in vitro studies have identified a novel gabapentin binding site in the neocortex and hippocampus of rat brain, additional studies are required to fully elucidate the identity and function of this binding site.

In animal test systems, gabapentin exhibits anticonvulsant activity similar to that of other commonly used anticonvulsant drugs. The drug protects against seizures induced in animals by electrical stimulation or pentylenetetrazole, suggesting that it may be effective in the management of tonic-clonic (grand mal) and partial seizures or absence (petit mal) seizures, respectively. However, available data in animals and humans are conflicting regarding the effect of gabapentin on EEG spike and wave activity associated with absence (petit mal) seizures. Gabapentin also prevents seizures in some animals with congenital epilepsy and protects against audiogenic tonic extensions and clonic seizures in mice.

Although the mechanism of action is unknown as yet, gabapentin also has demonstrated analgesic activity. In animals, gabapentin has been shown to prevent allodynia (pain-related behavior in response to normally innocuous stimuli) and hyperalgesia (exaggerated response to painful stimuli) in several models of neuropathic pain. Gabapentin also has been shown to decrease pain-related responses after peripheral inflammation in animals; however, the drug has not altered immediate pain-related behaviors. The clinical relevance of these findings is not known.

Gabapentin does not bind to plasma proteins, is not appreciably metabolized, does not induce hepatic enzyme activity, and does not appear to alter the pharmacokinetics of commonly used anticonvulsant drugs (e.g., carbamazepine, phenytoin, valproate, phenobarbital, diazepam) or oral contraceptives. In addition, the pharmacokinetics of gabapentin are not altered substantially by concomitant administration of other anticonvulsant drugs.

Children younger than 5 years of age have a higher clearance of gabapentin normalized for weight compared with those 5 years of age and older; clearance of the drug in children 5 years of age and older is consistent with that in adults after a single dose. Therefore, a higher daily dosage is required in children 3–5 years of age to achieve average plasma concentrations similar to those in patients 5 years of age and older. (See Dosage and Administration: Dosage.) Infants younger than 1 year of age have a highly variable clearance.

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.

Gabapentin

Oral		
Capsules	100 mg*	Gabapentin Capsules
		Neurontin*, Pfizer
	300 mg*	Gabapentin Capsules
		Neurontin*, Pfizer
	400 mg*	Gabapentin Capsules
		Neurontin*, Pfizer
Solution	250 mg/5 mL	Neurontin*, Pfizer
Tablets	100 mg*	Gabapentin Tablets
	300 mg*	Gabapentin Tablets
	400 mg*	Gabapentin Tablets
	600 mg*	Gabapentin Tablets
	800 mg*	Gabapentin Tablets
Tablets, film-coated	600 mg*	Gabapentin Tablets
		Neurontin*, Pfizer
	800 mg*	Gabapentin Tablets
		Neurontin*, Pfizer

*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

Lamotrigine

■ Lamotrigine is a phenyltriazine anticonvulsant.

Uses

■ **Seizure Disorders** ***Partial Seizures*** Lamotrigine is used in combination with other anticonvulsant agents in the management of partial seizures in adults and children. Lamotrigine also is used as monotherapy in patients converting from monotherapy with a hepatic enzyme-inducing anticonvulsant agent (e.g., phenytoin, carbamazepine, phenobarbital, primidone) in the management of partial seizures in adults.

In controlled clinical studies, adjunctive therapy with lamotrigine was effective in reducing seizure frequency in patients with simple and/or complex partial seizures refractory to therapy with one or more conventional anticonvulsant drugs (e.g., phenytoin, carbamazepine, phenobarbital); the median reduction in seizure frequency was 24–36%. In a controlled clinical study in children 2–16 years of age with partial seizures, the median reduction in frequency of all partial seizures was 36 or 7% in patients receiving lamotrigine or placebo, respectively, in addition to their current therapy (up to 2 conventional anticonvulsant drugs).

The effectiveness of lamotrigine monotherapy in adults with partial seizures who are converting from monotherapy with a hepatic enzyme-inducing anticonvulsant drug (e.g., phenytoin, carbamazepine, phenobarbital, primidone) was established in a controlled clinical study of patients who experienced at least 4 simple or complex partial seizures, with or without secondary generalization, during each of 2 consecutive 4-week baseline periods; during the baseline periods, patients were receiving either phenytoin or carbamazepine monotherapy. Patients were randomized either to lamotrigine (target dose: 500 mg daily) or valproic acid (1000 mg daily) therapy, which was added to their baseline regimen over a 4-week period. Patients were then converted to either lamotrigine or valproic acid monotherapy over another 4-week period and monotherapy continued for another 12-week period. Study end points were either successful completion of the 12-week monotherapy period or meeting a study "escape" criterion, relative to baseline. Escape criteria were defined as doubling of the mean monthly seizure count; doubling of the highest consecutive 2-day seizure frequency; emergence of a new seizure type (defined as a seizure that did not occur during the 8-week baseline period) that was more severe than the other seizure types occurring during the study period; or clinically important prolongation of generalized tonic-clonic seizures. The proportion of lamotrigine- or valproic acid-treated patients meeting escape criteria was 42 or 69%, respectively; no differences in efficacy were detected based on age, race, or gender. It was noted that the patients in the valproic acid control arm were treated intentionally with a relatively low valproic acid dosage because the intent of the study was to establish the effectiveness of lamotrigine monotherapy, and that the study results cannot be interpreted to imply the superiority of lamotrigine therapy to adequate valproic acid therapy. In addition, the manufacturer states that the use of lamotrigine therapy for the management of partial seizures has not been established as initial monotherapy; for conversion from monotherapy with anticonvulsant drugs that do *not* induce hepatic enzymes (e.g., valproate); or for simultaneous conversion to monotherapy from 2 or more concomitant anticonvulsant drugs.

Primary Generalized Tonic-Clonic Seizures Lamotrigine is used in combination with other anticonvulsant agents in the management of primary generalized tonic-clonic seizures in adults and children 2 years of age and older. Efficacy of the drug as adjunctive therapy was established in a placebo-controlled trial in adult and pediatric patients at least 2 years of age who had experienced at least 3 primary generalized tonic-clonic seizures during an 8-week baseline phase. Patients were randomized to receive either placebo or lamotrigine in a fixed-dose regimen (target dosages of 200–400 mg daily in adults and 3–12 mg/kg daily in children) for 19–24 weeks, which was added to their current anticonvulsant regimen of up to 2 anticonvulsant drugs. Patients receiving lamotrigine experienced a substantially greater median reduction in seizure frequency compared with baseline than did patients receiving placebo (66 and 34%, respectively).

Seizures Associated with Lennox-Gastaut Syndrome Lamotrigine also is used in combination with other anticonvulsant agents in the management of generalized seizures associated with Lennox-Gastaut syndrome in pediatric patients and adults. In a controlled clinical trial in patients with Lennox-Gastaut syndrome, adjunctive therapy with lamotrigine resulted in a 32, 34, and 36% decrease in major motor seizures, drop attacks, and tonic-clonic seizures, respectively.

■ **Bipolar Disorder** Lamotrigine is used in the maintenance therapy of bipolar I disorder to prevent or attenuate recurrences of bipolar episodes in patients who remain at high risk of relapse following treatment of an acute depressive or manic episode. The American Psychiatric Association (APA) currently recommends use of lamotrigine as an alternative to first-line maintenance therapies (e.g., lithium, valproic acid, or divalproex). The APA also states that both lamotrigine and lithium are effective in the maintenance treatment of bipolar I disorder; however, the results of two randomized, double-blind, placebo-controlled studies of 18 months' duration indicate that lamotrigine may be more effective in preventing depressive episodes while lithium may be more effective in preventing manic episodes.

Although efficacy of the drug in the acute treatment of mood episodes has yet to be fully established, lamotrigine is considered a first-line agent by the APA for the management of acute depressive episodes in patients with bipolar disorder†. The APA also recommends the use of lamotrigine as an alternative to lithium, valproic acid, or divalproex in the management of patients with rapid cycling bipolar disorder†, particularly in those with the bipolar 2 form of rapid cycling.

For further information on the management of bipolar disorder, see Uses: Bipolar Disorder, in Lithium Salts 28:28.

Dosage and Administration

■ **Administration** Lamotrigine is administered orally. The drug may be administered without regard to meals.

Lamotrigine conventional tablets should be swallowed whole. Lamotrigine chewable/dispersible tablets may be swallowed whole, chewed (and consumed with a small amount of water or diluted fruit juice to aid swallowing), or dispersed in water or diluted fruit juice. To disperse the tablets, they should be added to a small volume (i.e., 5 mL or enough to cover the tablet) of liquid and allowed to disperse completely (over approximately 1 minute); the solution then should be swirled and consumed immediately. Administration of partial quantities of the dispersed tablets should *not* be attempted; calculated doses that do not correspond to available strengths of whole tablets should be rounded down to the nearest whole tablet. Lamotrigine orally disintegrating tablets should be placed on the tongue and moved around in the mouth, where the tablet disintegrates rapidly in saliva, and then subsequently can be swallowed with or without water.

Patients who are currently receiving or beginning therapy with lamotrigine and/or any other anticonvulsant for any indication should be closely monitored for the emergence or worsening of depression, suicidal thoughts or behavior (suicidality), and/or any unusual changes in mood or behavior. (See Cautions: Precautions and Contraindications.)

Dispensing and Administration Precautions Dispensing errors have occurred because of the similarity in spelling between Lamictal® (the trade name for lamotrigine) and Lamisil® (terbinafine hydrochloride), lamivudine, labetalol hydrochloride, Lomotil® (the fixed combination of atropine sulfate and diphenoxylate hydrochloride), and Ludiomil® (the former trade name for maprotiline hydrochloride; no longer commercially available under this trade name in the US). Therefore, extra care should be exercised in ensuring the accuracy of both oral and written prescriptions for Lamictal® and these other drugs. The manufacturer recommends that clinicians consider including the intended use of the particular drug on the prescription, in addition to alerting patients to carefully check the drug they receive and promptly bring any question or concern to the attention of the dispensing pharmacist. The manufacturer also recommends that pharmacists assess various measures of avoiding dispensing errors and implement them as appropriate (e.g., by computerized filling and handling of prescriptions, patient counseling). (See Cautions: Precautions and Contraindications.)

■ **Dosage** Because of the possibility of increasing seizure frequency, anticonvulsant drugs, including lamotrigine, should *not* be discontinued abruptly, particularly in patients with preexisting seizure disorders. Discontinuance of lamotrigine therapy should be done gradually over at least 2 weeks, in a stepwise fashion (e.g., achieving a 50% reduction in the daily dosage of lamotrigine each week). However, concerns for patient safety with continued use of lamotrigine may require more rapid withdrawal of the drug.

The dosage regimen of lamotrigine used in combination with other anticonvulsant drugs depends on whether valproic acid or hepatic enzyme-inducing anticonvulsant drugs, or a combination of these, is administered concomitantly. Addition to lamotrigine therapy of an anticonvulsant drug that induces hepatic microsomal enzymes (e.g., carbamazepine, phenobarbital, phenytoin, primidone) may be expected to increase the clearance (i.e., reduce plasma concentrations) of lamotrigine; conversely, discontinuance of such a concomitantly administered anticonvulsant drug may result in decreased clearance (i.e., increased plasma concentrations) of lamotrigine. Addition of valproate sodium to lamotrigine therapy also decreases the clearance (i.e., increases plasma concentrations) of lamotrigine. Therefore, clinicians should be aware that addition of hepatic enzyme-inducing anticonvulsant drugs or valproic acid to, or their discontinuance from, an anticonvulsant regimen including lamotrigine may require modification of the dosage of lamotrigine and/or the other anticonvulsant agent(s). Exceeding the recommended initial dosage and subsequent dosage escalations of lamotrigine may increase the risk of developing a rash and is *not* recommended.

According to the manufacturer, the effect of anticonvulsants other than hepatic enzyme-inducing anticonvulsant drugs or valproic acid on the pharmacokinetics of lamotrigine has not been fully established, and specific dosing recommendations for patients receiving such drugs cannot be made at this time. Conservative initial dosages and dose escalations (as with concomitant valproic acid) are recommended, and an appropriate maintenance dosage probably would be greater than the maintenance dosage with valproic acid and lower than the maintenance dosage with a hepatic enzyme-inducing anticonvulsant drug.

Seizure Disorders **Adjunctive Therapy for Partial Seizures, Primary Generalized Tonic-Clonic Seizures, or Lennox-Gastaut Syndrome.** For adjunctive therapy in the management of partial seizures, primary generalized tonic-clonic seizures, or Lennox-Gastaut syndrome in adults and children older than 12 years of age who are receiving hepatic enzyme-inducing anticonvulsant drugs *without* concomitant valproic acid therapy, the usual initial dosage of lamotrigine is 50 mg once daily for 2 weeks, then 100 mg daily in 2 divided doses for 2 weeks. The daily dosage may then be increased by 100 mg every 1–2 weeks until an effective maintenance dosage of 300–500 mg daily given in 2 divided doses is reached.

