sertraline in patients receiving clozapine can increase plasma concentrations of the antipsychotic agent. In a study in schizophrenic patients receiving clozapine under steady-state conditions, initiation of paroxetine therapy resulted in only minor changes in plasma concentrations of clozapine and its metabolites; however, initiation of fluvoxamine therapy resulted in increases that were threefold compared with baseline. In other published reports, concomitant use of clozapine and selective serotonin reuptake-inhibitors (fluvoxamine, paroxetine, sertraline) resulted in modest increases (less than twofold) in clozapine and metabolite concentrations. The manufacturer of clozapine states that caution should be exercised and patients closely monitored if clozapine is used in patients receiving selective serotonin-reuptake inhibitors, and a reduction in clozapine dosage should be considered.

■ **Lithium** In a placebo-controlled trial, the administration of 2 doses of sertraline did not substantially alter steady-state plasma lithium concentrations or the renal clearance of lithium. Pending further accumulation of data, however, the manufacturers recommend that plasma lithium concentrations be monitored following initiation of sertraline in patients receiving lithium and that lithium dosage be adjusted accordingly. In addition, because of the potential risk of serotonin syndrome, caution is advised during concurrent sertraline and lithium use.

■ **Hypoglycemic Drugs** In a placebo-controlled study in healthy male volunteers, sertraline administration for 22 days (including 200 mg daily for the final 13 days) caused a small but statistically significant decrease (16%) in the clearance of a 1-g IV dose of tolbutamide compared with baseline values and an increase in the terminal elimination half-life (from 6.9 to 8.6 hours). The decrease in clearance was not accompanied by any substantial changes in the plasma protein binding or the apparent volume of distribution of tolbutamide, which suggests that the change in tolbutamide clearance may be caused by a slight inhibition of the cytochrome P-450 isoenzyme CYP2C9/10 when sertraline is given in the maximum recommended dosage. The clinical importance of these findings remains to be determined.

■ **Digoxin** In a placebo-controlled trial in healthy volunteers, sertraline administration for 17 days (including 200 mg daily for the final 10 days) did not alter serum digoxin concentrations or renal clearance of digoxin. The results of this study suggest that dosage adjustment of digoxin may not be necessary in patients receiving concomitant sertraline.

■ **Atenolol** In a double-blind, placebo-controlled, randomized, crossover study, a single, 100-mg dose of sertraline had no effect on the β-adrenergic blocking activity of atenolol when administered to a limited number of healthy males.

■ **Amiodarone** A decrease in the plasma concentrations of amiodarone and its active metabolite, desmethylamiodarone, to 82 and 85% of the baseline values, respectively, occurred in one patient following the discontinuance of sertraline and carbamazepine therapy, suggesting that sertraline may have been inhibiting the metabolism of amiodarone by CYP3A4.

■ **Phenytoin** In a randomized, double-blind, placebo-controlled trial, chronic administration of high dosages of sertraline (200 mg daily) did not substantially affect the pharmacokinetics or pharmacodynamics of phenytoin when the 2 drugs were given concurrently in healthy volunteers. However, substantial reductions in plasma sertaline concentrations have been observed in sertraline-treated patients concurrently receiving phenytoin; it was suggested that induction of the cytochrome P-450 isoenzymes may be responsible. In addition, concurrent administration of sertraline and phenytoin reportedly resulted in elevated phenytoin concentrations in 2 geriatric patients. Pending further accumulation of data, the manufacturers and some clinicians recommend that plasma phenytoin concentrations be monitored following initiation of sertraline therapy and that phenytoin dosage should be adjusted as necessary, particularly in patients with multiple underlying medical conditions and/or those receiving multiple concomitant drugs.

■ **Pimozide** Concomitant use of sertraline and pimozide has resulted in substantial increases in peak plasma concentrations and area under the plasma concentration-time curve (AUC) of pimozide. In one controlled study, administration of a single 2-mg dose of pimozide in individuals receiving sertraline 200 mg daily resulted in a mean increase in pimozide AUC and peak plasma concentrations of about 40%, but was not associated with changes in ECG parameters. The effect on QT interval and pharmacokinetic parameters of pimozide administered in higher doses (i.e., doses exceeding 2 mg) in combination with sertraline are as yet unknown. Concomitant use of sertraline and pimozide is contraindicated because of the low therapeutic index of pimozide and because the reported interaction between the 2 drugs occurred at a low dose of pimozide. The mechanism of this interaction is as yet unknown.

■ **Valproic Acid** The effect of sertraline on plasma valproic acid concentrations remains to be evaluated in clinical studies. In the absence of such data, the manufacturers recommend monitoring plasma valproic acid concentrations following initiation of sertraline therapy and adjusting the dosage of valproic acid as necessary.

Acute Toxicity

■ **Pathogenesis** The acute lethal dose of sertaline in humans is not known. One patient who ingested 13.5 g of sertraline alone subsequently recovered. However, death occurred in another patient who ingested 2.5 g of the drug alone.

In general, overdosage of sertraline may be expected to produce effects that are extensions of the drug's pharmacologic and adverse effects. The most common signs and symptoms associated with nonfatal sertraline overdosage include somnolence, nausea, vomiting, tachycardia, dizziness, agitation, and tremor. Other adverse events observed in patients who received overdosages of sertraline (alone or in combination with other drugs) include bradycardia, bundle branch block, coma, seizures, delirium, hallucinations, hypertension, hypotension, manic reaction, pancreatitis, QT-interval prolongation, serotonin syndrome, stupor, and syncope. Prolonged tachycardia, hypertension, hallucinations, hyperthermia, tremors of the extremities, and skin flushing have occurred in a child after accidental sertraline ingestion; the reaction resembled serotonin syndrome. Flushing, anger, emotional lability, and distractability developed 1 hour after an adult female ingested 2 g of sertraline; recovery was uneventful apart from watery bowel movements.

■ **Treatment** Because fatalities and severe toxicity have been reported when sertraline was ingested alone or in combination with other drugs and/or alcohol, the manufacturers and some clinicians recommend that any overdosage involving sertraline be managed aggressively. Clinicians also should consider the possibility of serotonin syndrome in patients presenting with similar clinical features and a recent history of sertraline and/or ingestion of other serotonergic agents. (See Drug Interactions: Drugs Associated with Serotonin Syndrome.)

Management of sertraline overdosage generally involves symptomatic and supportive care. A patent airway should be established and maintained, and adequate oxygenation and ventilation should be ensured. ECG and vital sign monitoring is recommended following acute overdosage with the drug, although the value of ECG monitoring in predicting the severity of sertraline-induced cardiotoxicity is not known. (See Acute Toxicity: Manifestations, in the Tricyclic Antidepressants General Statement 28:16.04.28.) There is no specific antidote for sertraline intoxication. Because suicidal ingestion often involves more than one drug, clinicians treating sertraline overdosage should be alert to possible manifestations caused by drugs other than sertraline.

If the patient is comatose, having seizures, or lacks the gag reflex, gastric lavage may be performed if an endotracheal tube with cuff inflated is in place to prevent aspiration of gastric contents. Since administration of activated charcoal (which may be used in conjunction with sorbitol) may be as effective as or more effective than induction of emesis or gastric lavage, its use has been recommended either in the initial management of sertraline overdosage or following induction of emesis or gastric lavage in patients who have ingested a potentially toxic quantity of the drug.

Limited data indicate that sertraline is not appreciably removed by hemodialysis. Because of the large volume of distribution of sertraline and its principal metabolite, peritoneal dialysis, forced diuresis, hemoperfusion, and/or exchange transfusion also are likely to be ineffective in removing substantial amounts of sertraline and *N*-desmethylsertraline from the body.

Clinicians should consult a poison control center for additional information on the management of sertraline overdosage.

Chronic Toxicity

Sertraline has not been studied systematically in animals or humans to determine whether therapy with the drug is associated with abuse, tolerance, or physical dependence.

The premarketing clinical experience with sertraline did not reveal any tendency for a withdrawal syndrome or any drug-seeking behavior. However, fatigue, severe abdominal cramping, memory impairment, and influenza-like symptoms were reported 2 days following abrupt discontinuance of sertraline in one patient; when sertraline was restarted, the symptoms remitted. Electric shock-like sensations occurred in another patient 1 day after the last administered dose of sertraline; these sensations became less intense and eventually disappeared 13 weeks after sertraline therapy was discontinued. When evaluating these cases and those reported with other serotonin-reuptake inhibitors, it appears that a withdrawal syndrome may occur within several days following abrupt discontinuance of these drugs. The most commonly observed symptoms are those that resemble influenza, such as fatigue, stomach complaints (e.g., nausea), dizziness or lightheadedness, tremor, anxiety, chills, sweating, and incoordination. Other reported symptoms include memory impairment, insomnia, paresthesia, shock-like sensations, headache, palpitations, agitation, or aggression. Such reactions appear to be self-limiting and improve over 1 to several weeks. Pending further experience, sertraline therapy should be discontinued gradually to prevent the possible development of withdrawal reactions.

As with other CNS-active drugs, clinicians should carefully evaluate patients for a history of substance abuse prior to initiating sertraline therapy. If sertraline therapy is initiated in patients with a history of substance abuse, such patients should be monitored closely for signs of misuse or abuse of the drug (e.g., development of tolerance, use of increasing doses, drug-seeking behavior).

The potential for misuse of sertraline in patients with concurrent eating disorders and/or those who may seek the drug for its appetite-suppressant effects also may be considered.

Pharmacology

The pharmacology of sertraline is complex and in many ways resembles that of other antidepressant agents, particularly those agents (e.g., fluoxetine, fluvoxamine, paroxetine, clomipramine, trazodone) that predominantly potentiate the pharmacologic effects of serotonin (5-HT). Like other selective serotonin-reuptake inhibitors (SSRIs), sertraline is a potent and highly selective reuptake inhibitor of serotonin and has little or no effect on other neurotransmitters.

■ **Nervous System Effects** The precise mechanism of antidepressant action of sertraline is unclear, but the drug has been shown to selectively inhibit the reuptake of serotonin at the presynaptic neuronal membrane. Sertraline-induced inhibition of serotonin reuptake causes increased synaptic concentrations of serotonin in the CNS, resulting in numerous functional changes associated with enhanced serotonergic neurotransmission. Like other selective serotonin-reuptake inhibitors (e.g., fluoxetine, fluvoxamine, paroxetine), sertraline appears to have only very weak effects on the reuptake of norepinephrine or dopamine and does not exhibit clinically important anticholinergic, antihistaminic, or adrenergic (α_1, α_2, β) blocking activity at usual therapeutic dosages.