For adjunctive therapy in the management of partial seizures, primary generalized tonic-clonic seizures, or Lennox-Gastaut syndrome in adults and children older than 12 years of age who are receiving an anticonvulsant regimen containing valproic acid, the usual initial dosage of lamotrigine is 25 mg every other day for 2 weeks, followed by 25 mg once daily for 2 weeks. The initial dosage of lamotrigine in patients also receiving valproic acid should not exceed 25 mg every other day because of an increased incidence of rash with concomitant lamotrigine and valproic acid therapy. After the initial 4 weeks of therapy, the daily dosage of lamotrigine may be increased by 25–50 mg every 1–2 weeks until an effective maintenance dosage of 100–400 mg daily given in 1 or 2 divided doses is reached. The usual maintenance dosage of lamotrigine when added to valproic acid alone in adults and children older than 12 years of age is 100–200 mg daily.

Although maintenance dosages of lamotrigine as high as 700 mg daily have been used in anticonvulsant drug regimens that included hepatic enzyme-inducing anticonvulsants but *not* valproic acid or as high as 200 mg daily in drug regimens that included valproic acid alone, dosages exceeding 300–500 mg daily (in regimens *not* containing valproic acid) or exceeding 200 mg daily (in regimens containing valproic acid alone) have not been evaluated in controlled studies.

For adjunctive therapy in the management of partial seizures, primary generalized tonic-clonic seizures, or Lennox-Gastaut syndrome in patients 2–12 years of age who are receiving hepatic enzyme-inducing anticonvulsant drugs *without* concomitant valproic acid therapy, the usual initial dosage of lamotrigine is 0.6 mg/kg daily (rounded down to the nearest whole tablet) in 2 divided doses for 2 weeks. During the subsequent 2 weeks of therapy, the usual dosage is 1.2 mg/kg daily (rounded down to the nearest whole tablet) in 2 divided doses. Subsequent daily doses should be increased every 1–2 weeks by 1.2 mg/kg (rounded down to the nearest whole tablet) until an effective daily maintenance dosage of 5–15 mg/kg (maximum of 400 mg/day in 2 divided doses) is reached. In patients weighing less than 30 kg, increases in maintenance dosages of up to 50% may be required based on the response and tolerance of the patient.

For adjunctive therapy in the management of partial seizures, primary generalized tonic-clonic seizures, or Lennox-Gastaut syndrome in patients 2–12 years of age who are receiving an anticonvulsant regimen containing valproic acid, the usual initial dosage of lamotrigine is 0.15 mg/kg daily (rounded down to the nearest whole tablet) in 1 or 2 divided doses for 2 weeks. During the subsequent 2 weeks of therapy, the usual dosage is 0.3 mg/kg daily (rounded down to the nearest whole tablet) in 1 or 2 divided doses. Subsequent daily doses should be increased every 1–2 weeks by 0.3 mg/kg (rounded down to the nearest whole tablet) until an effective daily maintenance dosage of 1–5 mg/kg (maximum of 200 mg/day in 1 or 2 divided doses) is reached. Usual maintenance dosages range from 1–3 mg/kg daily in patients receiving lamotrigine and valproic acid alone. In patients weighing less than 30 kg, increases in maintenance dosages of up to 50% may be required based on the response and tolerance of the patient.

Monotherapy for Partial Seizures. For subsequent monotherapy in the management of partial seizures in patients converted from monotherapy with a hepatic enzyme-inducing anticonvulsant drug, the usual lamotrigine maintenance dosage in adults and children 16 years of age or older is 500 mg daily given in 2 divided doses. The transition regimen for converting patients from monotherapy with a hepatic enzyme-inducing anticonvulsant drug to lamotrigine monotherapy is a 2-step process: the goal of the transition regimen is to ensure adequate seizure control while minimizing the possibility of developing a serious rash associated with the rapid titration of lamotrigine.

In the first step of the process, lamotrigine therapy is added to the current drug regimen (which should be maintained at a fixed dose) at a dosage of 50 mg once daily for 2 weeks, followed by 100 mg daily in 2 divided doses for 2 weeks; the daily dosage is then increased by 100 mg every 1–2 weeks until the maintenance dosage of 500 mg daily (in 2 divided doses) is reached. Once the maintenance lamotrigine dosage is reached, the concomitant hepatic enzyme-inducing anticonvulsant drug can then be withdrawn gradually over a period of 4 weeks; based on experience from the controlled clinical trial, the concomitant drug was withdrawn by 20% decrements each week over a 4-week period.

Bipolar Disorder For monotherapy in the maintenance treatment of bipolar disorder, the recommended initial adult dosage of lamotrigine is 25 mg once daily for 2 weeks, followed by 50 mg once daily for 2 weeks. After the initial 4 weeks of therapy, the daily dosage of lamotrigine may be doubled at weekly intervals until an effective maintenance dosage of 200 mg daily is reached. Because 400-mg daily dosages were shown to be no more effective than 200-mg daily dosages in clinical studies of lamotrigine monotherapy, the manufacturer recommends that daily dosages not exceed 200 mg daily.

For adjunctive therapy in the maintenance treatment of bipolar disorder in patients who are receiving carbamazepine or other hepatic enzyme-inducing drugs *without* concomitant valproic acid therapy, the usual initial adult dosage of lamotrigine is 50 mg once daily for 2 weeks, followed by 100 mg daily in 2 divided doses for 2 weeks; the daily dosage is then increased in 100-mg increments at weekly intervals until the maintenance dosage of 400 mg daily (in 2 divided doses) is reached.

For adjunctive therapy in the maintenance treatment of bipolar disorder in adults who are receiving valproic acid, the usual initial dosage of lamotrigine is 25 mg every other day for 2 weeks, followed by 25 mg once daily for 2 weeks. After the initial 4 weeks of therapy, the daily dosage of lamotrigine may be doubled at weekly intervals until an effective maintenance dosage of 100 mg daily is reached. To minimize the risk of potentially serious rash in patients receiving lamotrigine in conjunction with valproic acid, the recommended initial dosages and subsequent dose escalations of lamotrigine should not be exceeded.

Addition of hepatic enzyme-inducing drugs (e.g., carbamazepine) or hepatic enzyme-inhibiting drugs (e.g., valproic acid) to a regimen including lamotrigine may require modification of the dosage of lamotrigine and/or the hepatic enzyme-inducing or -inhibiting drug. In pivotal clinical studies, dosages of lamotrigine were halved immediately following the addition of valproic acid to treat an acute mood episode and maintained at that dosage as long as valproic acid was administered concomitantly with lamotrigine. Following addition of carbamazepine or other hepatic enzyme-inducing drugs to treat an acute mood episode, dosages of lamotrigine were gradually doubled (e.g., over a period of at least 3 weeks) and maintained at that dosage as long as these drugs were administered concomitantly with lamotrigine. Following the addition of other psychotropic agents with no known clinical pharmacokinetic interactions with lamotrigine, patients were maintained at current maintenance dosages of lamotrigine.

Discontinuance of hepatic enzyme-inducing drugs (e.g., carbamazepine) or hepatic enzyme-inhibiting drugs (e.g., valproic acid) from a regimen including lamotrigine may require modification of the dosage of lamotrigine. For patients discontinuing carbamazepine or other enzyme-inducing agents following resolution of the acute mood episode and achievement of a maintenance lamotrigine dosage, lamotrigine dosage should remain constant for the first week and then should be decreased in 100-mg daily increments at weekly intervals until an effective maintenance dosage of 200 mg daily is reached. For patients discontinuing valproic acid following resolution of the acute mood episode and achievement of a maintenance lamotrigine dosage, lamotrigine dosage should be increased in 50-mg daily increments at weekly intervals until an effective maintenance dosage of 200 mg daily is reached.

The optimum duration of lamotrigine therapy for the management of bipolar disorder has not been established, and the usefulness of the drug during prolonged therapy (i.e., longer than 18 months) should be reevaluated periodically.

■ **Dosage in Renal and Hepatic Impairment** Because clinical experience with lamotrigine is limited in patients with concomitant illness, the drug should be used with caution in patients with conditions (e.g., renal, hepatic, cardiac impairment) that may affect metabolism and elimination of the drug.

The manufacturer states that lamotrigine should be used with caution in patients with severe renal impairment because there is insufficient information from controlled clinical studies to establish the safety and efficacy of therapy with the drug in such patients. The initial dosage of lamotrigine in patients with renal impairment should be based on the patient's existing anticonvulsant drug regimen (see Dosage and Administration: Dosage). The manufacturer states that a reduced maintenance dosage of lamotrigine may be effective and generally should be used in patients with substantial renal impairment; however, the manufacturer currently makes no specific recommendation for dosage adjustment in such patients.

The manufacturer states that experience with lamotrigine therapy in patients with hepatic impairment is limited. Based on a clinical pharmacology study of the drug in a small number of patients with moderate to severe hepatic dysfunction, the manufacturer makes the general recommendation that initial, escalation, and maintenance doses of lamotrigine therapy should be decreased by approximately 50% in patients with moderate (e.g., Child-Pugh class B) and 75% in patients with severe (e.g., Child-Pugh class C) hepatic impairment. Escalation and maintenance dosages should be adjusted according to clinical response.

Cautions

Lamotrigine generally is well tolerated. However, there have been rare reports of serious dermatologic reactions (including some fatalities) in adults and children receiving lamotrigine. Nervous system and dermatologic effects are among the most frequently reported adverse effects of lamotrigine and among those most frequently requiring discontinuance of the drug. The most frequently occurring adverse effects associated with lamotrigine as adjunctive therapy in adults in controlled clinical trials include dizziness, ataxia, somnolence, headache, diplopia, blurred vision, nausea, vomiting, and rash. Discontinuance of lamotrigine because of adverse effects was required in about 11% of adult patients receiving the drug as adjunctive therapy in uncontrolled and controlled clinical trials; the adverse effects most frequently associated with discontinuance of lamotrigine in these trials were rash (3% of patients), dizziness (2.8% of patients), and headache (2.5% of patients). In children receiving lamotrigine as adjunctive therapy in controlled clinical trials, the most commonly reported adverse effects were infection, vomiting, rash, fever, somnolence, accidental injury, dizziness, diarrhea, abdominal pain, nausea, ataxia, tremor, asthenia, bronchitis, flu syndrome, and diplopia. Approximately 11.5% of pediatric patients receiving lamotrigine as adjunctive therapy in clinical trials discontinued the drug because of an adverse effect; the adverse effects most frequently associated with discontinuance of lamotrigine therapy in these patients were rash (4.4% of patients), reaction aggravated (1.7% of patients), and ataxia (0.6% of patients).

The most common adverse effects associated with lamotrigine as monotherapy in adults in the controlled clinical trial were vomiting, coordination abnormality, dyspepsia, nausea, dizziness, rhinitis, anxiety, insomnia, infection, pain, weight decrease, chest pain, and dysmenorrhea; during the conversion period (i.e., when lamotrigine was initially added on to an existing monotherapy regimen consisting of a hepatic enzyme-inducing anticonvulsant drug), the most commonly reported adverse effects were dizziness, headache, nausea, asthenia, coordination abnormality, vomiting, rash, somnolence, diplopia, ataxia, accidental injury, tremor, blurred vision, insomnia, nystagmus, diarrhea, lymphadenopathy, pruritus, and sinusitis. The adverse effects most commonly associated with discontinuance of the drug in this trial were rash (4.5% of patients), headache (3.1% of patients), and asthenia (2.4% of patients).

The adverse effect profiles in males and females in clinical trials of lamotrigine were similar and were independent of age; the rates of discontinuance of lamotrigine for individual adverse effects also were similar for males and females. In general, females receiving adjunctive therapy with lamotrigine or placebo in controlled trials were more likely to report adverse effects than were males; however, dizziness was the only adverse effect reported with at least 10% greater frequency (i.e., 16.5% greater frequency) in females than in males (without a corresponding difference by gender with placebo) in controlled trials.

Because clinical trials of lamotrigine therapy involved specific patient populations and use of the drug as adjunctive therapy or monotherapy following conversion from therapy with another single hepatic enzyme-inducing anticonvulsant drug, it is difficult to determine whether a causal relationship exists for many reported adverse effects, to compare adverse effect frequencies with those in other clinical reports, and/or to extrapolate the adverse effects experience from controlled clinical trials to usual clinical practice.

■ **Nervous System Effects** Nervous system effects were among the most frequent adverse effects reported in patients receiving lamotrigine as adjunctive therapy in controlled clinical trials. Dizziness, headache, and ataxia were the most frequent adverse nervous system effects, occurring in 38, 29, and 22% of adults, respectively, in controlled trials of lamotrigine adjunctive therapy. The frequency of dizziness and ataxia and the rate of discontinuance of lamotrigine because of these adverse effects were dose related in clinical trials; in a dose-response study, dizziness occurred in 54, 31, or 27% of patients receiving lamotrigine 500 mg/day, lamotrigine 300 mg/day, or placebo, respectively, while ataxia occurred in 28, 10, or 10% of those receiving these respective regimens. Limited data also suggest an increased incidence of adverse nervous system effects in patients receiving carbamazepine concomitantly with lamotrigine. (See Cautions: Precautions and Contraindications.)