Although the mechanism of antidepressant action of antidepressant agents may involve inhibition of the reuptake of various neurotransmitters (i.e., se-

rotonin, norepinephrine) at the presynaptic neuronal membrane, it has been suggested that postsynaptic receptor modification is mainly responsible for the antidepressant action observed during long-term administration of antidepressant agents. During long-term therapy with most antidepressants (e.g., tricyclic antidepressants, monoamine oxidase [MAO] inhibitors), these adaptive changes mainly consist of subsensitivity of the noradrenergic adenylate cyclase system in association with a decrease in the number of β-adrenergic receptors; such effects on noradrenergic receptor function are commonly referred to as "down regulation." In animal studies, long-term administration of sertraline has been shown to downregulate noradrenergic receptors in the CNS as has been observed with many other clinically effective antidepressants. In addition, some antidepressants (e.g., amitriptyline) reportedly decrease the number of serotonergic (5-HT) binding sites following chronic administration. Although changes in the density of type 2 serotonergic (5-HT_2) binding sites were not observed during chronic administration of sertraline in animals in one study, the drug caused desensitization of the 5-HT_2 receptor transmembrane signaling system; the clinical importance of these findings requires further study.

The precise mechanism of action that is responsible for the efficacy of sertraline in the treatment of obsessive-compulsive disorder is unclear. However, because of the potency of clomipramine and other selective serotonin-reuptake inhibitors (e.g., fluoxetine, fluvoxamine, paroxetine) in inhibiting serotonin reuptake and their efficacy in the treatment of obsessive-compulsive disorder, a serotonin hypothesis has been developed to explain the pathogenesis of the condition. The hypothesis postulates that a dysregulation of serotonin is responsible for obsessive-compulsive disorder and that sertraline and these other agents are effective because they correct this imbalance. Although the available evidence supports the serotonergic hypothesis of obsessive-compulsive disorder, additional studies are necessary to confirm this hypothesis.

Serotonergic mechanisms also appear to be involved at least in part in a number of other pharmacologic effects associated with selective serotonin-reuptake inhibitors, including sertraline, such as decreased food intake and altered food selection as well as decreased alcohol intake.

Serotonergic Effects Sertraline is a highly selective inhibitor of serotonin reuptake at the presynaptic neuronal membrane. Sertraline-induced inhibition of serotonin reuptake causes increased synaptic concentrations of the neurotransmitter, resulting in numerous functional changes associated with enhanced serotonergic neurotransmission.

Data from in vitro studies suggest that sertraline is more potent than fluvoxamine, fluoxetine, or clomipramine as a serotonin-reuptake inhibitor. Like some other serotonin-reuptake inhibitors, sertraline undergoes metabolism via *N*-demethylation to form *N*-desmethylsertraline, the principal metabolite. Data from in vivo and in vitro studies have shown that *N*-desmethylsertraline is approximately 5–10 times less potent as an inhibitor of serotonin reuptake than sertraline; however, the metabolite retains selectivity for serotonin reuptake compared with either norepinephrine or dopamine reuptake.

At therapeutic dosages (50–200 mg daily) in healthy individuals, sertraline has been shown to inhibit the reuptake of serotonin into platelets in a dose-dependent manner. Like other serotonin-reuptake inhibitors, sertraline inhibits the spontaneous firing of serotonergic neurons in the dorsal raphe nucleus. In vitro data have demonstrated that sertraline has substantial affinity for serotonergic (5-HT_{1A}, 5-HT_{1B}, 5-HT_2) receptors.

Effects on Other Neurotransmitters Like other serotonin-reuptake inhibitors, sertraline has been shown to have little or no activity in inhibiting the reuptake of norepinephrine. In addition, the drug has demonstrated a substantially higher selectivity ratio of serotonin-to-norepinephrine reuptake inhibiting activity than fluoxetine or tricyclic antidepressant agents, including clomipramine.

Although sertraline has only weak activity in inhibiting the reuptake of dopamine, the relative selectivity of sertraline for inhibiting serotonin reuptake relative to dopamine reuptake appears to be somewhat less than that of fluoxetine, fluvoxamine, zimelidine, or clomipramine. In addition, sertraline does not inhibit monoamine oxidase.

Unlike tricyclic and some other antidepressants, sertraline does not exhibit clinically important anticholinergic, α- or β-adrenergic blocking, or antihistaminic activity at usual therapeutic dosages. As a result, the incidence of adverse effects commonly associated with blockade of muscarinic cholinergic receptors (e.g., dry mouth, blurred vision, urinary retention, constipation, confusion), α-adrenergic receptors (e.g., orthostatic hypotension), and histamine H_1- and H_2-receptors (e.g., sedation) is lower in sertraline-treated patients. In vitro studies have demonstrated that sertraline does not possess clinically important affinity for α_1- or α_2-adrenergic, β-adrenergic, histaminergic, muscarinic, GABA, benzodiazepine, or dopamine receptors.

Effects on Sleep Like tricyclic and most other antidepressants, sertraline suppresses rapid eye movement (REM) sleep. Although not clearly established, there is some evidence that the REM-suppressing effects of antidepressant agents may contribute to the antidepressant activity of these drugs. In animal studies, sertraline suppressed REM sleep; the drug appears to reduce the amount of REM sleep by decreasing the number as well as the duration of REM episodes. Although the precise mechanism has not been fully elucidated, results of animal studies indicate that sertraline's effects on REM sleep are serotonergically mediated.

Effects on EEG Limited data currently are available regarding the effects of sertraline on the EEG. EEG changes in healthy individuals receiving single, 100-mg doses of sertraline resembled the EEG profiles of patients receiving desipramine-type antidepressants (increased alpha and decreased but accelerated delta activity) and suggest improved vigilance and psychometric performance. In individuals receiving higher single doses (200 and 400 mg) of the drug, sertraline produced EEG changes similar to imipramine-type antidepressants (reduced alpha and low beta activity and increased theta and fast beta activity), which reflect vigilance changes of the dissociative type and therefore possible sedative activity.

Effects on Psychomotor Function Sertraline does not appear to cause clinically important sedation and does not interfere with psychomotor performance. The drug did not appear to have any adverse effects on psychomotor performance when given to healthy women in single doses up to 100 mg. In healthy individuals over 50 years of age, single, 100-mg doses of sertraline increased the critical flicker fusion frequency slightly and the subjective perception of sedation; however, the drug had no depressant effect on objective tests of psychomotor performance. In addition, no adverse effects on psychomotor performance were observed in geriatric individuals who received the drug in a controlled study.

■ **Cardiovascular Effects** Sertraline appears to have little effect on the ECG. Data from controlled studies indicate sertraline does not produce clinically important changes in heart rate, cardiac conduction, or other ECG parameters in depressed patients.

■ **Effects on Appetite and Body Weight** Like some other serotonergic agents (e.g., fenfluramine [no longer commercially available in the US], fluoxetine, zimelidine), sertraline possesses anorexigenic activity. Limited data from animal studies suggest that fenfluramine has been the most effective inhibitor of food intake followed by fluoxetine and then sertraline. Although the precise mechanism has not been clearly established, results from animal studies indicate that sertraline's appetite-inhibiting action may result at least in part from serotonin-reuptake blockade and the resultant increase in serotonin availability at the neuronal synapse. Because sertraline's anorexigenic activity was not antagonized by prior administration of serotonergic antagonists, other mechanisms also may be involved but require further study. Following administration of single doses of sertraline in meal-fed animals, food intake was reduced in a dose-dependent manner. At a dose of 3 mg/kg, the reduction in food intake was substantially reduced and higher doses of 10 or 30 mg/kg reduced food intake by 45 or 74%, respectively.

Sertraline therapy has resulted in dose-dependent decreases in body weight in animals receiving the drug for 3 days; the weight loss was not accompanied by any overt signs of behavioral abnormality. Sertraline therapy also has resulted in decreases in body weight in individuals receiving the drug. However, weight loss is usually minimal and averaged about 0.45–0.9 kg in individuals treated with the drug in controlled clinical trials. (See Cautions: Metabolic Effects and see also Cautions: Pediatric Precautions.) Rarely, weight loss has required discontinuance of therapy.

■ **Effects on Alcohol Intake** Like some other serotonergic agents, sertraline produces a substantial decrease in voluntary alcohol intake in animals. Because serotonin appears to be involved in the regulation of alcohol intake, it has been suggested that selective serotonin-reuptake inhibitors may attenuate alcohol consumption via enhanced serotonergic neurotransmission. (See Cautions.)

■ **Neuroendocrine Effects** Limited data currently are available regarding the effects of sertraline on the endocrine system. In one animal study, sertraline did not demonstrate substantial neuroendocrine effects at a dose that substantially reduced gross activity.

Although a causal relationship has not been established, hypothyroidism, decreased serum thyroxine concentrations, and/or increased serum thyrotropin (thyroid-stimulating hormone, TSH) concentrations have been reported in a limited number of sertraline patients, some of whom were receiving thyroxine concurrently. (See Cautions: Other Adverse Effects and also see Precautions and Contraindications.)

■ **Other Effects** Sertraline appears to have a weak uricosuric effect; mean decreases in serum uric acid of approximately 7% have been reported in patients receiving the drug. The clinical importance of these findings is unknown, and there have been no reports of acute renal failure associated with the drug. (See Cautions: Precautions and Contraindications.)

Pharmacokinetics

In all human studies described in the Pharmacokinetics section, sertraline was administered as the hydrochloride salt; dosages and concentrations are expressed in terms of sertraline.

■ **Absorption** Sertraline appears to be slowly but well absorbed from the GI tract following oral administration. The oral bioavailability of sertraline in humans has not been fully elucidated to date because a preparation for IV administration is not available. However, the relative proportion of an oral dose that reaches systemic circulation unchanged appears to be relatively small because sertraline undergoes extensive first-pass metabolism. In animals, the oral bioavailability of sertraline ranges from 22–36%. The manufacturers state that the bioavailability of a single dose of sertraline hydrochloride tablets is ap-

proximately equal to that of an equivalent dose of sertraline hydrochloride oral solution. In a study in healthy adults who received a single 100-mg dose of sertraline as a tablet or oral solution, the solution to tablet ratios of the mean geometric AUC and peak plasma concentration were 114.8 and 120.6%, respectively.

The effect of food on the absorption of sertraline hydrochloride given as tablets or the oral solution has been studied in single-dose studies. Administration of a sertraline hydrochloride tablet with food slightly increased the area under the concentration-time curve (AUC) of sertraline, increased peak plasma concentrations by approximately 25%, and decreased the time to achieve peak plasma concentrations from about 8 to 5.5 hours. Administration of sertraline hydrochloride oral solution with food increased the time to achieve peak plasma concentrations from 5.9 to 7.0 hours.