Somnolence or insomnia occurred in 14 or 6%, respectively, of adults receiving lamotrigine as adjunctive therapy in controlled clinical trials. Incoordination or tremor was reported in 6 or 4%, respectively, of lamotrigine-treated adults; limited evidence suggests that incoordination and tremor may be dose related, and tremor may occur more frequently with concomitant administration of valproic acid and lamotrigine. Depression occurred in 4%, anxiety in 4%, irritability in 3%, speech disorder in 3%, and concentration disturbance in 2% of adults receiving lamotrigine as adjunctive therapy in controlled clinical trials. Seizure or seizure exacerbation has been reported in 3 or 2% of adults, respectively, receiving lamotrigine as adjunctive therapy in controlled trials; an increase in seizure frequency also has been reported with lamotrigine therapy. Treatment-emergent seizures diagnosed unequivocally as status epilepticus were reported in 7 of 2343 adults receiving adjunctive therapy with lamotrigine in clinical trials; however, the manufacturer states that valid estimates of the incidence of treatment-emergent status epilepticus are difficult to obtain because of variations in the definitions used by different investigators to identify such cases.

Coordination abnormality, dizziness, anxiety, and insomnia occurred in 7, 7, 5, and 5%, respectively, of adults receiving lamotrigine as monotherapy in a controlled trial; amnesia, ataxia, asthenia, depression, hypesthesia, libido increase, decreased or increased reflexes, nystagmus, and irritability, each occurred in 2% of such patients. Paresthesia or asthenia occurred in more than 1% of adults receiving lamotrigine as adjunctive therapy in controlled clinical trials but with equal or greater frequency in those receiving placebo.

Somnolence occurred in 17%, dizziness in 14%, ataxia in 11%, tremor in 10%, and asthenia in 8% of children receiving lamotrigine as adjunctive therapy in controlled clinical trials. Emotional lability, gait abnormality, thinking abnormality, seizures, nervousness, and vertigo each occurred in 2–4% of children receiving lamotrigine as adjunctive therapy in controlled clinical trials.

Amnesia, confusion, hostility, decreased memory, nervousness, nystagmus, thinking abnormality, or vertigo was reported in at least 1% of patients receiving lamotrigine in uncontrolled and controlled clinical trials. Abnormal dreams, abnormal gait, agitation, akathisia, apathy, aphasia, CNS depression, depersonalization, dysarthria, dyskinesia, dysphoria, emotional lability, euphoria, faintness, grand mal seizures, hallucinations, hyperkinesia, hypertonia, hypesthesia, increased libido, mind racing, myoclonus, panic attack, paranoid reaction, personality disorder, psychosis, migraine, sleep disorder, or stupor occurred in at least 0.1% but in less than 1% of such patients. Cerebellar syndrome, choreoathetosis, CNS stimulation, delirium, delusions, dystonia, hypoesthesia, hypotonia, hemiplegia, hyperalgesia, hyperesthesia, hypokinesia, hypomania, decreased libido, manic-depressive reaction, movement disorder, neuralgia, neurosis, or paralysis occurred in less than 0.1% of patients.

Suicidal ideation has been reported in 2–5% of adult patients receiving lamotrigine monotherapy for partial seizures in a controlled clinical trial and in less than 1% of pediatric and adult patients receiving the drug in uncontrolled and controlled clinical trials; suicide and/or suicide attempt has been reported rarely. The Food and Drug Administration (FDA) has analyzed suicidality reports from placebo-controlled studies involving 11 anticonvulsants, including lamotrigine, and found that patients receiving anticonvulsants had approximately twice the risk of suicidal behavior or ideation (0.43%) compared with patients receiving placebo (0.24%). (See Cautions: Precautions and Contraindications.)

Exacerbation of parkinsonian manifestations in patients with preexisting parkinsonian syndrome and the occurrence of tics have been reported during postmarketing experience with lamotrigine and/or in worldwide uncontrolled clinical trials; however, the manufacturer states that data are insufficient to provide an estimate of the incidence of such effects or to establish a causal relationship to lamotrigine.

■ **GI Effects** GI effects were among the most frequent adverse effects reported in adults receiving lamotrigine as adjunctive therapy in controlled clinical trials. Nausea was the most frequent adverse GI effect, occurring in 19% of adults in controlled clinical trials; vomiting was reported in 9% of patients in these trials. The frequency of nausea and vomiting appears to be dose related; in a dose-response study, nausea occurred in 25, 18, or 11% of patients receiving lamotrigine 500 mg daily, lamotrigine 300 mg daily, or placebo, respectively, while vomiting occurred in 18, 11, or 4% of those receiving these respective regimens. Diarrhea occurred in 6%, dyspepsia in 5%, abdominal pain in 5%, constipation in 4%, tooth disorder in 3%, and anorexia in 2% of adults receiving lamotrigine as adjunctive therapy in controlled clinical trials. Flatulence was reported in more than 1% of adults receiving lamotrigine as adjunctive therapy in controlled clinical trials but occurred with equal or greater frequency in patients receiving placebo. Vomiting, dyspepsia, and nausea occurred in 9, 7, and 7%, respectively, of adults receiving lamotrigine as monotherapy in a controlled trial; anorexia, dry mouth, rectal hemorrhage, and peptic ulcer each occurred in 2% of such patients.

Vomiting occurred in 20%, diarrhea in 11%, abdominal pain in 10%, and nausea in 10% of children receiving lamotrigine as adjunctive therapy in controlled clinical trials. Constipation, dyspepsia, and tooth disorder each occurred in 2–4% of children receiving lamotrigine as adjunctive therapy in controlled clinical trials.

Halitosis, dry mouth, dysphagia, gingivitis, glossitis, gum hyperplasia, increased appetite, increased salivation, mouth ulceration, stomatitis, taste perversion, thirst, or tooth disorder occurred in at least 0.1% but in less than 1% of patients receiving lamotrigine in uncontrolled and controlled clinical trials. Eructation, gastritis, GI hemorrhage, gum hemorrhage, hematemesis, hemorrhagic colitis, melena, gastric ulcer, taste loss, or tongue edema was reported in less than 0.1% of patients.

Esophagitis and pancreatitis have been reported during postmarketing experience with lamotrigine and/or in worldwide uncontrolled clinical trials; however, the manufacturer states that data are insufficient to provide an estimate of the incidence of such effects or to establish a causal relationship to lamotrigine.

■ **Dermatologic and Sensitivity Reactions** Serious dermatologic reactions (including some fatalities) have been reported in adults and children receiving lamotrigine therapy. Rash occurred in 10% of adults and 14% of children receiving lamotrigine as adjunctive therapy in controlled clinical trials. The incidence of severe rash associated with lamotrigine also appears to be higher in pediatric patients than in adults; the manufacturer states that severe rash, including Stevens-Johnson syndrome, has been reported in 0.8% of children younger than 16 years of age and in 0.3% of adults receiving lamotrigine as adjunctive therapy in clinical trials. There is evidence that most cases of rash associated with lamotrigine therapy are associated with transiently high plasma concentrations of the drug occurring during the initial weeks of therapy or with high plasma concentrations occurring during concomitant valproic acid therapy. Cases of life-threatening rashes associated with lamotrigine almost always have occurred within 2–8 weeks of treatment initiation; however, severe rashes rarely have presented following prolonged treatment (e.g., 6 months). Lamotrigine-associated rashes do not appear to have distinguishing features. Because it is not possible to distinguish benign rashes from those that may become severe and/or life-threatening, lamotrigine generally should be discontinued at the first sign of rash (unless the rash is known not to be drug related). However, a rash may become life-threatening or permanently disabling or disfiguring despite discontinuance of the drug. Discontinuance of lamotrigine because of rash was required in 3% of adults receiving the drug as adjunctive therapy and 4.5% of adults receiving the drug as monotherapy in controlled clinical trials; 4.4% of pediatric patients receiving lamotrigine in controlled clinical trials discontinued the drug because of the development of rash. The potential for development of a rash at the beginning of lamotrigine therapy may be decreased by employing low initial doses and by gradual escalation of dosage to avoid initially high plasma concentrations of the drug.

Rash, including serious and potentially life-threatening rash, appears to be more likely to occur in patients receiving concomitant valproic acid. Valproic acid can decrease clearance and increase plasma concentrations of lamotrigine more than twofold; exceeding the recommended reduced initial dosage of lamotrigine or the subsequent recommended schedule for escalation of lamotrigine dosage (see Dosage and Administration: Dosage and see Cautions: Precautions and Contraindications), particularly in patients receiving valproic acid, may increase the incidence of rash, including serious rash, in such patients. In clinical trials, 1% of adults and 1.2% of children receiving a drug regimen including lamotrigine concomitantly with valproic acid experienced a rash requiring hospitalization, while 0.16% of adults and 0.6% of children receiving a drug regimen of lamotrigine without valproic acid were hospitalized because of rash.

Rashes severe enough to cause hospitalization, including Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme, angioedema, and a hypersensitivity syndrome (usually consisting of fever, rash, facial swelling, and hematologic, hepatic, and/or lymphatic involvement), occurred in 0.3% of adults receiving lamotrigine in premarketing controlled and uncontrolled clinical trials and in about 0.8% of pediatric patients receiving the drug in clinical trials; death associated with rash has been reported rarely in postmarketing use of lamotrigine. Erythema multiforme has been reported in patients receiving lamotrigine in premarketing controlled and uncontrolled clinical trials in the US, while lupus-like syndrome and vasculitis have been reported during postmarketing experience with the drug and/or in worldwide uncontrolled clinical trials.

Pruritus occurred in 3% of adults receiving lamotrigine as adjunctive therapy in controlled clinical trials. Contact dermatitis, dry skin, peripheral edema, and sweating each occurred in 2% of adults receiving lamotrigine as monotherapy in a controlled trial. Eczema, facial edema, photosensitivity, and pruritus each were reported in 2% of children receiving lamotrigine as adjunctive therapy in controlled clinical trials. Acne, alopecia, facial edema, dry skin, erythema, hirsutism, maculopapular rash, peripheral edema, skin discoloration, Stevens-Johnson syndrome, sweating, urticaria, or vesiculobullous rash occurred in at least 0.1% but in less than 1% of patients receiving lamotrigine in uncontrolled and controlled clinical trials. Angioedema, erythema multiforme, fungal dermatitis, herpes zoster, leukoderma, petechial rash, pustular rash, seborrhea, or photosensitivity occurred in less than 0.1% of patients.

Hypersensitivity reactions, which can be fatal or life-threatening, have been reported in patients treated with lamotrigine. In some cases, manifestations of these reactions have included multiorgan dysfunction (including hepatic abnormalities) and disseminated intravascular coagulation (see Cautions: Hepatic Effects). Early signs of a possible hypersensitivity reaction, such as fever and lymphadenopathy, should prompt immediate evaluation of the patient; a rash may or may not be present. Unless another cause for the signs or symptoms is found, lamotrigine should be discontinued.

■ **Cardiovascular Effects** Hemorrhage was reported in 2% of pediatric patients receiving lamotrigine as adjunctive therapy in controlled clinical trials. Chest pain occurred in more than 1% of adults receiving lamotrigine as adjunctive therapy in controlled clinical trials but occurred with equal or greater frequency in patients receiving placebo. Chest pain also occurred in 5% of adults receiving lamotrigine as monotherapy in a controlled clinical trial. Flushing, hot flushes, palpitations, postural hypotension, syncope, tachycardia, or vasodilation occurred in at least 0.1% but in less than 1% of patients receiving lamotrigine in uncontrolled and controlled clinical trials. Cerebrovascular accident, cerebral sinus thrombosis, deep thrombophlebitis, myocardial infarction, atrial fibrillation, angina pectoris, hemorrhage, or hypertension occurred in less than 0.1% of patients receiving lamotrigine in uncontrolled and controlled clinical trials.

■ **Respiratory Effects** Rhinitis occurred in 14%, pharyngitis in 10%, increased cough in 8%, and flu-like syndrome in 7% of adults receiving lamotrigine as adjunctive therapy in controlled clinical trials. Respiratory disorder was reported in more than 1% of adults receiving lamotrigine as adjunctive therapy in controlled clinical trials but occurred with equal or greater frequency in patients receiving placebo. Rhinitis occurred in 7% of adults receiving lamotrigine as monotherapy in a controlled trial; epistaxis, bronchitis, and dyspnea each occurred in 2% of such patients. Pharyngitis, bronchitis, and increased cough occurred in 14, 7, and 7%, respectively, of children receiving lamotrigine as adjunctive therapy in controlled clinical trials. Sinusitis and bronchospasm each were reported in 2% of children in these trials. Dyspnea, epistaxis, or hyperventilation occurred in at least 0.1% but in less than 1% of patients in uncontrolled and controlled clinical trials, and bronchospasm, hiccups, or sinusitis occurred in less than 0.1% of patients. Apnea has been reported during postmarketing experience with lamotrigine and/or in worldwide uncontrolled clinical trials; however, the manufacturer states that data are insufficient to provide an estimate of the incidence of this adverse effect or to establish a causal relationship to lamotrigine.