Peak plasma sertraline concentrations usually occur within 4.5–8.4 hours following oral administration of 50–200 mg once daily for 14 days. Peak plasma sertraline concentrations following administration of single oral doses of 50–200 mg are proportional and linearly related to dose. Peak plasma concentrations and bioavailability are increased in geriatric individuals.

Following multiple dosing, steady-state plasma sertraline concentrations should be achieved after approximately 1 week of once-daily dosing. When compared with a single dose, there is an approximate twofold accumulation of sertraline after multiple daily dosing in dosages ranging from 50–200 mg daily. *N*-Desmethylsertraline, sertraline's principal metabolite, exhibits time-related, dose-dependent increases in AUC (0–24 hour), peak plasma concentrations, and trough plasma concentrations with about a 5- to 9-fold increase in these parameters between day 1 and 14.

As with other serotonin-reuptake inhibitors, the relationship between plasma sertraline and *N*-desmethylsertraline concentrations and the therapeutic and/or toxic effects of the drug has not been clearly established.

■ **Distribution** Distribution of sertraline and its metabolites into human body tissues and fluids has not been fully characterized. However, limited pharmacokinetic data suggest that the drug and some of its metabolites are widely distributed in body tissues. Although the apparent volume of distribution of sertraline has not been determined in humans, values exceeding 20 L/kg have been reported in rats and dogs. The drug crosses the blood-brain barrier in humans and animals.

At in vitro plasma concentrations ranging from 20–500 ng/mL, sertaline is approximately 98% bound to plasma proteins, principally to albumin and α_1-acid glycoprotein. Protein binding is independent of plasma concentrations from 20–2000 mcg/mL. However, sertraline and *N*-desmethylsertraline did not alter the plasma protein binding of 2 other highly protein bound drugs, warfarin or propranolol, at concentrations of 300 and 200 ng/mL, respectively.

Sertraline and *N*-desmethylsertraline are distributed into milk. In a study involving 12 lactating women who received oral dosages of sertraline ranging from 25–200 mg daily, both sertraline and *N*-desmethylsertraline were present in all breast milk samples, with the highest concentrations observed in hind milk 7–10 hours after the maternal dose. Detectable concentrations of sertraline were found in 3 and *N*-desmethylsertraline in 6, respectively, out of 11 nursing infants.

■ **Elimination** The elimination half-life of sertraline averages approximately 25–26 hours and that of desmethylsertraline averages about 62–104 hours. In geriatric adults elimination half-life may be increased (e.g., to about 36 hours); however, such prolongation does not appear clinically important and does not warrant dosing alterations.

The exact metabolic fate of sertraline has not been fully elucidated. Sertraline appears to be extensively metabolized, probably in the liver, to *N*-desmethylsertraline and several other metabolites. Like some other serotonin-reuptake inhibitors, sertraline undergoes metabolism via *N*-demethylation to form *N*-desmethylsertraline, the principal metabolite. Unlike some other serotonin-reuptake inhibitors, the drug metabolizing isoenzyme CYP2D6 (a cytochrome P-450 isoenzyme implicated in the sparteine/debrisoquine polymorphism) does not appear to have a major role in the conversion of sertraline to *N*-desmethylsertraline. Nonetheless, sertraline has the potential for clinically important inhibition of this enzyme. (See Drug Interactions: Drugs Undergoing Hepatic Metabolism or Affecting Hepatic Microsomal Enzymes.) In vitro, the conversion of sertraline to *N*-desmethylsertraline correlates more with CYP3A3/4 activity than with CYP2D6 activity. Data from in vivo and in vitro studies have shown that *N*-desmethylsertraline is approximately 5–10 times less potent as an inhibitor of serotonin reuptake than sertraline; however, the metabolite retains selectivity for serotonin reuptake compared with either norepinephrine or dopamine reuptake. Both sertraline and desmethylsertraline undergo oxidative deamination and subsequent reduction, hydroxylation, and glucuronide conjugation. Desmethylsertraline has an elimination half-life approximately 2.5 times that of sertraline.

Following oral administration, sertraline and its metabolites are excreted in both urine and feces. Following oral administration of a single, radiolabeled dose in 2 healthy males, unchanged sertraline accounted for less than 5% of plasma radioactivity. Approximately 40–45% of the radiolabeled dose was excreted in urine within 9 days. Unchanged sertraline was not detectable in urine. During the same period, approximately 40–45% of the radiolabeled drug was eliminated in feces, including 12–14% of unchanged sertraline.

The effect of age on the elimination of sertraline has not been fully elucidated. Plasma clearance of sertaline was approximately 40% lower in a group of 16 geriatric patients (8 males and 8 females) who received 100 mg of the drug for 14 days than that reported in a similar study involving younger individuals (from 25–32 years of age). Based on these results, the manufacturers state that steady-state should be achieved in about 2–3 weeks in older individuals. In addition, decreased clearance of *N*-desmethylsertraline was noted in older males but not in older females.

Because sertraline is extensively metabolized by the liver, hepatic impairment can affect the elimination of the drug. In one study in patients with chronic mild hepatic impairment (Child-Pugh scores of 5–8) who received 50 mg of sertraline daily for 21 days, sertraline clearance was reduced resulting in a 2–3 times greater exposure to the drug and its metabolite (desmethylsertraline) than that reported for age-matched individuals without hepatic impairment. In a single-dose study in patients with mild, stable cirrhosis, the elimination half-life of sertraline was prolonged to a mean of 52 hours compared with 22 hours in individuals without hepatic disease. In addition, peak plasma concentrations and AUC values for sertraline were 1.7- and 4.4-fold higher, respectively, in patients with hepatic impairment when compared with healthy individuals without liver disease, reflecting decreased clearance of the drug. The pharmacokinetics of sertraline have not been studied to date in patients with moderate and severe hepatic impairment; therefore, the manufacturers recommend that sertraline be administered with caution and in reduced dosage or less frequently in patients with hepatic impairment. (See Cautions: Precautions and Contraindications and see Dosage and Administration: Dosage in Renal and Hepatic Impairment.)

Because sertraline is extensively metabolized in the liver and renal clearance of the drug is negligible, the manufacturers state that clinically important decreases in sertraline clearance are not anticipated if the drug is used in patients with renal impairment. Results of a multiple-dose study indicate that the pharmacokinetics of sertraline are not affected by renal impairment. In this study, individuals with mild to moderate renal impairment (creatinine clearance: 30–60 mL/minute), moderate to severe renal impairment (creatinine clearance: 10–29 mL/minute), or severe renal impairment (undergoing hemodialysis) received 200 mg of sertraline daily for 21 days; the pharmacokinetics and protein binding of the drug in these patients were similar to those reported for age-matched individuals without renal impairment. (See Cautions: Precautions and Contraindications and see Dosage and Administration: Dosage in Renal and Hepatic Impairment.)

Limited data indicate that sertraline is not appreciably removed by hemodialysis. Because of the large volume of distribution of sertraline and its principal metabolite, peritoneal dialysis, forced diuresis, hemoperfusion, and/or exchange transfusion also are likely to be ineffective in removing substantial amounts of sertraline and *N*-desmethylsertraline from the body.

Chemistry and Stability

■ **Chemistry** Sertraline, a selective serotonin-reuptake inhibitor antidepressant agent, is a naphthalenamine (naphthylamine)-derivative. Sertraline differs structurally from other selective serotonin-reuptake inhibitor antidepressants (e.g., citalopram, fluoxetine, paroxetine) and also differs structurally and pharmacologically from other currently available antidepressants (e.g., tricyclic antidepressants, monoamine oxidase inhibitors). Like most other serotonin-reuptake inhibitors, sertraline contains an asymmetric carbon; therefore, there are 2 existing optical isomers of the drug. However, only one of the optical isomers is present in the commercially available form of the drug.

Sertraline is commercially available as the hydrochloride salt, which occurs as a white, crystalline powder that is slightly soluble in water and isopropyl alcohol and sparingly soluble in ethanol. Commercially available sertraline hydrochloride oral solution is a clear, colorless solution with a menthol scent containing 20 mg of sertraline per mL and 12% alcohol.

■ **Stability** Commercially available sertraline hydrochloride tablets and oral solution should be stored at 25°C, but may be exposed to temperatures ranging from 15–30°C. Sertraline hydrochloride oral solution should be diluted only in the liquids specified by the manufacturer, and should be used immediately after dilution.

Preparations

Excipients in commercially available drug preparations may have clinically important effects in some individuals; consult specific product labeling for details.

Sertraline Hydrochloride

Oral		
For solution, concentrate	20 mg (of sertraline) per mL*	**Sertraline Hydrochloride Oral Solution** **Zoloft®** (with calibrated dropper dispenser containing latex rubber), Pfizer
Tablets, film-coated	25 mg (of sertraline)*	**Sertraline Hydrochloride Tablets** **Zoloft®** (scored), Pfizer
	50 mg (of sertraline)*	**Sertraline Hydrochloride Tablets** **Zoloft®** (scored), Pfizer

100 mg (of sertraline)*	**Sertraline Hydrochloride Tablets**
	Zoloft® (scored), Pfizer
150 mg (of sertraline)*	**Sertraline Hydrochloride Tablets,** Ranbaxy
200 mg (of sertraline)*	**Sertraline Hydrochloride Tablets,** Ranbaxy

*available from one or more manufacturer, distributor, and/or repackager by generic (nonproprietary) name
†Use is not currently included in the labeling approved by the US Food and Drug Administration

SEROTONIN MODULATORS 28:16.04.24

Nefazodone Hydrochloride

■ Nefazodone is a phenylpiperazine-derivative antidepressant agent that differs chemically and pharmacologically from selective serotonin-reuptake inhibitors, monoamine oxidase inhibitors, and tricyclic and tetracyclic antidepressant agents.

Uses

■ **Major Depressive Disorder** Nefazodone is used in the treatment of major depressive disorder. Because of the risk of hepatic failure associated with nefazodone therapy, it may be appropriate to reserve the drug for patients whose disease fails to respond adequately to appropriate courses of other antidepressants. (See Hepatic Precautions under Dosage and Administration: Administration.) Efficacy of nefazodone for the management of major depression has been established by controlled studies of 6–8 weeks' duration, principally in patients with major depressive episodes of at least moderate severity, in outpatient settings. Most clinical studies have shown that the antidepressant effect of usual dosages of nefazodone in patients with moderate to severe depression is greater than placebo and comparable to that of usual dosages of tricyclic antidepressants. In these studies, no gender-related differences in safety or efficacy were noted. In addition, nefazodone has been evaluated in controlled trials of 6 weeks' duration in a hospital setting in patients who had major depression and, in most cases, melancholia. The safety and efficacy of nefazodone for relapse prevention also have been demonstrated in controlled trials of up to 36 weeks' duration in patients who responded to an initial 16-week course of treatment with the drug for major depression. For further information on treatment of major depressive disorder and considerations in choosing the most appropriate antidepressant for a particular patient, including considerations related to patient tolerance, patient age, and cardiovascular, sedative, and suicidal risks, see Considerations in Choosing Antidepressants under Uses: Major Depressive Disorder, in Fluoxetine Hydrochloride 28:16.04.20.