■ **Ocular and Otic Effects** Ocular effects were among the most frequent adverse effects reported in patients receiving lamotrigine as adjunctive therapy in controlled clinical trials. Diplopia was the most frequent adverse ocular effect reported in adults receiving lamotrigine as adjunctive therapy in controlled trials, occurring in 28% of such patients, and blurred vision occurred in 16% of patients. The frequency of diplopia and blurred vision appears to be dose related; in a dose-response study, diplopia occurred in 49, 24, or 8% of patients receiving lamotrigine 500 mg daily, lamotrigine 300 mg daily, or placebo, respectively, while blurred vision occurred in 25, 11, or 10% of patients receiving these respective regimens. Limited data also indicate an increased incidence of some adverse effects, including diplopia and blurred vision, in patients receiving carbamazepine concomitantly with lamotrigine. (See Cautions: Precautions and Contraindications.)

Vision abnormality occurred in 3% of adults receiving lamotrigine as adjunctive therapy in controlled clinical trials and in 2% of adults receiving lamotrigine as monotherapy in a controlled trial. Diplopia, blurred vision, or vision abnormality occurred in 5, 4, or 2%, respectively, of children receiving lamotrigine as adjunctive therapy in controlled clinical trials. Abnormality of accommodation, conjunctivitis, oscillopsia, or photophobia occurred in at least 0.1% but in less than 1% of patients in uncontrolled and controlled clinical trials, and dry eyes, lacrimation disorder, strabismus, ptosis, or uveitis occurred in less than 0.1% of patients.

Ear disorder was reported in 2% of children receiving lamotrigine as adjunctive therapy in controlled clinical trials. Otic pain or tinnitus occurred in at least 0.1% but in less than 1% of patients in uncontrolled and controlled

clinical trials. Deafness was reported in less than 0.1% of patients in uncontrolled and controlled clinical trials.

■ **Musculoskeletal Effects** Neck pain and arthralgia each occurred in 2% of adults receiving lamotrigiuc as adjunctive therapy in controlled clinical trials. Back pain or myalgia occurred in more than 1% of patients receiving lamotrigine as adjunctive therapy in controlled trials but with equal or greater frequency in patients receiving placebo. Joint disorder, myasthenia, muscle spasm, or twitching occurred in at least 0.1% but in less than 1% of patients in uncontrolled and controlled trials, and arthritis, bursitis, leg cramps, tendinous contracture, or pathological fracture occurred in less than 0.1% of patients. Rhabdomyolysis has been observed in patients experiencing hypersensitivity reactions during postmarketing experience with lamotrigine and/or in worldwide uncontrolled trials; however, the manufacturer states that data are insufficient to provide an estimate of the incidence of this adverse effect or to establish a causal relationship to lamotrigine.

■ **Genitourinary Effects** Dysmenorrhea occurred in 7%, vaginitis in 4%, and amenorrhea in 2% of women receiving lamotrigine as adjunctive therapy in controlled clinical trials. Dysmenorrhea occurred in 5% of women receiving lamotrigine as monotherapy in a controlled trial. Menstrual disorder or urinary tract infection occurred in more than 1% of adults receiving adjunctive lamotrigine therapy in controlled trials but with equal or greater frequency in patients receiving placebo. Urinary tract infection occurred in 3% of children receiving lamotrigine as adjunctive therapy in controlled clinical trials; penis disorder was reported in 2% of male pediatric patients receiving lamotrigine in these trials.

Lactation (in females), vaginal candidiasis, hematuria, polyuria, urinary frequency, urinary incontinence, or urinary retention occurred in at least 0.1% but in less than 1% of patients receiving lamotrigine therapy in uncontrolled and controlled clinical trials. Abnormal ejaculation, impotence, epididymitis, cystitis, urine abnormality, dysuria, kidney pain, kidney failure, acute kidney failure, or menorrhagia occurred in less than 0.1% of patients in uncontrolled and controlled clinical trials.

■ **Endocrine and Metabolic Effects** Goiter or hyperthyroidism occurred in less than 0.1% of patients receiving lamotrigine in uncontrolled and controlled clinical trials. Weight decrease occurred in 5% of adults receiving lamotrigine as monotherapy in a controlled trial. Weight loss or weight gain occurred in at least 0.1% but in less than 1% of patients in uncontrolled and controlled clinical trials. Edema occurred in 2% of children receiving lamotrigine as adjunctive therapy in controlled clinical trials. Edema or hyperglycemia occurred in less than 0.1% of patients in uncontrolled and controlled clinical trials.

■ **Hepatic Effects** Fatalities associated with multiorgan failure and various degrees of hepatic failure have been reported rarely during premarketing trials of lamotrigine as adjunctive therapy. A young woman receiving concomitant valproic acid and carbamazepine developed a possible hypersensitivity syndrome consisting of headache, fever, and a maculopapular rash 3 weeks following addition of lamotrigine to therapy; fulminant hepatic failure and hepatic coma developed within 3 days, and despite subsequent clinical improvement, the patient died of a massive pulmonary embolus 2 months later. Multiorgan (including renal and/or hepatic) failure and disseminated intravascular coagulation associated with frequent generalized seizures or status epilepticus have been reported in several patients receiving lamotrigine; it has been suggested that this syndrome may have resulted from rhabdomyolysis caused by uncontrolled generalized seizures. The majority of these cases of hepatic and/or multiorgan failure occurred in association with other serious medical events (e.g., status epilepticus, overwhelming sepsis), making it difficult to identify the initiating cause. However, disseminated intravascular coagulation, rhabdomyolysis, renal failure, maculopapular rash, ataxia, and increased liver enzymes (e.g., AST [SGOT]) in the absence of generalized seizures also have been reported rarely with lamotrigine as adjunctive therapy. Abnormal liver function test results occurred in at least 0.1% but in less than 1% of patients receiving lamotrigine in uncontrolled and controlled clinical trials, and hepatitis, increased alkaline phosphatase, or bilirubinemia occurred in less than 0.1% of patients.

■ **Hematologic Effects** Blood dyscrasias that may or may not be associated with hypersensitivity reactions, including neutropenia, leukopenia, anemia, thrombocytopenia, pancytopenia, and rarely, aplastic anemia and pure red cell aplasia (PRCA), have been reported with lamotrigine. Lymphadenopathy occurred in 2% of children receiving lamotrigine as adjunctive therapy in controlled clinical trials. Anemia, ecchymosis, petechiae, leukocytosis, leukopenia, or lymphadenopathy occurred in at least 0.1% but in less than 1% of patients receiving lamotrigine in uncontrolled and controlled clinical trials. Eosinophilia, fibrin decrease, fibrinogen decrease, iron deficiency anemia, lymphocytosis, macrocytic anemia, or thrombocytopenia occurred in less than 0.1% of patients receiving lamotrigine in uncontrolled and controlled clinical trials.

Disseminated intravascular coagulation has been reported rarely in conjunction with multiorgan (e.g., renal and/or hepatic) failure in patients receiving lamotrigine as adjunctive therapy. (See Cautions: Hepatic Effects.) Agranulocytosis, aplastic anemia, hemolytic anemia, neutropenia, pancytopenia, red cell aplasia, and progressive immunosuppression have been reported during postmarketing experience with lamotrigine and/or in worldwide uncontrolled clinical trials; however, the manufacturer states that data are insufficient to provide an estimate of the incidence of such effects or to establish a causal relationship to lamotrigine.

■ **Other Adverse Effects** Flu syndrome or fever occurred in 7 or 6%, respectively, of adults receiving lamotrigine as adjunctive therapy in controlled clinical trials. Pain and infection each occurred in 5% and fever in 2% of adults receiving lamotrigine as monotherapy in a controlled trial. Infection occurred in 20%, fever in 15%, accidental injury in 14%, flu syndrome in 7%, and pain in 5% of children receiving lamotrigine as adjunctive therapy in controlled clinical trials. Pain occurred in at least 1% of patients receiving lamotrigine in uncontrolled and controlled clinical trials. Accidental injury, infection, chills, and malaise occurred in at least 0.1% but in less than 1% of patients receiving lamotrigine in uncontrolled and controlled clinical trials. Breast pain, breast abscess, breast neoplasm, enlarged abdomen, increase in serum creatinine concentration, parosmia, or alcohol intolerance occurred in less than 0.1% of patients.

■ **Precautions and Contraindications** Because of the possibility of increased seizure frequency, anticonvulsant drugs, including lamotrigine, should not be discontinued suddenly, particularly in patients with preexisting seizure disorders. Unless safety concerns dictate a more rapid withdrawal of the drug, discontinuance of lamotrigine should be done gradually over a period of 2 weeks. (See Dosage and Administration: Dosage.) Seizure exacerbation and/or status epilepticus have been reported in patients receiving lamotrigine as adjunctive therapy in the management of seizure disorders, although the incidence of these adverse effects has been difficult to determine conclusively. (See Cautions: Nervous System Effects.) The use and dosage of all anticonvulsant drugs in a regimen including lamotrigine should be reevaluated if there is a change in seizure control or appearance or worsening of adverse effects, and patients should be instructed to report immediately any worsening of seizure control.

The US Food and Drug Administration (FDA) has informed healthcare professionals about an increased risk of suicidality (suicidal behavior or ideation) observed in an analysis of studies using various anticonvulsants compared with placebo. FDA's analysis included 199 randomized, placebo-controlled studies of 11 anticonvulsants (carbamazepine, felbamate, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, pregabalin, tiagabine, topiramate, valproate, and zonisamide) involving over 43,000 patients 5 years of age or older; the studies evaluated the effectiveness of the anticonvulsants in epilepsy, psychiatric disorders (e.g., bipolar disorder, depression, anxiety), and other conditions (e.g., migraine, neuropathic pain). The analysis revealed that patients receiving these anticonvulsants had approximately twice the risk of suicidal behavior or ideation (0.43%) compared with patients receiving placebo (0.24%); this increased suicidality risk was observed as early as one week after beginning therapy and continued through 24 weeks. The results were generally consistent among the 11 drugs studied. In addition, patients who were treated for epilepsy, psychiatric disorders, and other conditions were all found to be at increased risk for suicidality when compared with placebo; there did not appear to be a specific demographic subgroup of patients to which the increased risk could be attributed. However, the relative risk for suicidality was found to be higher in patients with epilepsy compared with patients who were given one of the drugs for psychiatric or other conditions.

Based on the current analysis of the available data, FDA recommends that all patients who are currently receiving or beginning therapy with any anticonvulsant for any indication be closely monitored for the emergence or worsening of depression, suicidal thoughts or behavior (suicidality), and/or unusual changes in mood or behavior. Symptoms such as anxiety, agitation, hostility, mania, and hypomania may be precursors to emerging suicidality. Clinicians should inform patients, their families, and caregivers of the potential for an increased risk of suicidality so that they are aware and able to notify their clinician of any unusual behavioral changes. Patients, family members, and caregivers also should be advised not to make any changes to the anticonvulsant regimen without first consulting with the responsible clinician. They should pay close attention to any day-to-day changes in mood, behavior, and actions; since changes can happen very quickly, it is important to be alert to any sudden differences. In addition, patients, family members, and caregivers should be aware of common warning signs that may signal suicide risk (e.g., talking or thinking about wanting to hurt oneself or end one's life, withdrawing from friends and family, becoming depressed or experiencing worsening of existing depression, becoming preoccupied with death and dying, giving away prized possessions). If these or any new and worrisome behaviors occur, the responsible clinician should be contacted immediately. FDA also recommends that clinicians who prescribe lamotrigine or any other anticonvulsant balance the risk for suicidality with the risk of untreated illness. Epilepsy and many other illnesses for which anticonvulsants are prescribed are themselves associated with an increased risk of morbidity and mortality and an increased risk of suicidal thoughts and behavior. If suicidal thoughts and behavior emerge during anticonvulsant therapy, the clinician must consider whether the emergence of these symptoms in any given patient may be related to the illness being treated.

During the premarketing development of lamotrigine, 20 sudden and unexplained deaths were reported among a cohort of 4700 patients with epilepsy receiving adjunctive therapy with the drug (5747 patient-years of exposure). Although the rate of these deaths exceeds that expected to occur in a healthy (nonepileptic) population matched for age and gender, this rate was similar to that occurring in a similar population of epileptic patients receiving a chemically unrelated anticonvulsant agent. This evidence suggests, but does not prove, that the incidence of sudden, unexplained death observed with lamotrigine adjunctive therapy may be reflective of the population itself rather than the effects of lamotrigine.

Some evidence suggests that use of lamotrigine concomitantly with valproic acid increases the risk of serious rash. The incidence of rash also appears to increase with the magnitude of the initial dose of lamotrigine and the subsequent rate of dosage escalation; exceeding the recommended dosage of lamotrigine at initiation of therapy appears to increase the risk of rash requiring withdrawal of therapy. (See Dosage and Administration: Dosage.) A benign initial appearance of a rash in a patient receiving lamotrigine therapy cannot predict an entirely benign outcome. Patients receiving lamotrigine, especially in conjunction with valproic acid, should be cautioned that rash, in some cases potentially life-threatening, may occur, and that any occurrence of rash should immediately be reported by the patient to their clinician.