As with other antidepressants, the possibility that nefazodone may precipitate hypomanic or manic attacks in patients with bipolar or other major affective disorder should be considered.

Dosage and Administration

■ **Administration** Nefazodone hydrochloride is administered orally, usually in 2 equally divided doses daily. Concomitant administration of nefazodone and food delays absorption and decreases bioavailability of the drug by about 20%. However, the manufacturer states that this effect is unlikely to be clinically important and that nefazodone generally can be given orally without regard to meals.

Although the effects of concomitant use of nefazodone and monoamine oxidase (MAO) inhibitors have not been evaluated in humans or animals, serious (sometimes fatal) reactions related to serotonin syndrome have occurred in patients receiving MAO inhibitors concomitantly with other antidepressants that have pharmacologic properties similar to nefazodone (e.g., selective serotonin-reuptake inhibitors). Therefore, nefazodone should not be used concomitantly with MAO inhibitors and it is recommended that at least 2 weeks elapse between discontinuance of an MAO inhibitor and initiation of nefazodone and that an interval of at least 1 week elapse between discontinuance of nefazodone and initiation of an MAO inhibitor. For information on the serotonin syndrome, see Drug Interactions: Drugs Associated with Serotonin Syndrome, in the Monoamine Oxidase Inhibitors General Statement 28:16.04.12 and see Serotonin Syndrome under Drug Interactions: Drugs Associated with Serotonin Syndrome, in Fluoxetine Hydrochloride 28:16.04.20.

The manufacturer states that concomitant use of nefazodone is contraindicated in patients receiving terfenadine (no longer commercially available in the US), astemizole (no longer commercially available in the US), cisapride, or pimozide since nefazodone may inhibit metabolism of these drugs and increase the potential for serious adverse cardiac effects. Concomitant use of carbamazepine and nefazodone is contraindicated since this may reduce plasma concentrations of nefazodone and hydroxynefazodone by 95% resulting in levels insufficient to achieve an antidepressant effect. Concomitant use of nefazodone and alprazolam or triazolam results in clinically important increases in plasma concentrations of these benzodiazepines but does not affect the pharmacokinetics of nefazodone. Concomitant use of triazolam and nefazodone should be avoided for most patients, including the elderly; however, in exceptional cases when concomitant use of the drugs may be considered appropriate, triazolam dosage should be reduced 75% and the lowest possible dosage should be used. If alprazolam is used concomitantly with nefazodone, a 50% reduction in initial dosage of the benzodiazepine is recommended.

Dispensing and Administration Precautions Because of similarity in spelling between Serzone® (the former trade name for nefazodone hydrochloride; no longer commercially available in the US under this trade name) and Seroquel® (the trade name for quetiapine fumarate, an antipsychotic agent), dispensing errors have been reported to the US Food and Drug Administration (FDA) and the manufacturer of Seroquel® (AstraZeneca). According to the medication error reports, the overlapping strengths (100 and 200 mg), dosage forms (tablets), and dosing intervals (twice daily) and the fact that these 2 drugs were stored closely together in pharmacies also were critical in causing these errors. These medication errors may be associated with adverse CNS (e.g., mental status deterioration, hallucination, paranoia, muscle weakness, lethargy, dizziness) and GI effects (e.g., nausea, vomiting, diarrhea). As of November 2001, 4 patients required emergency room visits and 3 patients were reportedly hospitalized because of dispensing errors involving these 2 agents. One female patient 25 years of age experienced fever and respiratory arrest after mistakenly taking Seroquel® for 3 days instead of taking Serzone®, and eventually died, although a causal relationship has not been established. FDA also is concerned that several patients unintentionally ingested Serzone® or Seroquel® for a prolonged period of time before the error was discovered. Therefore, extra care should be exercised in ensuring the accuracy of both oral and written prescriptions for Seroquel® and Serzone®. Although the Serzone brand was discontinued in June 2004, clinicians may continue to refer to nefazodone by the former brand name in prescribing. Some experts recommend that pharmacists assess the measures of avoiding dispensing errors and implement them as appropriate (e.g., by verifying all orders for these agents by spelling both the trade and generic names to prescribers, using computerized name alerts, attaching reminders to drug containers and pharmacy shelves, separating the drugs on pharmacy shelves, counseling patients).

Patients should be advised to question the dispensing pharmacist regarding any changes in the appearance of their prescription in terms of shape, color, or size of the tablets. Dispensing errors involving Serzone® (nefazodone) and Seroquel® (quetiapine) should be reported to the manufacturers or directly to the FDA MedWatch program by phone (800-FDA-1088), fax (800-FDA-0178), by the Internet (http://www.fda.gov/medwatch), or by mail (FDA Safety Information and Adverse Event Reporting Program, FDA, 5600 Fishers Lane, Rockville, MD 20852-9787).

Hepatic Precautions Severe, life-threatening, and in some cases fatal hepatic failure has been reported in patients receiving nefazodone. The onset of hepatic injury generally occurred after approximately 2 weeks to 6 months of nefazodone therapy in patients who subsequently developed hepatic failure that resulted in liver transplantation or death. Although some reports described prodromal symptoms (e.g., anorexia, malaise, other GI symptoms) or dark urine occurring before onset of jaundice, such prodromal symptoms were not reported in other cases. The incidence of hepatic failure resulting in death or liver transplantation in the US associated with nefazodone use has been estimated to be approximately 1 case per 250,000–300,000 patient-years of use (3–4 times the estimated rate of hepatic failure in the general population). However, this is considered an underestimate because of underreporting, and the true risk of nefazodone-related hepatic failure may be substantially greater.

Although there is no evidence to suggest that the presence of preexisting liver disease increases the likelihood of developing hepatic failure, nefazodone therapy generally should not be initiated in patients with active liver disease or elevated serum transaminase concentrations since baseline abnormalities can complicate monitoring of such patients. Early detection of drug-induced hepatic injury along with immediate withdrawal of the suspected drug is believed to enhance the likelihood of recovery. Therefore, patients receiving nefazodone should be advised to be alert for manifestations of hepatic dysfunction (e.g., jaundice, anorexia, GI complaints, malaise) and to contact their clinician immediately if they occur. Nefazodone should be discontinued if clinical signs or symptoms suggest hepatic failure. The drug also should be discontinued and should not be reinitiated in patients who develop evidence of hepatocellular injury (e.g., serum aminotransferase [AST or ALT] concentrations of 3 times the upper limit of normal or higher). Development of hepatocellular injury during nefazodone therapy is a contraindication to future use of the drug.

Suicidality Precautions Worsening of depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior may occur in both adult and pediatric (see Pediatric Precautions under Dosage and Administration: Administration) patients with major depressive disorder or other psychiatric disorders, whether or not they are taking antidepressants. This risk may persist until clinically important remission occurs. Suicide is a known risk of depression and certain other psychiatric disorders, and these disorders themselves are the strongest predictors of suicide. However, there has been a long-standing concern that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients during the early phases of treatment. Pooled analyses of short-term, placebo-controlled studies of antidepressants (i.e., selective serotonin-reuptake inhibitors and other antidepressants) have shown an increased risk of suicidality in children, adolescents, and young adults (18–24 years of age) with major

Sertraline Hydrochloride

Dosing & Indications

- **Adult Dose**
  - Major depressive disorder: 50 mg/day ORALLY as a single dose in the morning or the evening; may be increased at intervals of at least 1 week to a MAX dose of 200 mg/day
  - Obsessive-compulsive disorder: 50 mg/day ORALLY as a single dose in the morning or the evening; may be increased at intervals of at least 1 week to a MAX dose of 200 mg/day
  - Panic disorder: 25 mg/day ORALLY as a single dose in the morning or the evening for 1 week, then increase to 50 mg/day; may then be increased at intervals of at least 1 week to a MAX dose of 200 mg/day
  - Posttraumatic stress disorder: 25 mg/day ORALLY as a single dose in the morning or the evening for 1 week, then increase to 50 mg/day; may then be increased at intervals of at least 1 week to a MAX dose of 200 mg/day
  - Premenstrual dysphoric disorder: daily dosing, 50 mg/day ORALLY as a single dose in the morning or the evening throughout the menstrual cycle; may be increased at 50-mg increments/menstrual cycle up to 150 mg/day; OR
  - Premenstrual dysphoric disorder: luteal phase dosing, 50 mg/day ORALLY only during the luteal phase; may be increased up to 100 mg/day if needed; if 100-mg dose is necessary, each new luteal-phase dosing cycle should begin with 50 mg/day for 3 days before increasing to 100-mg/day dose
  - Social phobia: 25 mg/day ORALLY as a single dose in the morning or the evening for 1 week, then increase to 50 mg/day; may then be increased at intervals of at least 1 week to a MAX dose of 200 mg/day
- **Pediatric Dose**
  - Obsessive-compulsive disorder: children 6 to 12 years, 25 mg/day ORALLY as a single dose in the morning or the evening; may be increased at intervals of at least 1 week to a MAX dose of 200 mg/day
  - Obsessive-compulsive disorder: children 13 to 17 years, 50 mg/day ORALLY as a single dose in the morning or the evening; may be increased at intervals of at least 1 week to a MAX dose of 200 mg/day
- **Dose Adjustments**
  - renal impairment: dose adjustment not necessary
  - hepatic impairment: lower or less frequent doses should be used
- **FDA Labeled Indications**
  - Major depressive disorder
    - ◇ FDA Approval:
      Adult, yes
      Pediatric, no
    - ◇ Efficacy:
      Adult, Effective
      Pediatric, Evidence favors efficacy
    - ◇ Strength of Recommendation:
      Adult, Class I
      Pediatric, Class IIb

- Strength of Evidence:
  Adult, Category B
  Pediatric, Category B

- Obsessive-compulsive disorder

  - FDA Approval:
    Adult, yes
    Pediatric, yes 6 years and older

  - Efficacy:
    Adult, Effective
    Pediatric, Effective

  - Strength of Recommendation:
    Adult, Class I
    Pediatric, Class I

  - Strength of Evidence:
    Adult, Category B
    Pediatric, Category B

- Panic disorder

  - FDA Approval:
    Adult, yes
    Pediatric, no

  - Efficacy:
    Adult, Effective

  - Strength of Recommendation:
    Adult, Class IIa

  - Strength of Evidence:
    Adult, Category B

- Posttraumatic stress disorder

  - FDA Approval:
    Adult, yes
    Pediatric, no

  - Efficacy:
    Adult, Effective

  - Strength of Recommendation:
    Adult, Class I

  - Strength of Evidence:
    Adult, Category B

- Premenstrual dysphoric disorder

  - FDA Approval:

Adult, yes
Pediatric, no

- Efficacy:
  Adult, Effective
- Strength of Recommendation:
  Adult, Class I
- Strength of Evidence:
  Adult, Category B

- Social phobia
  - FDA Approval:
    Adult, yes
    Pediatric, no
  - Efficacy:
    Adult, Effective
  - Strength of Recommendation:
    Adult, Class I
  - Strength of Evidence:
    Adult, Category B

- **Non-FDA Labeled Indications**
  - Bipolar disorder, depressed phase; Adjunct
    - FDA Approval:
      Adult, no
      Pediatric, no
    - Efficacy:
      Adult, Evidence favors efficacy
    - Strength of Recommendation:
      Adult, Class IIb
    - Strength of Evidence:
      Adult, Category B
  - Depression - Myocardial infarction, Post
    - FDA Approval:
      Adult, no
      Pediatric, no
    - Efficacy:
      Adult, Evidence favors efficacy
    - Strength of Recommendation:
      Adult, Class IIb

- Strength of Evidence:
  Adult, Category B

- Dysthymia

  - FDA Approval:
    Adult, no
    Pediatric, no

  - Efficacy:
    Adult, Evidence favors efficacy

  - Strength of Recommendation:
    Adult, Class IIb

  - Strength of Evidence:
    Adult, Category B

- Generalized anxiety disorder

  - FDA Approval:
    Adult, no
    Pediatric, no

  - Efficacy:
    Adult, Evidence favors efficacy
    Pediatric, Evidence is inconclusive

  - Strength of Recommendation:
    Adult, Class IIb
    Pediatric, Class IIb

  - Strength of Evidence:
    Adult, Category B
    Pediatric, Category B

- Night eating syndrome

  - FDA Approval:
    Adult, no
    Pediatric, no

  - Efficacy:
    Adult, Evidence favors efficacy

  - Strength of Recommendation:
    Adult, Class IIb

  - Strength of Evidence:
    Adult, Category B

- Severe major depression with psychotic features; Adjunct

  - FDA Approval:
    Adult, no
    Pediatric, no

- Efficacy:
  Adult, Evidence favors efficacy

- Strength of Recommendation:
  Adult, Class IIb

- Strength of Evidence:
  Adult, Category B

Black Box WARNING

Antidepressants increased the risk of suicidal thinking and behavior in children, adolescents, and young adults with major depressive disorder (MDD) and other psychiatric disorders in short-term studies. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared with placebo in adults older than 24 years, and there was a reduction in risk with antidepressants compared with placebo in adults aged 65 or older. This risk must be balanced with the clinical need. Monitor patients closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. Sertraline hydrochloride is not approved for use in pediatric patients except for patients with obsessive compulsive disorder (OCD) .

Contraindications/Warnings

- **Contraindications**

  - concomitant use of disulfiram (oral concentrate)
  - concomitant use of MAOIs, including linezolid or IV methylene blue, within 14 days of sertraline discontinuation or use of sertraline within 14 days of discontinuing an MAOI; increased risk of serotonin syndrome
  - concomitant use of pimozide
  - hypersensitivity to sertraline or any other component of the product

- **Precautions**

  - suicidal ideation and behavior or worsening depression; increased risk, particularly in children, adolescents, and young adults during the first few months of therapy or following changes in dosage; monitoring recommended
  - bipolar disorder; increased risk of precipitation of a mixed/manic episode
  - bleeding events, including life-threatening hemorrhages, have been reported with SSRIs; risk may be increased with concomitant use of aspirin, NSAIDs, warfarin, and other anticoagulants
  - concomitant use of alcohol is not recommended
  - diabetes mellitus, new onset, has been reported
  - glycemic control, loss of (including hypoglycemia and hyperglycemia), has been reported in patients with and without preexisting diabetes; monitoring recommended
  - glaucoma, narrow-angle (angle-closure glaucoma) or increased intraocular pressure, history or at risk for; increased risk of mydriasis
  - hyponatremia, usually the result of SIADH, has occurred; increased risk with volume-depletion, elderly age, or concurrent diuretic therapy; discontinuation recommended with symptomatic hyponatremia
  - latex allergy; oral concentrate dropper dispenser contains dry natural rubber
  - liver disease or impairment; risk of drug toxicity; lower or less frequent dose may be required
  - mania and hypomania have been reported
  - seizure disorder; seizures have been reported rarely, usually in patients with a personal or family history of seizure disorder
  - serotonin syndrome has been reported, often with concurrent use with other serotonergic drugs (eg, triptans, tricyclic antidepressants, fentanyl, lithium, tramadol, buspirone, tryptophan, St John's

wort), MAOIs (including methylene blue IV and linezolid), and other drugs that impair serotonin metabolism; monitoring recommended; discontinue use if suspected
- withdrawal, abrupt; serious discontinuation symptoms have been reported; gradual reduction is recommended when possible

- **Pregnancy Category**
  - Sertraline: C (FDA)
  - Sertraline: C (AUS)
- **Breast Feeding**
  - Sertraline: AAP: Drugs for which the effect on nursing infants is unknown but may be of concern.
  - Sertraline: Micromedex: Infant risk is minimal.

Drug Interactions

- **Contraindicated**
  - ◇ Clorgyline (probable)
  - ◇ Furazolidone (theoretical)
  - ◇ Iproniazid (probable)
  - ◇ Isocarboxazid (probable)
  - ◇ Levomethadyl (theoretical)
  - ◇ Linezolid (probable)
  - ◇ Methylene Blue (theoretical)
  - ◇ Moclobemide (probable)
  - ◇ Nialamide (probable)
  - ◇ Pargyline (probable)
  - ◇ Phenelzine (probable)
  - ◇ Pimozide (probable)
  - ◇ Procarbazine (probable)
  - ◇ Rasagiline (theoretical)
  - ◇ Selegiline (probable)
  - ◇ Toloxatone (probable)
  - ◇ Tranylcypromine (probable)
- **Major**
  - ◇ Abciximab (probable)
  - ◇ Acenocoumarol (probable)
  - ◇ Almotriptan (theoretical)
  - ◇ Amitriptyline (probable)
  - ◇ Amoxapine (probable)
  - ◇ Ancrod (probable)
  - ◇ Anisindione (probable)
  - ◇ Antithrombin III Human (probable)
  - ◇ Apixaban (theoretical)
  - ◇ Ardeparin (probable)
  - ◇ Aspirin (probable)
  - ◇ Astemizole (probable)
  - ◇ Bivalirudin (probable)
  - ◇ Certoparin (probable)
  - ◇ Cilostazol (probable)
  - ◇ Citalopram (theoretical)
  - ◇ Clomipramine (probable)
  - ◇ Clopidogrel (probable)

- Clozapine (established)
- Cyclobenzaprine (theoretical)
- Dabrafenib (theoretical)
- Dalteparin (probable)
- Danaparoid (probable)
- Defibrotide (probable)
- Dermatan Sulfate (probable)
- Desipramine (probable)
- Desirudin (probable)
- Desvenlafaxine (theoretical)
- Dexfenfluramine (theoretical)
- Dextromethorphan (theoretical)
- Diclofenac (probable)
- Dicumarol (probable)
- Dipyridamole (probable)
- Dothiepin (probable)
- Doxepin (probable)
- Droperidol (theoretical)
- Duloxetine (theoretical)
- Eletriptan (theoretical)
- Enoxaparin (probable)
- Eptifibatide (probable)
- Erythromycin (probable)
- Escitalopram (theoretical)
- Fenfluramine (theoretical)
- Fentanyl (theoretical)
- Flecainide (probable)
- Fluoxetine (theoretical)
- Fluvoxamine (theoretical)
- Fondaparinux (probable)
- Fosphenytoin (probable)
- Frovatriptan (probable)
- Heparin (probable)
- Imipramine (probable)
- Iobenguane I 123 (theoretical)
- Levomilnacipran (theoretical)
- Lofepramine (probable)
- Lorcaserin (theoretical)
- Milnacipran (theoretical)
- Nadroparin (probable)
- Naratriptan (probable)
- Nortriptyline (probable)
- Oxcarbazepine (probable)
- Oxycodone (probable)
- Parnaparin (probable)
- Paroxetine (theoretical)
- Pazopanib (theoretical)
- Pentosan Polysulfate Sodium (probable)
- Phenindione (probable)
- Phenprocoumon (probable)
- Phenytoin (probable)
- Prasugrel (probable)
- Protriptyline (probable)
- Reviparin (probable)
- Rizatriptan (probable)
- Sibutramine (probable)
- St John's Wort (probable)
- Sumatriptan (theoretical)

- Tamoxifen (theoretical)
- Tapentadol (theoretical)
- Terfenadine (probable)
- Ticlopidine (probable)
- Tinzaparin (probable)
- Tirofiban (probable)
- Tramadol (theoretical)
- Trazodone (theoretical)
- Trimipramine (probable)
- Tryptophan (theoretical)
- Vilazodone (theoretical)
- Warfarin (probable)
- Zolmitriptan (probable)

- **Moderate**

  - Alprazolam (probable)
  - Bupropion (probable)
  - Carbamazepine (probable)
  - Cimetidine (probable)
  - Darunavir (established)
  - Efavirenz (established)
  - Fluphenazine (probable)
  - Ginkgo (probable)
  - Lamotrigine (probable)
  - Lithium (established)
  - Metoclopramide (probable)
  - Propafenone (probable)
  - Propranolol (probable)
  - Rifampin (probable)
  - Thiotepa (probable)
  - Zolpidem (probable)

Adverse Effects

- **COMMON**

  - Gastrointestinal: Constipation (3% to 8%), Diarrhea (13% to 24%), Indigestion (6% to 13%), Nausea (13% to 30%), Nausea and vomiting (2% to 30%)
  - Neurologic: Dizziness (6% to 17%), Headache (25%), Insomnia (12% to 28%), Somnolence (2% to 15%), Tremor (5% to 11%)
  - Reproductive: Abnormal ejaculation (7% to 19%), Reduced libido (up to 11%)
  - Other: Fatigue (10% to 16%)