The concomitant use of valproic acid and/or hepatic enzyme-inducing anticonvulsant drugs (e.g., phenobarbital, primidone, carbamazepine, phenytoin) can increase or decrease the metabolism and elimination of lamotrigine, requiring dosage adjustments to maintain efficacy and/or avoid toxicity. (See Dosage and Administration: Dosage.) Addition of valproic acid to lamotrigine therapy reduces lamotrigine clearance and increases steady-state plasma lamotrigine concentrations by slightly more than 50% whether or not hepatic enzyme-inducing anticonvulsant drugs are given concomitantly. Conversely, steady-state plasma concentrations of lamotrigine are decreased by about 40% when phenobarbital, primidone, or carbamazepine is added to lamotrigine therapy and by about 45–54% when phenytoin is added to lamotrigine therapy; the magnitude of the effect with phenytoin is dependent on the total daily dosage of phenytoin (from 100–400 mg daily). Discontinuance of an enzyme-inducing anticonvulsant drug can be expected to increase, and discontinuance of valproic acid can be expected to decrease, the elimination half-life and plasma concentrations of lamotrigine. Although the manufacturer states that a therapeutic plasma concentration range has not been established for lamotrigine and that dosage should be based on therapeutic response, the change in plasma lamotrigine concentrations resulting from addition or discontinuance of enzyme-inducing anticonvulsant drugs or valproic acid should be considered when these drugs are added to or withdrawn from an existing anticonvulsant drug regimen that includes lamotrigine.

Addition of lamotrigine to existing therapy with phenytoin or carbamazepine generally does *not* appreciably alter the steady-state plasma concentrations of these concomitantly administered drugs. Addition of lamotrigine to carbamazepine therapy reportedly has resulted in increased plasma concentrations of a pharmacologically active metabolite of carbamazepine (carbamazepine-10,11-epoxide) and an increased incidence of some adverse effects (e.g., dizziness, headache, diplopia, blurred vision, ataxia, nausea, nystagmus). However, elevations in carbamazepine-10,11-epoxide plasma concentrations and/or increased toxicity have not been consistently observed with concomitant administration of lamotrigine and carbamazepine, and the mechanism of the interaction between these drugs remains unclear.

Addition of lamotrigine to valproic acid therapy in healthy individuals resulted in a 25% reduction in trough steady-state plasma concentrations of valproic acid over a 3-week period, followed by stabilization of these concentrations.

The manufacturer states that the effects of adding lamotrigine to an existing regimen including valproic acid, phenytoin, and/or carbamazepine may be expected to be similar to those associated with addition of each drug independently (i.e., valproic acid concentrations decrease, phenytoin and carbamazepine concentrations do not change).

Lamotrigine is a weak inhibitor of dihydrofolate reductase. Although clinically important alterations in blood folate concentrations or hematologic parameters have not been documented in clinical studies of lamotrigine therapy of at least 5 years duration, the manufacturer states that clinicians should be aware of this effect when prescribing other drugs that inhibit folate metabolism.

Multiorgan failure and various degrees of hepatic failure, in some cases fatal, have been reported rarely with lamotrigine as adjunctive therapy. (See Cautions: Hepatic Effects.) The possibility of such potentially fatal adverse effects should be considered in patients who exhibit signs and symptoms associated with multiorgan and/or hepatic impairment following initiation of lamotrigine as adjunctive therapy.

Lamotrigine can produce drowsiness and dizziness, and patients should be cautioned that the drug may impair their ability to perform hazardous activities requiring mental alertness or physical coordination (e.g., operating machinery, driving a motor vehicle).

Limited information indicates that the elimination half-life of lamotrigine is prolonged in patients with severe chronic renal failure (mean creatinine clearance of 13 mL/minute) not receiving other anticonvulsant drugs. In a study of a limited number of patients and healthy individuals receiving a single 100-mg dose of lamotrigine, the mean plasma half-life of the drug was 42.9 hours in patients with chronic renal failure, 57.4 hours between treatments in dialysis patients, and 26.2 hours in healthy individuals. The mean plasma half-life of lamotrigine was decreased to 13 hours during hemodialysis; an average of 20% (range: 5.6–35.1%) of the total body load of lamotrigine was eliminated during a 4-hour hemodialysis treatment. The manufacturer states that a reduced maintenance dosage of lamotrigine generally should be used in patients with substantial renal impairment; however, the manufacturer currently makes no specific recommendations for dosage adjustment in such patients. (See Dosage and Administration: Dosage in Renal and Hepatic Impairment.)

The manufacturer states that experience with use of lamotrigine in patients with impaired liver function is limited. Following a single 100-mg dose of lamotrigine, the median half-life of the drug in patients with mild, moderate, or severe hepatic impairment (Child-Pugh class A, B, or C, respectively) was 36, 60, or 100 hours, respectively, compared with 32 hours in healthy individuals. The manufacturer recommends reduction of initial, escalation, and maintenance dosages of lamotrigine in patients with moderate or severe hepatic impairment. (See Dosage and Administration: Dosage in Renal and Hepatic Impairment.)

Because lamotrigine is transformed in the liver principally to glucuronide metabolites, that are eliminated renally, the drug should be used with caution in patients with diseases or conditions (e.g., renal, hepatic, or cardiac impairment) that could affect metabolism and/or elimination of the drug. In dogs, lamotrigine is extensively metabolized to its 2-*N*-methyl metabolite, which has caused dose-dependent prolongations of the PR interval, widening of the QRS complex, and at high dosages, complete AV block. There have been no consistent effects of lamotrigine metabolites on cardiac conduction in humans. Trace amounts of the 2-*N*-methyl metabolite of lamotrigine have been found in urine, but not in plasma, with chronic dosing of lamotrigine in humans. However, the manufacturer states that it is possible that increased plasma concentrations of the 2-*N*-methyl metabolite could occur in patients with hepatic disease who have decreased ability to glucuronidate lamotrigine.

Lamotrigine binds to melanin-containing ocular tissue in pigmented rats and cynomolgus monkeys, but evidence of this manifestation has not been reported in humans. Although ophthalmologic testing was conducted in one controlled clinical trial of lamotrigine therapy, the manufacturer states that it was inadequate to detect subtle effects or injury resulting from long-term administration of lamotrigine and that the ability of available tests to detect potentially adverse effects associated with the binding of lamotrigine to melanin is unknown. The manufacturer further states that while no specific recommendations for periodic ophthalmologic monitoring of patients receiving long-term lamotrigine therapy can be provided, prolonged administration of the drug could potentially result in its accumulation and possible toxic effects in melanin-rich tissues, including those of the eye, and that clinicians should be aware of possible adverse ophthalmologic effects occurring as a result of binding of the drug to melanin.

Because of similarity in spelling between Lamictal® (the trade name for lamotrigine) and labetalol, Lamisil® (terbinafine hydrochloride), lamivudine, Lomotil® (the fixed combination of atropine sulfate and diphenoxylate hydrochloride), and Ludiomil® (no longer commercially available under this trade name in the US; maprotiline hydrochloride), dispensing errors have been reported to the manufacturer of Lamictal® (GlaxoSmithKline). These medication errors may be associated with serious adverse events either due to lack of appropriate therapy for seizures (e.g., in patients not receiving the prescribed anticonvulsant, lamotrigine, which may lead to status epilepticus) or, alternatively, to the risk of developing adverse effects (e.g., serious rash) associated with the use of lamotrigine in patients for whom the drug was not prescribed and consequently was not properly titrated. Therefore, extra care should be exercised in ensuring the accuracy of both oral and written prescriptions for Lamictal® and these other drugs. When appropriate, clinicians might consider including the intended use of the particular drug on the prescription in addition to alerting patients to carefully check the drug they receive and promptly bring any question or concern to the attention of the dispensing pharmacist. The manufacturer also recommends that pharmacists assess various measures of avoiding dispensing errors and implement them as appropriate (e.g., by computerized filling and handling of prescriptions, patient counseling). Medication errors also may occur between the different formulations of lamotrigine. Depictions of Lamictal® conventional tablets, chewable/dispersible tablets, and orally disintegrating tablets may be found in the medication guide; patients are strongly advised to visually inspect their tablets to verify that they are Lamictal® as well as the correct formulation of Lamictal® each time they fill their prescription.

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

■ **Pediatric Precautions** Safety and efficacy of lamotrigine have not been established in pediatric patients younger than 2 years of age. Safety and efficacy in children 2–16 years of age have not been established for uses other than adjunctive therapy of partial seizures, primary generalized tonic-clonic seizures, or seizures associated with Lennox-Gastaut syndrome.

Safety and efficacy of lamotrigine for the management of bipolar disorder in patients younger than 18 years of age have not been established.

The incidence of severe rashes requiring hospitalization and discontinuance of the drug appears to be higher in pediatric patients compared with adults (about 0.8% versus 0.3%).

Analyses of population pharmacokinetic data for children 2–18 years of age demonstrated that lamotrigine clearance is influenced mainly by total body weight and concomitant anticonvulsant therapy. Oral clearance of lamotrigine is higher in children than adults when calculated on the basis of body weight; patients weighing less than 30 kg have a higher clearance on a weight-adjusted basis than patients weighing more than 30 kg and may require increases in maintenance dosage. (See Dosage and Administration: Dosage.)

■ **Geriatric Precautions** The manufacturer states that clinical trials of lamotrigine did not include sufficient numbers of patients older than 65 years of age to determine whether they respond differently than younger patients. Because of the greater frequency of decreased hepatic, renal, and/or cardiac function and of concomitant diseases and drug therapy in geriatric patients, the manufacturer suggests that patients in this age group receive initial dosages of the drug in the lower end of the usual range.

■ **Mutagenicity and Carcinogenicity** No evidence of mutagenicity was demonstrated by lamotrigine in vitro in the Ames *Salmonella* microbial mutagen test or the mammalian mouse lymphoma assay. Lamotrigine also did not increase the incidence of structural or numerical chromosomal abnormalities in the in vitro human lymphocyte assay and the in vivo rat bone marrow assay.

No evidence of carcinogenicity was demonstrated by lamotrigine in studies in mice receiving 30 mg/kg daily and in rats receiving 10–15 mg/kg daily for up to 2 years. Steady-state plasma lamotrigine concentrations produced by these dosages ranged from 1–4 mcg/mL in mice and from 1–10 mcg/mL in rats. In humans receiving the recommended lamotrigine dosage of 300–500 mg daily, plasma lamotrigine concentrations generally are in the range of 2–5 mcg/mL, although plasma concentrations up to 19 mcg/mL have been reported.

■ **Pregnancy, Fertility, and Lactation** The safety of lamotrigine when used during pregnancy in humans is unknown, and the drug should be used during pregnancy only when the potential benefits justify the possible risks to the fetus. Patients should be advised to notify their clinician if they become pregnant or intend to become pregnant. The manufacturer, in collaboration with the US Centers for Disease Control and Prevention (CDC), maintains a lamotrigine pregnancy registry to monitor fetal outcomes of pregnant women exposed to lamotrigine. Clinicians aware of patients who have received lamotrigine at any time during their pregnancy and who wish to register these cases before fetal outcome is known (e.g., through ultrasound, amniocentesis, birth) may obtain information by calling the Lamotrigine Pregnancy Registry at 800-336-2176. Patients can enroll themselves in the North American Antiepileptic Drug (NAAED) Pregnancy Registry by calling 888-233-2334; registry information also is available on the website at http://www.aedpregnancyregistry.org/.

Preliminary information from the NAAED Pregnancy Registry suggests a possible association between exposure to lamotrigine monotherapy during the first trimester of pregnancy and an increased incidence of cleft lip or cleft palate in infants. Of 564 pregnant women listed in the NAAED Pregnancy Registry who received lamotrigine monotherapy during the first trimester, 5 cases of oral clefts (2 cases of isolated cleft lips, 3 cases of isolated cleft palate) occurred, yielding a total prevalence of 8.9 cases per 1000 exposures compared with a prevalence of 0.5–2.16 reported among infants of nonepileptic women who were not receiving lamotrigine. However, other pregnancy registries of similar size have not replicated this observation, and the validity of this association cannot be established until additional data are collected in NAAED Pregnancy Registry, in other pregnancy registries, or by additional research. The US Food and Drug Administration (FDA) states that the clinical importance of this preliminary report remains uncertain pending further data collection and more research is needed. FDA recommends that women who are pregnant should not begin or discontinue lamotrigine therapy without first talking to their clinician.

Although there are no adequate and controlled studies to date in humans, lamotrigine has been shown to produce maternal toxicity and secondary fetal toxicity (e.g., reduced fetal weight and/or delayed ossification) in mice and rats receiving oral dosages up to 1.2 or 0.5 times (on a mg/m² basis), respectively, the maximum usual human maintenance dosage of 500 mg daily during the period of organogenesis. However, no evidence of teratogenicity was found in mice, rats, or rabbits receiving the drug orally in dosages up to 1.2, 0.5, or 1.1 times (on a mg/m² basis), respectively, the maximum usual human daily maintenance dosage. Maternal toxicity and fetal death occurred in rats receiving lamotrigine orally during late gestation (days 15–20) in dosages of 0.1, 0.14, or 0.3 times (on a mg/m² basis) the maximum usual human daily maintenance dosage; food consumption and weight gain were reduced in dams, and the gestation period was slightly prolonged. Stillborn pups were found in all three groups of rats receiving lamotrigine, with the greatest number of stillborn pups in the group receiving the highest dosage. Postnatal death of pups occurred between days 1 and 20 only in the group of rats receiving 0.14 or 0.3 times (on a mg/m² basis) the maximum usual human daily maintenance dosage. Some of these deaths appeared to be drug related and not secondary to maternal toxicity. No evidence of teratogenicity was demonstrated in rats receiving lamotrigine in dosages 0.4 times (on a mg/m² basis) the maximum usual human daily maintenance dosage prior to and during mating and throughout gestation and lactation. However, the incidence of intrauterine death without signs of teratogenicity was increased in rat dams receiving lamotrigine isethionate by rapid IV injection in a dosage 0.6 times (on a mg/m² basis) the maximum usual human daily maintenance dosage. In a study designed to determine the effects of lamotrigine on postnatal development, pregnant rats received lamotrigine orally in dosages 0.1 and 0.5 times (on a mg/m² basis) the recommended human daily dosage during the period of organogenesis. At day 21 postpartum, pups born to dams receiving the lower dosage (5 mg/kg daily) exhibited a longer latent period for open field exploration and a lower frequency of rearing. Pups born to dams receiving the higher dosage (25 mg/kg daily) demonstrated an increased time to completion of a swimming maze test performed 39–44 days postpartum. No evidence of adverse effects on development of pups was demonstrated by lamotrigine in a group of rats receiving the drug in dosages 0.4 times (on a mg/m² basis) the maximum usual human daily maintenance dosage prior to and during mating, and throughout gestation and lactation.

Because lamotrigine is a dihydrofolate reductase inhibitor, it decreases fetal folate concentrations in rats, an effect known to be associated with teratogenesis in animals and humans. However, there are no adequate and well-controlled studies in pregnant women, and animal reproduction studies are not always predictive of human response. Decreased plasma folate concentrations in rats were partially returned to normal by administration of leucovorin. Clinicians should be aware of lamotrigine's dihydrofolate reductase inhibiting activity, especially when prescribing other drugs that inhibit folate metabolism.

The effect of lamotrigine on labor and delivery in humans is unknown.

Reproduction studies revealed no adverse effects on fertility in rats receiving lamotrigine in oral dosages 0.4 times (on a mg/m² basis) the maximum usual human daily maintenance dosage prior to and during mating, and throughout gestation and lactation. The effect of lamotrigine on human fertility is unknown.

Preliminary data indicate that lamotrigine is distributed into milk. Because of the potential for serious adverse reactions to lamotrigine 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.

Description

Lamotrigine is a phenyltriazine anticonvulsant agent. The drug differs structurally from other currently available anticonvulsant agents. Although the precise mechanism of anticonvulsant action of lamotrigine is unknown, studies in animals indicate that the drug may stabilize neuronal membranes by blocking voltage-sensitive sodium channels, which inhibits the release of excitatory amino acid neurotransmitters (e.g., glutamate, aspartate) that play a role in the generation and spread of epileptic seizures. In animal test systems, lamotrigine exhibits anticonvulsant activity similar to that of phenytoin, phenobarbital, and carbamazepine. The drug protects against seizures induced by electrical stimulation or pentylenetetrazole, suggesting that it may be effective in the management of tonic-clonic (grand mal) and partial seizures or absence (petit mal) seizures, respectively. Lamotrigine also is active in electrically evoked afterdischarge tests, indicating activity against simple and complex partial seizures, and in rat cortical kindling tests, which may indicate activity against complex partial seizures. The mechanism(s) of action of lamotrigine in bipolar disorder has not been established.

In vitro studies indicate that lamotrigine has weak inhibitory effects on type 3 serotonergic ($5\text{-}HT_3$) receptors, and does not exhibit high affinity for type 2 serotoninergic ($5\text{-}HT_2$), adenosine A_1 or A_2, α_1- or α_2-adrenergic, β-adrenergic, dopamine D_1 or D_2, γ-aminobutyric acid (GABA) A or B, histamine H_1, opiate κ, or cholinergic muscarinic receptors. The drug has weak agonist effects at opiate σ receptors. Lamotrigine apparently has no effect on dihydropyridine-sensitive calcium channels or *N*-methyl-d-aspartate (NMDA) receptors and does not inhibit the uptake of norepinephrine, dopamine, serotonin, or aspartic acid.

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.

Lamotrigine

Oral		
Tablets	25 mg	**Lamictal®** (scored), GlaxoSmithKline
	100 mg	**Lamictal®** (scored), GlaxoSmithKline
	150 mg	**Lamictal®** (scored), GlaxoSmithKline
	200 mg	**Lamictal®** (scored), GlaxoSmithKline
Tablets, chewable/dispersible	2 mg	**Lamictal®**, GlaxoSmithKline
	5 mg	**Lamictal®**, GlaxoSmithKline
	25 mg	**Lamictal®**, GlaxoSmithKline
Tablets, orally disintegrating	25 mg	**Lamictal® ODT**, GlaxoSmithKline
	50 mg	**Lamictal® ODT**, GlaxoSmithKline
	100 mg	**Lamictal® ODT**, GlaxoSmithKline
	200 mg	**Lamictal® ODT**, GlaxoSmithKline

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

■ **Elimination** The elimination half-life of citalopram averages approximately 35 hours in adults with normal renal and hepatic function.

The exact metabolic fate of citalopram has not been fully elucidated; however, metabolism of citalopram is mainly hepatic and involves *N*-demethylation. Citalopram is metabolized to demethylcitalopram, didemethylcitalopram, citalopram-*N*-oxide, and a deaminated propionic acid derivative. In vitro studies have indicated that cytochrome P-450 (CYP) 3A4 and 2C19 isoenzymes are the principal enzymes involved in the *N*-demethylation of citalopram to demethylcitalopram and that demethylcitalopram is further *N*-demethylated to didemethylcitalopram by CYP2D6. Because citalopram is metabolized by multiple enzyme systems, inhibition of a single enzyme is unlikely to appreciably decrease the clearance of citalopram. Unlike some other selective serotonin-reuptake inhibitors, the demethylated metabolites of citalopram, demethylcitalopram and didemethylcitalopram, are substantially less active than the parent compound as inhibitors of serotonin reuptake. Thus, citalopram's metabolites are unlikely to contribute to the antidepressant and other clinical actions of the drug.

In humans, unchanged citalopram is the predominant compound in plasma. At steady state, the concentrations of demethylcitalopram and didemethylcitalopram in plasma are approximately one-half and one-tenth, respectively, that of the parent drug. Following IV (parenteral dosage form not commercially available in the US) administration of citalopram, the fraction of drug recovered in urine as citalopram and demethylcitalopram was about 10 and 5%, respectively.

Following oral administration of a single, radiolabeled dose of citalopram in healthy individuals, approximately 75% of the dose was excreted in urine and approximately 10% was eliminated in feces within 17 days. An analysis of the urinary composition showed that besides the known metabolites of citalopram, 3 glucuronides were present. The relative amounts of citalopram, demethylcitalopram, didemethylcitalopram, and the *N*-oxide metabolite present in urine collected for 7 days were 26, 19, 9, and 7%, respectively, with glucuronidated metabolites accounting for the remainder.

Following IV administration, the mean systemic clearance of citalopram is approximately 330 mL/minute, with approximately 20% of that due to renal clearance.

The effect of age on the elimination of citalopram has not been fully elucidated. Studies in healthy geriatric individuals and depressed geriatric patients have found higher AUC values and longer elimination half-lives compared with younger individuals. (See Pharmacokinetics: Absorption.) In healthy geriatric individuals, the elimination half-life of citalopram was increased by 50% in a single-dose study and by 30% in a multiple-dose study. It has been suggested that these differences in pharmacokinetic parameters may reflect declining liver and kidney function. In addition, the stereoselective metabolism of the enantiomers for citalopram and demethylcitalopram in older individuals appears to differ from that reported in younger patients, suggesting possible age-associated changes in CYP2C19 activities. (See Dosage and Administration: Dosage in Geriatric Patients and see Cautions: Geriatric Precautions.)

Because citalopram is extensively metabolized in the liver, hepatic impairment can affect the elimination of the drug. Following oral administration, the clearance of citalopram in patients with impaired hepatic function was reduced by 37% and the elimination half-life was increased twofold compared with that in healthy individuals. Therefore, the manufacturer recommends that in depressed patients with hepatic impairment, citalopram therapy should be initiated at 20 mg once daily, and titrated to 40 mg once daily *only* in nonresponders. (See Dosage and Administration: Dosage in Hepatic and Renal Impairment and see Cautions: Precautions and Contraindications.)

The effect of renal impairment on the pharmacokinetics of citalopram has not been fully evaluated to date. In patients with moderate renal impairment, the renal clearance of citalopram and its 2 principal metabolites was reduced and the elimination half-life of citalopram was slightly prolonged to an average of about 50 hours. In a study comparing the pharmacokinetics of citalopram in a limited number of patients with severe renal failure undergoing hemodialysis and in healthy individuals, no substantial differences were found between the 2 groups in any of the pharmacokinetic parameters, with the exception of the renal clearance of citalopram, which was significantly lower in the renal failure group than in the control group (11.7 mL/minute versus 66 mL/minute). Therefore, moderate to severe renal failure does not appear to markedly affect the pharmacokinetics of citalopram suggesting that dosage adjustment in such patients may not be necessary. Additional studies evaluating long-term citalopram therapy in patients with severe renal impairment are necessary to confirm these findings. (See Dosage and Administration: Dosage in Hepatic and Renal Impairment.)

Limited data indicate that citalopram and demethylcitalopram are not appreciably removed by hemodialysis. In a limited number of patients, hemodialysis cleared only about 1% of an oral dose of citalopram as the parent drug and 1% as demethylcitalopram. Because of the large volume of distribution of citalopram, hemodialysis, peritoneal dialysis, forced diuresis, hemoperfusion, and/or exchange transfusion also are unlikely to be effective in removing substantial amounts of citalopram from the body.

Chemistry and Stability

■ **Chemistry** Citalopram hydrobromide, a selective serotonin-reuptake inhibitor (SSRI), is a bicyclic phthalane-derivative antidepressant. The drug differs structurally from most other selective serotonin-reuptake inhibitors (e.g., fluoxetine, fluvoxamine, paroxetine, sertraline) and also differs structurally and pharmacologically from tricyclic and tetracyclic antidepressants. The commercially available drug is a 50:50 racemic mixture of the *R*- and *S*-enantiomers. The inhibition of serotonin reuptake by citalopram is principally due to the *S*-enantiomer, escitalopram (see Escitalopram Oxalate 28:16.04.20).

Citalopram hydrobromide occurs as a fine white to off-white powder that is sparingly soluble in water and soluble in ethanol. The drug has a pK_a of 9.5.

Citalopram hydrobromide is commercially available for oral administration as tablets and as an oral solution. Commercially available Celexa® (citalopram hydrobromide) oral solution is a clear, colorless to opalescent solution with a peppermint flavor and containing 10 mg of citalopram per 5 mL. Citalopram hydrobromide oral solution contains methylparahens and propylparahens as preservatives. Citalopram also is commercially available in some countries as an IV injection†; however, this dosage form currently is not available in the US.

■ **Stability** Citalopram hydrobromide tablets and oral solution should be stored at a temperature of 25°C but may be exposed to temperatures ranging from 15–30°C. When stored as directed, the tablets and oral solution have an expiration date of 2 years and 18 months, respectively, following the date of manufacture.

Preparations

Because of similarity in spelling of Celexa® (citalopram hydrobromide), Celebrex® (celecoxib), and Cerebyx® (fosphenytoin sodium), extra care should be exercised in ensuring the accuracy of prescriptions for these drugs.

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

Citalopram Hydrobromide

Oral		
Tablets, film-coated	10 mg (of citalopram)*	Celexa®, Forest (also promoted by Pfizer)
		Citalopram Hydrobromide Film-coated Tablets
	20 mg (of citalopram)*	Celexa® (scored), Forest (also promoted by Pfizer)
		Citalopram Hydrobromide Film-coated Tablets
	40 mg (of citalopram)*	Celexa® (scored), Forest (also promoted by Pfizer)
		Citalopram Hydrobromide Film-coated Tablets
Solution	10 mg (of citalopram) per 5 mL*	Celexa®, Forest (also promoted by Pfizer)
		Citalopram Hydrobromide Oral Solution

*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

Escitalopram Oxalate

■ Escitalopram, the *S*-enantiomer of citalopram, is a selective serotonin-reuptake inhibitor (SSRI) and an antidepressant.

Uses

■ **Major Depressive Disorder** Escitalopram oxalate is used for the acute and maintenance treatment of major depressive disorder in adults and adolescents 12–17 years of age.