- **SERIOUS**

  - Dermatologic: Stevens-Johnson syndrome
  - Endocrine metabolic: Hyponatremia
  - Immunologic: Anaphylaxis
  - Musculoskeletal: Rhabdomyolysis
  - Neurologic: Seizure (rare)
  - Psychiatric: Depression, Exacerbation, Mania (rare), Suicidal thoughts (rare), Suicide (rare)
  - Other: Serotonin syndrome

Name Info

- **US Trade Names**
  - Zoloft
- **Class**
  - Antidepressant
  - Serotonin Reuptake Inhibitor
- **Regulatory Status**
  - RX
- **Generic Availability**
  - Yes

Mechanism of Action/Pharmacokinetics

- **Mechanism of Action**
  - Sertraline HCl is a serotonin reuptake inhibitor (SSRI). The mechanism of action as antidepressant may be due to its inhibition of CNS neuronal uptake of serotonin. It has only very weak effects on norepinephrine and dopamine neuronal uptake.
- **Pharmacokinetics**
  - **Absorption**
    - Oral: time to peak concentration, 4.5 h to 8.4 h
    - Effect of food: (tablet), slightly increased AUC but Cmax was 25% greater, while Tmax decreased from 8 h to 5.5 h
    - Effect of food: (solution), Tmax slightly prolonged from 5.9 h to 7 h
  - **Distribution**
    - Protein binding: 98%
  - **Metabolism**
    - Hepatic; glucuronide conjugation, hydroxylation, N-demethylation, oxidative deamination, and reduction
    - Metabolite: N-desmethylsertraline
  - **Excretion**
    - Fecal: 40% to 45%, 12% to 14% unchanged
    - Renal: 40% to 45%
    - Dialyzable: no
  - **Elimination Half Life**
    - 26 h (average)

Administration/Monitoring

- **Administration**

- Oral
  - Oral: (oral concentrate) dilute immediately before use; do not mix in advance
  - Oral: (oral concentrate) dilute in 4 ounces (one-half cup) using only water, ginger ale, lemon/lime soda, lemonade, or orange juice

- **Monitoring**
  - reduction or resolution of symptoms
  - serum glucose, especially in patients with diabetes
  - thyroid function periodically
  - worsening of depression, suicidality, or unusual changes in behavior, especially at initiation of therapy or when the dose increases or decreases

How Supplied

- Generic
  - Oral Solution: 20 MG/ML
  - Oral Tablet: 25 MG, 50 MG, 100 MG
- Zoloft
  - Oral Solution: 20 MG/ML
  - Oral Tablet: 25 MG, 50 MG, 100 MG

Toxicology

- **Clinical Effects**
  - SERTRALINE
    - USES: Sertraline is used for depressive disorders, panic attacks, anxiety, obsessive-compulsive disorders and posttraumatic stress disorders. EPIDEMIOLOGY: Sertraline overdose is fairly common, but only rarely results in serious toxicity. However, deaths have occasionally been reported. PHARMACOLOGY: It is a selective serotonin reuptake inhibitor (SSRI). TOXICOLOGY: Typically, sertraline overdose is mainly associated with CNS depression. Seizures have rarely been reported. Serotonergic toxicity, especially after congestions with other serotonergic agents (MAO inhibitors, serotonin releasers, and other serotonin reuptake inhibitors) may be observed. QTc prolongation, but not torsade de pointes has been reported. ADVERSE EFFECTS: Somnolence, insomnia, vertigo, headache, palpitations, nausea, diarrhea, diaphoresis are often reported. MILD TO MODERATE TOXICITY: Somnolence, dizziness, nausea, constipation, diarrhea, tachycardia, hypertension and mydriasis. SEVERE TOXICITY: Marked CNS depression. Serotonergic toxicity, such as hyperreflexia, clonus, altered mental status, or hemodynamic instability may be seen, usually when sertraline is taken in combination with other serotonergic agents, but serotonin syndrome has been reported after sertraline overdose. Seizures have been reported.

- **Treatment of Exposure**
  - SERTRALINE
    - Support: MANAGEMENT OF MILD TO MODERATE TOXICITY: Primarily supportive care; activated charcoal may be helpful in patients presenting shortly after ingestion. Give benzodiazepines titrated to effect for anxiety and seizures. MANAGEMENT OF SEVERE TOXICITY: Consider activated charcoal if patients present early after ingestion. If significant CNS depression occurs, intubate the patient for airway protection before giving charcoal. Consider intravenous

lipid therapy early for patients with ventricular dysrhythmias or hypotension. Give benzodiazepines for seizures. Treat serotonin toxicity with benzodiazepine, and consider cyproheptadine, if symptoms persist. Severe cases may require neuromuscular paralysis.

- Decontamination: PREHOSPITAL: Activated charcoal may be considered if the patient is alert and able to protect their airway. HOSPITAL: Activated charcoal, gastric lavage may be considered if a large ingestion.
- Airway management: Early orotracheal intubation in patients with signs of severe intoxication (CNS depression, seizures, agitation).
- Antidote: There is no specific antidote.
- Fat emulsion: Patients who develop significant cardiovascular toxicity should be treated with intravenous lipids. Administer 1.5 mL/kg of 20% lipid emulsion over 2 to 3 minutes as an IV bolus, followed by an infusion of 0.25 mL/kg/min. If possible, discontinue after 30 to 60 minutes. Longer periods of lipid therapy should be considered if the patient's hemodynamic stability is dependent on continued lipid infusion.
- Serotonin syndrome: Treat initially with benzodiazepines. Cyproheptadine is sometimes used for moderate cases (ADULT: 12 mg orally then 2 mg every 2 hours until symptoms improve; maximum 24 mg/day. CHILD: 0.25 mg/kg/day divided every 6 hours; maximum dose 12 mg/day). Patients with severe serotonin syndrome (ie, severe hyperthermia, agitation, rigidity, hypertension, tachycardia, acidosis) may require neuromuscular paralysis.
- Monitoring of patient: Monitor vital signs and mental status. Sertraline serum levels are not rapidly available and not helpful in managing overdose. No specific lab work is needed in most patients. Obtain an ECG and institute continuous cardiac monitoring in patients with moderate to severe toxicity (ie, CNS depression, seizures, coma, serotonin toxicity). Monitor serum electrolytes, creatinine phosphokinase and lactate levels in patients with serotonin toxicity, seizures, or coma.
- Enhanced elimination procedure: There is no role for repeat-dose activated charcoal. Hemodialysis is not useful given the large volume of distribution (20 L/kg) and high protein binding (99%).
- Patient disposition: HOME CRITERIA: Asymptomatic or mildly symptomatic (nausea, discrete somnolence, diaphoresis, mydriasis) patients can be managed at home, if the ingestion was inadvertent and 250 mg or less. OBSERVATION CRITERIA: Patients with deliberate ingestions, patients with more than mild symptoms, and those with inadvertent ingestions of more than 250 mg should be referred to a healthcare facility for evaluation and treatment. If symptoms resolve after 6 to 12 hours of observation the patient may be discharged. ADMISSION CRITERIA: Any patients experiencing more than mild effects that do not resolve after 6 to 12 hours of observation should be admitted to the hospital. CONSULT CRITERIA: Consult a poison center or medical toxicologist for assistance in managing patients with severe toxicity (ie, CNS depression, seizures, serotonin toxicity), or in whom the diagnosis is unclear.

- **Range of Toxicity**

  - SERTRALINE
    - TOXICITY: Expect mild toxicity in sertraline naive patients even at therapeutic dosages. Ingestion of up to 250 mg is not expected to result in more than mild toxicity. SEVERE: Serious toxicity is not expected after an overdose of up to 2 g of sertraline. Complete recovery after an ingestion of 8 g and 13.5 g of sertraline, respectively has been reported, however, in another case, 2.5 g of sertraline was fatal. Adding sertraline to an established therapy with serotonergic agents may lead to serotonin toxicity. THERAPEUTIC DOSE: ADULT: DEPRESSION and PANIC DISORDER: 50 mg orally once daily; may increase the dosage up to a maximal dose of 200 mg daily. ANXIETY: 50 mg orally once daily. POSTTRAUMATIC STRESS DISORDER: 25 mg orally once daily up to 200 mg/day. PEDIATRIC: OBSESSIVE COMPULSIVE DISORDER: Ages 6 to 12 years: Initial dose: 25 mg once daily; and 50 mg once daily in adolescents (ages 13 to 17 years); maximum dose 200 mg daily. The safety and efficacy of sertraline for other conditions in children under 18 years has not been studied.

Clinical Teaching

- Advise patient to avoid activities requiring mental alertness or coordination until drug effects are realized.
- Warn patient with latex allergy to use caution with oral concentrate. The dropper contains dry natural rubber.
- Instruct patient to report symptoms of serotonin syndrome (eg, mental status changes, autonomic instability, gastrointestinal symptoms, neuromuscular changes, seizures) .
- Drug may cause ejaculation failure, dry mouth, increased sweating, somnolence, dizziness, tremor, fatigue, diarrhea, dyspepsia, nausea, insomnia, or reduced libido.
- Advise patient that symptomatic improvement may not be seen for a few weeks.
- Instruct patient to report worsening depression, suicidal ideation, or unusual changes in behavior.
- Advise patient against sudden discontinuation of drug, as this may cause dysphoric mood, irritability, agitation, dizziness, sensory disturbances, anxiety, confusion, headache, lethargy, emotional lability, insomnia, or hypomania.
- Instruct patient using oral concentrate that dilution is required prior to dose (eg, water, ginger ale, lemon/lime soda, lemonade, orange juice) .
- Warn patient that alcohol use is not advised with drug.