Efficacy of escitalopram for the acute management of major depression in adults was established in 3 placebo-controlled studies of 8 weeks' duration in adult outpatients who met DSM-IV criteria for major depressive disorder. In these studies, 10- and 20-mg daily dosages of escitalopram were more effective than placebo in improving scores on the Montgomery Asberg Depression Rating Scale (MADRS), the Hamilton Rating Scale for Depression (HAM-D), and the Clinical Global Impression Improvement and Severity of Illness Scale. Escitalopram also was more effective than placebo in improving other aspects of depressive disorder, including anxiety, social functioning, and overall quality of life. Substantial improvement in MADRS and HAM-D scores was noted in patients receiving either dosage of escitalopram compared with those receiving placebo after 1–2 weeks of therapy. In addition, escitalopram dosages of 10–20 mg daily appeared to be at least as effective as racemic citalopram dosages of 20–40 mg daily. No age-, race-, or gender-related differences in efficacy were noted in these studies.

Efficacy of escitalopram for the acute management of major depressive disorder in adolescents 12–17 years of age was established in an 8-week, flexible-dose, placebo-controlled study in outpatients who met DSM-IV criteria for major depressive disorder. Escitalopram-treated patients in this study demonstrated substantially greater improvement on the Children's Depression Rating Scale–Revised (CDRS-R) compared with those receiving placebo. Efficacy of

escitalopram in the acute treatment of major depressive disorder in adolescents was also established on the basis of extrapolation from an 8-week, flexible-dose, placebo-controlled study with racemic citalopram 20–40 mg daily. In this outpatient study conducted in children and adolescents 7–17 years of age who met DSM-IV criteria for major depressive disorder, citalopram-treated patients demonstrated substantially greater improvement on the CDRS-R compared with those receiving placebo; the positive results in this trial came largely from the adolescent subgroup. Two additional flexible-dose, placebo-controlled depression studies (one for escitalopram in patients 7–17 years of age and one for citalopram in adolescents) did not demonstrate efficacy.

In a longer-term study, 274 adults with major depressive disorder who had responded to escitalopram 10 or 20 mg daily during an initial 8-week, open-label, flexible dosage treatment phase were randomized to continue escitalopram at the same dosage or receive placebo for up to 36 weeks of observation for relapse in the double-blind phase. Relapse during the double-blind phase was defined as an increase in the MADRS total score to 22 or greater or discontinuance due to insufficient clinical response. Escitalopram-treated patients experienced a substantially longer time to relapse of depression compared with those receiving placebo. In addition, more placebo recipients relapsed compared with patients receiving escitalopram (cumulative relapse rates were approximately 40 and 26%, respectively).

Although efficacy of escitalopram as maintenance therapy in adolescent patients has not been systematically evaluated, such efficacy can be extrapolated from adult data along with comparisons of escitalopram pharmacokinetic parameters in adults and adolescent patients.

The manufacturer states that if escitalopram is used for extended periods, the need for continued therapy should be reassessed periodically.

There is some evidence that escitalopram may offer some clinical advantages compared with citalopram or other selective serotonin-reuptake inhibitors (e.g., increased efficacy, more rapid onset of therapeutic effect, fewer adverse effects); however, additional studies are needed to confirm these initial findings.

Efficacy of escitalopram in hospital settings has not been established to date.

For further information on use of SSRIs in the treatment of major depressive disorder and considerations in choosing the most appropriate antidepressant agent for a particular patient, see Uses: Major Depressive Disorder, in Citalopram Hydrobromide 28:16.04.20.

■ **Generalized Anxiety Disorder** Escitalopram is used in the management of generalized anxiety disorder in adults. Efficacy for the management of generalized anxiety disorder was established in 3 multicenter, flexible-dose, placebo-controlled studies of 8-weeks' duration in adult outpatients who met DSM-IV criteria for generalized anxiety disorder. In these studies, patients receiving 10–20 mg daily of escitalopram had substantially greater mean improvements in scores on the Hamilton Anxiety Scale (HAM-A) than those receiving placebo.

For further information on the treatment of generalized anxiety disorder, see Uses: Anxiety Disorders, in Paroxetine 28:16.04.20.

Dosage and Administration

■ **Administration** Escitalopram oxalate is administered orally once daily, in the morning or evening, without regard to meals. Commercially available escitalopram oxalate tablets and oral solution are bioequivalent.

Patients receiving escitalopram 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 Worsening of Depression and Suicidality Risk under Warnings/Precautions: Warnings, in Cautions.)

The manufacturer recommends that at least 2 weeks elapse between discontinuance of a monoamine oxidase (MAO) inhibitor and initiation of escitalopram and vice versa. (See Serotonin Syndrome or Neuroleptic Malignant Syndrome [NMS]-like Reactions under Warnings/Precautions: Other Warnings and Precautions, in Cautions and see also Drug Interactions: Monoamine Oxidase Inhibitors.)

■ **Dosage** Dosage of escitalopram oxalate is expressed in terms of escitalopram.

Major Depressive Disorder For the acute management of major depressive disorder in adults, the recommended initial dosage of escitalopram is 10 mg once daily. Although efficacy has been established at dosages of 10 or 20 mg once daily, no additional benefit was observed with the 20-mg dosage in a fixed-dose study. If a dosage exceeding 10 mg daily is considered necessary, dosage may be increased to 20 mg daily after a minimum of 1 week.

For the acute management of major depressive disorder in adolescents 12–17 years of age, the recommended initial dosage of escitalopram is 10 mg once daily. Efficacy has been established at dosages of 10–20 mg daily in a flexible-dose study. If dosage is increased to 20 mg daily, this should occur after a minimum of 3 weeks.

While the optimum duration of escitalopram oxalate 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 dosage of escitalopram oxalate required to induce remission is identical to the dosage needed to maintain and/or sustain euthymia is unknown. Systematic evaluation of escitalopram oxalate has shown that its antidepressant efficacy is maintained for periods of up to 36 weeks in adults receiving 10–20 mg daily. Nevertheless, the manufacturer recommends that the usefulness of escitalopram be reevaluated periodically in patients receiving long-term therapy.

Generalized Anxiety Disorder For the management of generalized anxiety disorder in adults, the recommended initial dosage of escitalopram is 10 mg once daily. If no clinical improvement is apparent, dosage may be increased to 20 mg daily after a minimum of 1 week.

Although the manufacturer states that the efficacy of escitalopram for long-term therapy (i.e., longer than 8 weeks) has not been demonstrated in controlled studies to date, generalized anxiety disorder is a chronic condition. If escitalopram is used for extended periods, the need for continued therapy with the drug should be reassessed periodically.

Discontinuance of Therapy Because withdrawal effects may occur (see Withdrawal of Therapy under Warnings/Precautions: Other Warnings and Precautions, in Cautions), the manufacturer and many experts recommend that dosage of escitalopram and other SSRIs be tapered gradually (e.g., over a period of several weeks) and the patient monitored closely. Abrupt discontinuance of the drug should be avoided.

If intolerable symptoms occur following a decrease in the dosage or upon discontinuance of therapy, escitalopram therapy may be reinstituted at the previously prescribed dosage. Subsequently, the clinician may continue decreasing the dosage but at a more gradual rate.

■ **Special Populations** The recommended dosage of escitalopram in most geriatric patients and those with hepatic impairment is 10 mg daily. Dosage adjustment in patients with mild to moderate renal impairment is not necessary, but the drug should be used with caution in those with severe renal impairment.

Treatment of Pregnant Women during the Third Trimester Because some neonates exposed to escitalopram 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 escitalopram therapy in the third trimester prior to delivery if the drug is administered during pregnancy. (See Pregnancy, under Warnings/Precautions: Specific Populations, in Cautions.)

Cautions

■ **Contraindications** Concurrent or recent (i.e., within 2 weeks) therapy with a monoamine oxidase (MAO) inhibitor. (See Serotonin Syndrome or Neuroleptic Malignant Syndrome [NMS]-like Reactions under Warnings/Precautions: Other Warnings and Precautions, in Cautions and see also Drug Interactions: Monoamine Oxidase Inhibitors.)

Concomitant use with pimozide. (See Drug Interactions: Antipsychotic Agents and Other Dopamine Antagonists.)

Known hypersensitivity to escitalopram, citalopram, or any ingredient in the formulation.

■ **Warnings/Precautions** ***Warnings*** **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. 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 [SSRIs] 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 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. If a decision is made to discontinue therapy, taper escitalopram dosage as rapidly as is feasible but consider the risks of abrupt discontinuance. (See Discontinuance of Therapy, under 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.

Other Warnings and Precautions **Serotonin Syndrome or Neuroleptic Malignant Syndrome (NMS)-like Reactions.** Potentially life-threatening serotonin syndrome or neuroleptic malignant syndrome (NMS)-like reactions have been reported with SSRIs, including escitalopram, and selective serotonin- and norepinephrine-reuptake inhibitors (SNRIs) alone, but particularly with concurrent use of other serotonergic drugs (including serotonin [5-hydroxytryptamine; 5-HT] type 1 receptor agonists ["triptans"]), drugs that impair the metabolism of serotonin (e.g., MAO inhibitors), or antipsychotics or other dopamine antagonists. Manifestations 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). In its most severe form, serotonin syndrome may resemble NMS, which is characterized by hyperthermia, muscle rigidity, autonomic instability with possible rapid fluctuation in vital signs, and mental status changes. Monitor patients receiving escitalopram for the development of serotonin syndrome or NMS-like signs and symptoms. (See Contraindications and see also Drug Interactions.)

Concurrent or recent (i.e., within 2 weeks) therapy with MAO inhibitors intended to treat depression is contraindicated. (See Contraindications and see also Drug Interactions: Monoamine Oxidase Inhibitors.)

If concurrent therapy with escitalopram and a 5-HT_1 receptor agonist (triptan) 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 escitalopram and serotonin precursors (e.g., tryptophan) is not recommended.

If signs and symptoms of serotonin syndrome or NMS occur, immediately discontinue treatment with escitalopram and any concurrently administered serotonergic or antidopaminergic agents, including antipsychotic agents, and initiate supportive and symptomatic treatment.

Withdrawal of Therapy. Withdrawal symptoms, including dysphoric mood, irritability, agitation, dizziness, sensory disturbances (e.g., paresthesias such as electric shock sensations), anxiety, confusion, headache, lethargy, emotional lability, insomnia, hypomania, tinnitus, and seizures, have been reported during the postmarketing surveillance period for escitalopram and other SSRIs and SNRIs, particularly upon abrupt discontinuance of these drugs. While these events are generally self-limiting, there have been reports of serious discontinuance symptoms. Therefore, patients should be monitored for these symptoms when discontinuing escitalopram therapy. A gradual reduction in the dosage rather than abrupt cessation is recommended whenever possible. (See Discontinuance of Therapy under Dosage and Administration: Dosage.)

If intolerable symptoms occur following dosage reduction or discontinuance, reinstitute the previously prescribed dosage until symptoms abate, then resume more gradual dosage reductions.

Seizures. Although anticonvulsant effects of racemic citalopram have been observed in animal studies, escitalopram has not been systematically evaluated in patients with seizure disorders. Seizures have been reported in patients receiving escitalopram in clinical trials; therefore, as with other antidepressants, initiate therapy with caution in patients with a history of seizure disorder.

Activation of Mania/Hypomania. Activation of mania and hypomania has occurred in patients receiving escitalopram or citalopram. Use with caution in patients with a history of mania.

Hyponatremia/Syndrome of Inappropriate Antidiuretic Hormone Secretion. Treatment with SNRIs and SSRIs, including escitalopram, may result in hyponatremia. In many cases, hyponatremia appears to be due to the syndrome of inappropriate antidiuretic hormone secretion (SIADH). Cases with serum sodium concentrations lower than 110 mEq/L have been reported. Geriatric individuals and patients receiving diuretics or who are otherwise volume depleted may be at greater risk of developing hyponatremia. Signs and symptoms of hyponatremia include headache, difficulty concentrating, memory impairment, confusion, weakness, and unsteadiness, which may lead to falls; more severe and/or acute cases have been associated with hallucinations, syncope, seizures, coma, respiratory arrest, and death. Initiate appropriate medical intervention and consider drug discontinuance in patients with symptomatic hyponatremia.

Abnormal Bleeding. SNRIs and SSRIs, including escitalopram, may increase the risk of bleeding events. Concurrent administration of aspirin, nonsteroidal anti-inflammatory agents, warfarin, and other anticoagulants may add to this risk. Case reports and epidemiologic studies have demonstrated an association between the use of drugs that interfere with serotonin reuptake and the occurrence of GI bleeding. Bleeding events related to SNRI and SSRI use have ranged from ecchymoses, hematomas, epistaxis, and petechiae to life-threatening hemorrhages. The manufacturer recommends that patients be advised of the risk of bleeding associated with the concomitant use of escitalopram with aspirin or other nonsteroidal anti-inflammatory agents, warfarin, or other drugs that affect coagulation. (See Drug Interactions: Drugs Affecting Hemostasis.)

Interference with Cognitive and Motor Performance. In a study in healthy volunteers, escitalopram 10 mg daily did not impair intellectual function or psychomotor performance. However, because any psychoactive drug may impair judgment, thinking, or motor skills, caution patients about operating hazardous machinery, including driving a motor vehicle, until they are reasonably certain that the drug does not affect their ability to engage in such activities.