Last Modified: September 12, 2013

Images & Imprints

Ingredients: Sertraline Hydrochloride (50 MG)
Color: Light Blue
Shape: Oblong
Pattern: Solid
Imprint: ZOLOFT; 50 MG
NDC: 00049-4900-30, 00049-4900-41, 00049-4900-66, 00049-4900-73, 00049-4900-94, 13411-0152-03, 16590-0250-30, 49999-0292-15, 49999-0292-30, 54868-2192-05, 54868-2192-06, 54868-2192-07, 55045-2224-00, 55045-2224-02, 55045-2224-07, 55045-2224-08, 55289-0409-30, 55289-0409-60, 55887-0487-30, 55887-0487-60, 55887-0487-82, 55887-0487-90, 58864-0707-30, 63874-0555-01, 63874-0555-10, 63874-0555-14, 63874-0555-15, 63874-0555-20, 63874-0555-30, 63874-0555-60, 68115-0366-00, 68115-0366-30, 68115-0366-60

Ingredients: Sertraline Hydrochloride (100 MG)
Color: Light Yellow
Shape: Oblong
Pattern: Solid
Imprint: ZOLOFT; 100 MG
NDC: 00049-4910-30, 00049-4910-41, 00049-4910-66, 00049-4910-73, 00049-4910-94, 13411-0153-03, 16590-0251-30, 49999-0375-00, 49999-0375-15, 49999-0375-30, 54868-2637-08, 55045-2208-01, 55045-2208-03, 55045-2208-07, 55045-2208-08, 55289-0550-30, 55887-0967-15, 55887-0967-30, 55887-0967-60, 55887-0967-90, 57866-6305-00, 57866-6305-01, 58864-0627-15, 58864-0627-30, 63874-0596-01, 63874-0596-10, 63874-0596-14, 63874-0596-15, 63874-0596-20, 63874-0596-30, 63874-0596-60, 68115-0365-00, 68115-0365-15, 68115-0365-30, 68115-0365-45, 68115-0365-60

Ingredients: Sertraline Hydrochloride (20 MG/ML)
NDC: 00049-4940-23

Ingredients: Sertraline Hydrochloride (25 MG)
Color: Light Green
Shape: Oblong
Pattern: Solid
Imprint: ZOLOFT; 25 MG(Score is between "25" and "MG".)
NDC: 00049-4960-30, 00049-4960-50, 52959-0787-30, 55887-0519-20, 55887-0519-30, 55887-0519-60, 55887-0519-82, 55887-0519-90, 68115-0765-50

Ingredients: Sertraline Hydrochloride (25 MG)
Color: Light Green
Shape: Oval
Pattern: Solid
Imprint: 9 3(Score between 9 & 3.); 7175
NDC: 00093-7175-10, 00093-7175-56, 00172-5672-10, 00172-5672-80

Ingredients: Sertraline Hydrochloride (50 MG)
Color: Light Blue
Shape: Oval
Pattern: Solid
Imprint: 9 3(Score between 9 & 3.); 7176
NDC: 00093-7176-10, 00093-7176-56, 00172-5673-10, 16590-0457-15, 16590-0457-28, 16590-0457-56, 68071-0548-60

Ingredients: Sertraline Hydrochloride (100 MG)
Color: Light Yellow
Shape: Oval
Pattern: Solid
Imprint: 9 3(Score between 9 & 3.); 7177
NDC: 00093-7177-10, 00093-7177-56, 00172-5674-10, 16590-0416-15, 16590-0416-30, 16590-0416-60, 16590-0416-90

Ingredients: Sertraline Hydrochloride (50 MG)
Color: Blue
Shape: Capsule-shape
Pattern: Solid
Imprint: WPI; 32 39
NDC: 00591-3239-10, 00591-3239-19, 00591-3239-30

Ingredients: Sertraline Hydrochloride (100 MG)
Color: Yellow
Shape: Capsule-shape
Pattern: Solid
Imprint: WPI; 32 40
NDC: 00591-3240-10, 00591-3240-19, 00591-3240-30

Ingredients: Sertraline Hydrochloride (50 MG)
Color: Light Blue
Shape: Oval
Pattern: Solid
Imprint: I G(The tablet is debossed with I on the left side of the bisect and G on the right side of the bisect on one side and 213 on the other side.); 213
NDC: 12634-0904-71, 16590-0457-45, 16590-0457-90, 31722-0213-05, 31722-0213-30, 47463-0770-30, 47463-0770-60, 47463-0770-90, 50436-6304-01, 54458-0944-10, 54569-5818-00, 54569-5818-01, 54569-5818-02, 55048-0770-30, 55048-0770-60, 55048-0770-90, 63629-3309-04, 63629-3309-05, 68071-0548-28, 68071-0548-56, 68258-7086-03, 68258-7086-06, 68258-7086-09, 68645-0425-54

Ingredients: Sertraline Hydrochloride (100 MG)
Color: Light Yellow
Shape: Oval
Pattern: Solid
Imprint: I G(The tablet is debossed with I on the left side of the bisect and G on the right side of the bisect on one side and 214 on the other side.); 214
NDC: 16590-0416-10, 31722-0214-05, 31722-0214-30, 50436-6305-01, 54458-0945-10, 54569-5819-00, 54569-5819-01, 54569-5819-02, 54868-5638-07, 54868-5638-08, 63629-3289-01, 68071-0702-28, 68258-7054-01, 68258-7054-03, 68258-7054-06, 68258-7054-08, 68258-7054-09, 68645-0426-54

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Appendix A. Strength of Recommendation and Evidence

Strength of Recommendation:

Class I - Recommended
The given test or treatment has been proven to be useful, and should be performed or administered.

Class IIa - Recommended, In Most Cases
The given test, or treatment is generally considered to be useful, and is indicated in most cases.

Class IIb - Recommended, In Some Cases
The given test, or treatment may be useful, and is indicated in some, but not most, cases.

Class III - Not Recommended
The given test, or treatment is not useful, and should be avoided.

Class Indeterminant - Evidence Inconclusive

Strength of Evidence:

Category A
Category A evidence is based on data derived from: Meta-analyses of randomized controlled trials with homogeneity with regard to the directions and degrees of results between individual studies. Multiple, well-done randomized clinical trials involving large numbers of patients.

Category B
Category B evidence is based on data derived from: Meta-analyses of randomized controlled trials with conflicting conclusions with regard to the directions and degrees of results between individual studies. Randomized controlled trials that involved small numbers of patients or had significant methodological flaws (e.g., bias, drop-out rate, flawed analysis, etc.). Nonrandomized studies (e.g., cohort studies, case-control studies, observational studies).

Category C
Category C evidence is based on data derived from: Expert opinion or consensus, case reports or case series.

No Evidence

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    Appendices
    Appendix A. Strength of Recommendation and Evidence

Program Name: BadgerCare Plus and Medicaid Handbook Area: Pharmacy

10/04/2013

Claims : Drug Utilization Review

Topic #1978

A Comprehensive Overview

The federal OBRA '90 (Omnibus Reconciliation Act of 1990) established program requirements regarding several aspects of pharmacy practice. One of the requirements of OBRA '90 was a DUR (Drug Utilization Review) program for BadgerCare Plus, Medicaid, and SeniorCare members to improve the quality and cost-effectiveness of care.

The OBRA '90 requires that BadgerCare Plus, Medicaid, and SeniorCare DUR program includes all of the following:

- Prospective DUR.
- Retrospective DUR.
- An educational program using DUR program data on common drug therapy.

Individual pharmacies are responsible for prospective DUR, while BadgerCare Plus, Medicaid, and SeniorCare are responsible for retrospective DUR and educational programming. Additional differences between prospective and retrospective DUR can be found in the following table.

Prospective Versus Retrospective DUR	
Prospective DUR	Retrospective DUR
• Performed before a drug is dispensed • Identifies a potential problem before it occurs • Provides real-time response to a potential problem • Has preventive and corrective action	• Performed after a drug is dispensed • Warns when a potential problem has occurred • Useful for detecting patterns and designing targets for intervention • Has corrective action

The DUR Board, required by federal law, consists of three physicians, five pharmacists, and one nurse practitioner. The DUR Board and the DHS (Department of Health Services) review and approve all DUR criteria and establish a hierarchy of alerts for prospective and retrospective DUR.

Providers should refer to Phar. 7.01(1)(e) and 7.08, Wis. Admin. Code, and s. 450.01(16)(i), Wis. Stats., for additional information about DUR program requirements.

Topic #12657

Additive Toxicity

The additive toxicity DUR (Drug Utilization Review) alert is activated when a prescribed drug causes a cumulative effect with other drugs in the claims history. Points accumulate for side effects based on the severity and the frequency of the side effect. Once a defined threshold is reached, an alert is sent to the provider.

Topic #1983

Alerts and Alert Hierarchy

The DUR (Drug Utilization Review) Board established a hierarchy for the order in which multiple alerts appear if more than one alert is activated for a drug claim. Factors taken into account in determining the hierarchy include the potential for avoidance of adverse consequences, improvement of the quality of care, cost savings, likelihood of a false positive, retrospective DUR experience, and a review of alerts used by other state Medicaid programs for prospective DUR. The clinical drug tables used to establish the alerts are provided to BadgerCare Plus, Medicaid, and SeniorCare by First DataBank, Inc.

For information about overriding DUR alerts, providers may refer to the Prospective Drug Utilization Review System topic.

BadgerCare Plus, Medicaid, and SeniorCare activate alerts that identify the following problems. These alerts are listed in hierarchical order according to the following prospective DUR conflict codes:

- DD — Drug-drug interaction.
- Drug-disease contraindication.
    - MC — reported.
    - DC — inferred.
- TD — Therapeutic duplication.
- PG — Pregnancy alert.
- ER — Overuse.
- AT — Additive toxicity.
- LR — Underuse.
- NS — Insufficient Quantity.

Topic #12618

Drug-Disease Contraindication

The drug-disease contraindication DUR (Drug Utilization Review) alert is activated when a drug is prescribed for a member who has a disease for which the drug is contraindicated. Acute diseases remain in the member's medical profile for a limited period of time, while chronic diseases remain permanently. The disease may have been reported on a medical claim or inferred from a drug in claims history.

Contraindications include the following:

- Reported — The diagnosis is extracted from the member's medical profile. A medical profile includes previously reimbursed claims, including pharmacy claims, where a diagnosis is submitted.
- Inferred — Infer that the member has a disease based on a drug present in claims history. This inference is made if there is one disease indicated for a drug.

Topic #12617

Drug-Drug Interaction

The drug-drug interaction DUR (Drug Utilization Review) alert is activated when another drug in claims history interacts with the drug being filled. The system reviews not only the prescriptions at the current pharmacy, but all of the prescriptions reimbursed by BadgerCare Plus, Medicaid, and SeniorCare.

Topic #1981

Edits and Audits

The claims processing system includes certain edits and audits. Edits check the validity of data on each individual claim. For example, a claim with an invalid NDC (National Drug Code) will be denied with an edit. In contrast, audits review claim history. For example, if the same claim is filed at two different pharmacies on the same day, the claim at the second pharmacy will be denied with an audit.

Only payable claims that are not denied by an edit or audit are submitted to prospective DUR (Drug Utilization Review). Prospective DUR alerts inform providers of potential drug therapy problems. With the exception of the overuse precaution ("ER") alert, providers can override any of these alerts.

Topic #1980

Educational Programming

A number of educational programs are generated by the DUR (Drug Utilization Review) Board. One of the primary means of education is the distribution of educational newsletters to prescribers and pharmacists. Topics for newsletters include:

- Current treatment protocols.
- How to best use the information received in the intervention letter.
- New drug-drug interactions.
- Utilization and cost data for selected therapeutic classes of drugs.
- Comparison of efficacy and cost of drugs within a therapeutic class.

In addition, the intervention letters sent out generate additional calls to the DUR pharmacy staff that provide an opportunity for a one-on-one educational activity with the prescriber.

Topic #12660

High Dose

Providers receive the high dose prospective DUR (Drug Utilization Review) alert on claims for drugs listed in the table below if the dose exceeds daily limit indicated.

Drug	Daily Limit
Acetaminophen	Greater than 4,000 mg/day, for all members
Alprazolam	Greater than 2 mg/day, for members 65 or older
Amitriptyline	Greater than 150 mg/day, for all members
Cyclobenzaprine	Greater than 30 mg/day, for all members
Escitalopram	Greater than 30 mg/day, for all members
Tramadol	Greater than 300 mg/day, for members 65 or older
Zolpidem	Greater than 10 mg/day for members 65 or older

Topic #12637

Overuse Precaution

The overuse precaution DUR (Drug Utilization Review) alert is activated when a member is requesting an early refill of a prescription. The alert is sent to the provider if a claim is submitted before 80 percent of the previous claim's days' supply for the same drug, drug strength, and dosage form has been taken. The alert indicates the number of days that should remain on the prescription, not the day that the drug can be refilled without activating the alert. Drugs with up to a 10-day supply are excluded from this alert.

A comprehensive list of drug categories are monitored for the "ER" prospective DUR alert if a member requests a refill before 80 percent of a previous claim's days supply has been taken. Antibiotics, insulins, IV solutions, electrolytes (except potassium, blood components and factors), and diagnostic

drugs are excluded.

The Prospective Drug Utilization Review System topic includes more information about override policies.

Topic #12620

Pregnancy Alert

The pregnancy DUR (Drug Utilization Review) alert is activated when the prescribed drug is contraindicated in pregnancy. This alert is activated when all of the following conditions are met:

- The member is a woman between 12 and 60 years of age.
- ForwardHealth receives a medical or pharmacy claim for a member that indicates pregnancy using a diagnosis code.
- A pharmacy claim for a drug that possesses a clinical significance of D, X, or 1 (as assigned by the FDA (Food and Drug Administration) or First DataBank, Inc.) is submitted for a member.

Clinical Significance Codes	
D	There is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans. However, potential benefits may warrant use of the drug in pregnant women despite potential risks if the drug is needed in a life-threatening situation or for a serious disease for which safer drugs cannot be used or are ineffective. This is a FDA-assigned value.
X	Studies in animals or humans have demonstrated fetal abnormalities and/or there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience, and the risks involved in use of the drug in pregnant women clearly outweigh potential benefits. This is an FDA-assigned value.
1	No FDA rating but is contraindicated or not recommended; may have animal and/or human studies or pre- or post-marketing information. This is a First DataBank, Inc.-assigned value.

The pregnancy diagnosis will be deactivated from a member's medical profile after 260 days or if an intervening diagnosis indicating delivery or other pregnancy termination is received on a claim.

Topic #1977

Prospective Drug Utilization Review System

To help individual pharmacies comply with their prospective DUR (Drug Utilization Review) responsibility, BadgerCare Plus, Medicaid, and SeniorCare developed a prospective DUR system. The system screens certain drug categories for clinically significant potential drug therapy problems before a drug is dispensed to a member. Prospective DUR enhances clinical quality and cost-effective drug use.

Prospective DUR is applied to all BadgerCare Plus, Medicaid, and SeniorCare real-time POS (Point-of-Sale) claims submitted to ForwardHealth. Prospective DUR alerts are returned to pharmacy providers as a conflict code. Providers may refer to the ForwardHealth Payer Sheet: (P-00272) NCPDP (National Council for Prescription Drug Programs) Version D.0 for more information about prospective DUR.

Although the prospective DUR system alerts pharmacy providers to a variety of potential problems, it is not intended to replace pharmacists' professional judgment. Potential drug therapy problems may exist which do not trigger the prospective DUR system. Prospective DUR remains the responsibility of the pharmacy, as required by federal and state law. The system is an additional tool to assist

pharmacists in meeting this requirement.

Claims Reviewed by the Prospective Drug Utilization Review System

Under the prospective DUR system, only reimbursable claims for BadgerCare Plus, Medicaid, and SeniorCare members submitted through the real-time pharmacy POS system are reviewed. Although paper claims and compound drug claims are not reviewed by the prospective DUR system, pharmacy providers are still required under provisions of OBRA '90 (Omnibus Budget Reconciliation Act of 1990) to perform prospective DUR independently.

Claims for Assisted Living Facility, Group Home, and Nursing Facility Members

Real-time claims for assisted living facility, group home, and nursing facility members are reviewed through the prospective DUR system; however, they do not require a response to obtain reimbursement since claims submission for these members does not always occur at the same time the drug is dispensed. The assisted living facility, group home, or nursing facility pharmacist consultant is responsible for prospective DUR. Although assisted living facility, group home, and nursing facility claims are exempt from denial, an informational alert will be received on POS claims.

Overriding Prospective Drug Utilization Review Alerts

When a claim is processed for a drug that has the potential to cause problems for a member, BadgerCare Plus, Medicaid, or SeniorCare return an alert to inform the pharmacy provider about the potential problem. The provider is then required to respond to the alert to obtain reimbursement. For certain drugs, providers may override the claim in the POS system. The provider is required to resubmit the claim and include information about the action taken and the resulting outcome.

For other drugs, pharmacy providers are required to call the DAPO (Drug Authorization and Policy Override) Center to request authorization.

If a provider receives a prospective DUR alert and subsequently receives an override through DAPO Center, the DUR alert pre-override is not required on the resubmitted claim. If multiple DUR alerts are received for a claim and an override from the DAPO Center is obtained for one DUR alert, the provider may be required to pre-override/override the additional prospective DUR alerts, as appropriate.

Providers are strongly encouraged to contact their software vendors to ensure that they have access to these necessary fields. Providers may also refer to the payer sheet for information about NCPDP transactions.

Prospective DUR allows pre-overrides if a drug in claims history will activate an alert for a drug that will dispensed from the same pharmacy. Providers may not pre-override claims for certain drugs for which the overuse precaution ("ER") DUR alert will activate.

Early Refill Prospective Drug Utilization Review Overrides

Examples of when an early refill override request may be approved through the DAPO Center include, but are not limited to, the following:

- If the member has an appropriate medical need (e.g., the member's medications were lost or stolen, the member has requested a vacation supply).
- A member has been taking too much of a medication because he or she misunderstood the directions for administration from the prescriber.
- A prescriber changed the directions for administration of the drug and did not inform the pharmacy provider.

Pharmacy providers should call prescribers to verify the directions for use or to determine whether or not the directions for use changed.

If the pharmacist determines that it is not appropriate to refill the drug early, the pharmacy may instruct the member to return to the pharmacy to pick up the refill after 80 percent of the previous claim's days supply has been taken. Providers may refer to NCPDP field 544-FY (DUR Free Text Message) to determine the date the member may pick up the refill of a drug.

When pharmacy providers submit noncompound drug claims or reversals with a response to a prospective DUR alert at a minimum, the following fields are required:

- Reason for Service Code (NCPDP field 439-E4).

- Professional Service Code (NCPDP field 440-E5).
- Result of Service Code (NCPDP field 441-E6).

The following table indicates the specific fields that providers are required to submit for prospective DUR claims. The "X" denotes a required field with a prospective DUR claim submission.

Policy Requirements	Drug Utilization Review/PPS Code Counter	Reason for Service Code	Professional Service Code	Result of Service Code
Prospective DUR Override	X	X	X	X

The following table provides additional prospective DUR claim submission examples for when providers submit responses to the prospective DUR alert services in the same transaction.

Example	Reason for Service Code	Professional Service Code	Result of Service Code	Drug Utilization Review or Pharmaceutical Care
A	AT	M0	15	DUR
B	AT	RE	1E	DUR
C	AT	RE	1E	DUR
D	AT	RE	1E	DUR
	SR	M0	1F	Not applicable
F	AT	RE	1E	DUR
	SR	M0	1F	Not applicable

Topic #1975

Retrospective Drug Utilization Review

Retrospective DURs (Drug Utilization Reviews) are performed by BadgerCare Plus, Medicaid, and SeniorCare on a monthly basis. Review of drug claims against DUR Board-approved criteria generates patient profiles that are individually reviewed for clinical significance.

Each month, all BadgerCare Plus, Medicaid, and SeniorCare pharmacy claims are examined by a software program for potential adverse drug concerns. Criteria are developed by BadgerCare Plus, Medicaid, and SeniorCare and are reviewed and approved by the DUR Board. Problems that are reviewed include drug-drug interactions, overuse (i.e., early refill), drug-disease contraindications, duplicate therapy, high dose, and drug pregnancy contraindication.

If a potential drug problem is discovered, intervention letters are sent to all prescribers who ordered a drug relevant to an identified problem. Also included with an intervention letter is a response form for the prescriber to complete, a pre-addressed return envelope, and a patient drug profile.

Topic #12619

Therapeutic Duplication

The therapeutic duplication DUR (Drug Utilization Review) alert is activated when another drug is present in claims history in the same therapeutic class as the drug being dispensed. The message sent to the provider includes the drug name in claims history that is causing the alert. The therapeutic classes for the duplication alert include:

- Anti-anxiety agents.
- Antidepressants.
- Antihistamines.
- Antihypertensives.
- Antipsychotics.
- Antithrombotics.
- Barbiturates.
- Cardiovascular agents.
- Diuretics.
- Histamine H2 receptor inhibitors.
- Hypoglycemics.
- Narcotic analgesics.
- NSAIDs (nonsteroidal anti-inflammatory drugs) (including COX-2 selective agents).
- Oral contraceptives.
- Platelet aggregation inhibitors.
- PPI (proton pump inhibitor) drugs.
- Sedatives and hypnotics.
- Skeletal muscle relaxants.

Topic #12659

Underuse Precaution

The underuse precaution DUR (Drug Utilization Review) alert is activated when a member is late in obtaining a refill of a maintenance drug. The alert is sent to the provider when a drug is refilled and exceeds 125 percent of the days' supply on the same drug in history. The number of days late is calculated as the days after the prescription should have been refilled. Drugs with up to a 10-day supply are excluded from this alert. This alert applies, but is not limited to, the following therapeutic categories:

- ACE (angiotensin converting enzyme) inhibitor drugs.
- Alpha-blockers.
- Antilipidemics.
- Angiotensin-2 receptor antagonists.
- Anti-arrhythmics.
- Anticonvulsants.
- Antidepressants.
- Antipsychotics.
- Beta-blockers.
- Calcium channel blockers.
- Digoxin.
- Diuretics.
- Oral hypoglycemics.