Concomitant Illnesses. Experience with escitalopram in patients with certain concomitant diseases is limited. (See Renal Impairment and see Hepatic Impairment under Warnings/Precautions: Specific Populations, in Cautions.)

Escitalopram has not been systematically evaluated in patients with a recent history of myocardial infarction or unstable cardiovascular disease; such patients were generally excluded from clinical studies. Use with caution in patients with diseases or conditions that produce altered metabolism or hemodynamic responses.

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

Complications, sometimes severe and requiring prolonged hospitalization, respiratory support, enteral nutrition, and other forms of supportive care, have been reported in some neonates exposed to escitalopram, other SSRIs, or selective serotonin- and norepinephrine-reuptake inhibitors (SNRIs) late in the third trimester; such complications may arise immediately upon delivery. In addition, an increased risk of persistent pulmonary hypertension of the newborn (PPHN) has been observed in infants exposed to SSRIs during late pregnancy; PPHN is associated with substantial neonatal morbidity and mortality.

Clinicians should carefully consider the potential risks and benefits of escitalopram therapy when used during the third trimester of pregnancy. However, clinicians also should be aware that women who discontinued antidepressant therapy during pregnancy were more likely to experience a relapse of depression than those who remained on antidepressant therapy according to results of one longitudinal study involving women with a history of major depressive disorder who were euthymic while receiving antidepressant therapy at the beginning of pregnancy. Clinicians may consider tapering the dosage of escitalopram in women in the third trimester of pregnancy. (See Pregnancy under Cautions: Pregnancy, Fertility, and Lactation, in Citalopram Hydrobromide 28:16.04.20.)

Lactation. Like racemic citalopram, escitalopram is distributed into human milk. Potential for serious adverse effects (e.g., excessive somnolence, decreased feeding, weight loss) in nursing infants exists. Discontinue nursing or the drug, taking into account the potential risk in nursing infants and the importance of the drug to the mother.

Pediatric Use. Safety and efficacy of escitalopram have not been established in pediatric patients younger than 12 years of age with major depressive disorder. Safety and effectiveness have been established in adolescents 12–17 years of age for the acute treatment of major depressive disorder. Although efficacy of escitalopram as maintenance therapy in adolescent patients with major depressive disorder has not been systematically evaluated, such efficacy can be extrapolated from adult data along with comparisons of pharmacokinetic parameters in adults and adolescent patients. (See Uses: Major Depressive Disorder.)

Safety and efficacy of escitalopram have not been established in pediatric patients younger than 18 years of age with generalized anxiety disorder.

FDA warns that a greater risk of suicidal thinking or behavior (suicidality) occurred during first few months of antidepressant treatment compared with placebo 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 (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 escitalopram in a child or adolescent for any clinical use. (See Worsening of Depression and Suicidality Risk under Warnings/Precautions: Warnings, in Cautions.)

Geriatric Use. Approximately 6% of patients studied in clinical trials of escitalopram for major depressive disorder and generalized anxiety disorder were 60 years of age or older; geriatric patients in these trials received daily dosages of 10–20 mg daily. Experience in geriatric patients in these trials was insufficient to determine whether they respond differently from younger adults; however, increased sensitivity cannot be ruled out.

SNRIs and SSRIs, including escitalopram, have been associated with clinically important hyponatremia in geriatric patients, who may be at greater risk for this adverse effect. (See Hyponatremia/Syndrome of Inappropriate Antidiuretic Hormone Secretion under Warnings/Precautions: Other Warnings and Precautions, 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.)

Renal Impairment. Use with caution in patients with severe renal impairment (i.e., creatinine clearance less than 20 mL/minute). (See Dosage and Administration: Special Populations.)

Hepatic Impairment. In clinical studies, clearance of racemic citalopram was decreased by 37% and elimination half-life was doubled relative to that in patients with normal hepatic function. Dosage reduction recommended for patients with hepatic impairment. (See Dosage and Administration: Special Populations.)

■ **Common Adverse Effects** Adverse effects reported in approximately 5% or more of patients with generalized anxiety or major depressive disorder receiving escitalopram and with an incidence of at least twice that of placebo include insomnia, nausea, increased sweating, sexual dysfunction (ejaculation disorder [primarily ejaculatory delay], decreased libido, anorgasmia), fatigue, and somnolence.

Drug Interactions

■ **Drugs Affecting or Metabolized by Hepatic Microsomal Enzymes** Inhibitors or inducers of cytochrome P-450 (CYP) 3A4 (e.g., carbamazepine, ketoconazole, ritonavir, triazolam) and 2C19 isoenzymes: clinically important pharmacokinetic interaction unlikely since escitalopram is metabolized by multiple enzyme systems. However, possibility that carbamazepine may increase clearance of escitalopram should be considered.

Substrates of CYP2D6 isoenzyme (e.g., desipramine, metoprolol): potential pharmacokinetic (increased peak plasma concentrations and AUC of the substrate) interactions. Use with caution. Increased plasma concentrations of metoprolol have been associated with decreased cardioselectivity.

■ **Drugs Affecting Hemostasis** Pharmacokinetics of warfarin were not affected by racemic citalopram; however, prothrombin time increased by 5%. The effects of escitalopram have not been evaluated, and the clinical importance of this interaction is unknown.

Altered anticoagulant effects, including increased bleeding, have been reported when SSRIs or selective serotonin- and norepinephrine-reuptake inhibitors (SNRIs) were concurrently administered with warfarin or other anticoagulants. The manufacturer of escitalopram recommends carefully monitoring patients receiving warfarin during initiation and discontinuance of escitalopram therapy.

Potential pharmacologic (increased risk of bleeding) interaction with aspirin or other nonsteroidal anti-inflammatory agents; use with caution.

■ **Antipsychotic Agents and Other Dopamine Antagonists** Potential pharmacologic interaction (potentially serious, sometimes fatal serotonin syndrome or NMS-like reactions) if used concurrently with antipsychotic agents or other dopamine antagonists. If signs and symptoms of serotonin syndrome or NMS occur, immediately discontinue treatment with escitalopram and any concurrently administered antidopaminergic or serotonergic agents and initiate supportive and symptomatic treatment. (See Serotonin Syndrome or Neuroleptic Malignant Syndrome [NMS]-like Reactions under Warnings/Precautions: Other Warnings and Precautions, in Cautions.)

Pimozide In a controlled study, concurrent administration of a single, 2-mg dose of pimozide in individuals receiving citalopram (40 mg once daily for 11 days) was associated with mean increases in the corrected QT (QT_c) interval of approximately 10 msec compared with pimozide given alone. Citalopram did not substantially affect the mean area under the plasma concentration-time curve (AUC) or peak plasma concentrations of pimozide. The mechanism for this potential pharmacodynamic interaction is not known. In addition, concomitant use of citalopram and pimozide rarely may result in potentially serious, sometimes fatal serotonin syndrome or NMS-like reactions. The manufacturer of escitalopram states that concurrent use of escitalopram and pimozide is contraindicated.

■ **5-HT_1 Receptor Agonists ("Triptans")** Potential pharmacologic interaction (potentially serious, sometimes fatal serotonin syndrome or NMS-like reactions) if used concurrently with 5-HT_1 receptor agonists (e.g., almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan, zolmitriptan). If concomitant use is clinically warranted, the patient should be observed carefully, particularly during treatment initiation, when dosage is increased, or when another serotonergic agent is initiated. (See Serotonin Syndrome or Neuroleptic Malignant Syndrome [NMS]-like Reactions under Warnings/Precautions: Other Warnings and Precautions, in Cautions.)

■ **Monoamine Oxidase Inhibitors** Potential pharmacologic interaction (potentially serious, sometimes fatal serotonin syndrome or NMS-like reactions). Concomitant use of monoamine oxidase (MAO) inhibitors with escitalopram is contraindicated. In addition, at least 2 weeks should elapse between discontinuance of an MAO inhibitor and initiation of escitalopram and vice versa. (See Serotonin Syndrome or Neuroleptic Malignant Syndrome [NMS]-like Reactions under Warnings/Precautions: Other Warnings and Precautions, in Cautions.)

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 escitalopram.

Isoniazid Potential pharmacologic interaction (potentially serious serotonin syndrome) when isoniazid, an antituberculosis agent that appears to have some MAO-inhibiting activity, is used concomitantly with escitalopram.

■ **Selective Serotonin-reuptake Inhibitors and Selective Serotonin- and Norepinephrine-reuptake Inhibitors** Potential pharmacologic interaction (potentially serious, sometimes fatal serotonin syndrome or NMS-like reactions); concurrent administration not recommended. (See Serotonin Syndrome or Neuroleptic Malignant Syndrome [NMS]-like Reactions under Warnings/Precautions: Other Warnings and Precautions, in Cautions.)

■ **Other Serotonergic Drugs** Potential pharmacologic interaction (potentially serious, sometimes fatal serotonin syndrome or NMS-like reactions) with drugs affecting serotonergic neurotransmission, including tramadol and St. John's wort (*Hypericum perforatum*); use concomitantly with caution. If signs and symptoms of serotonin syndrome or NMS occur, immediately discontinue treatment with escitalopram and any concurrently administered serotonergic or antidopaminergic agents and initiate supportive and symptomatic treatment. Concurrent administration of escitalopram and serotonin precursors (such as tryptophan) is not recommended. (See Serotonin Syndrome or Neuroleptic Malignant Syndrome [NMS]-like Reactions under Warnings/Precautions: Other Warnings and Precautions, in Cautions.)

■ **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.

■ **Citalopram** Potential pharmacologic interaction (potentially serious, sometimes fatal serotonin syndrome or NMS-like reactions).

Because escitalopram is the more active isomer of racemic citalopram, the 2 agents should not be used concomitantly.

■ **CNS-active Drugs** Potential pharmacologic interaction when given with other centrally acting drugs; use concomitantly with caution.

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

■ **Lithium** Concurrent administration of racemic citalopram and lithium did not substantially affect the pharmacokinetics of either drug. However, pending further accumulation of data, the manufacturer of escitalopram recommends that plasma lithium concentrations be monitored in patients concurrently receiving escitalopram and that lithium dosage be adjusted accordingly.

Potential pharmacologic interaction (enhanced serotonergic effects of escitalopram and potentially serious, sometimes fatal serotonin syndrome or NMS-like reactions); use concomitantly with caution.

■ **Ritonavir** Combined administration of a single 600-mg dose of ritonavir, a CYP3A4 substrate and potent inhibitor of CYP3A4, and escitalopram 20 mg did not substantially affect the pharmacokinetics of either drug.

■ **Sibutramine** Potential pharmacologic interaction (potentially serious, sometimes fatal serotonin syndrome or NMS-like reactions). Use concomitantly with caution.

■ **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.

■ **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

Importance of providing copy of written patient information (medication guide) each time escitalopram is dispensed. Importance of advising patients to read the patient information before taking escitalopram and each time the prescription is refilled.

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.)

Importance of informing patients of potential risk of serotonin syndrome and neuroleptic malignant syndrome (NMS)-like reactions, particularly with concurrent use of escitalopram and 5-HT_1 receptor agonists (also called triptans), tramadol, tryptophan, other serotonergic agents, or antipsychotic agents. Importance of immediately contacting clinician if signs and symptoms of these syndromes develop (e.g., restlessness, hallucinations, loss of coordination, fast heart beat, increased body temperature, muscle stiffness, labile blood pressure, diarrhea, coma, nausea, vomiting, confusion).

Risk of psychomotor impairment; importance of exercising caution while operating hazardous machinery, including driving a motor vehicle, until the drug's effects on the individual are known.

Importance of patients being aware that withdrawal effects may occur when stopping escitalopram, especially with abrupt discontinuance of the drug.

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 advising patients that, although they may notice improvement with escitalopram therapy within 1–4 weeks, they should continue therapy as directed.

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

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.

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†; cataplexy†; 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: Serotonergic Drugs, 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 (SSRIs; e.g., citalopram, escitalopram, fluoxetine, paroxetine, sertraline), selective serotonin- and norepinephrine-reuptake inhibitors (SNRIs; e.g., desvenlafaxine, duloxetine, venlafaxine), 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, maprotiline, nefazodone, trazodone). 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

AHFS® DRUG INFORMATION

22 March 2010

Fluvoxamine Maleate

AHFS Class: Selective Serotonin-reuptake Inhibitors (28:16.04.20)

VA Class: CN609

Chemical Name: *O*-(2-aminoethyl)oxime 5-methoxy-1-(4-(trifluoromethyl)phenyl)-1-pentanone (*Z*)-2-butenedioate (1:1)

Molecular Formula: $C_{15}H_{21}F_3N_2O_2 \cdot C_4H_4O_4$

Make a selection below to quickly jump to a specific section.

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[Posted 11/17/2009] FDA notified healthcare professionals of new safety information concerning an interaction between clopidogrel (Plavix), an anti-clotting medication, and omeprazole (Prilosec/Prilosec OTC), a proton pump inhibitor (PPI) used to reduce stomach acid. New data show that when clopidogrel and omeprazole are taken together, the effectiveness of clopidogrel is reduced. Patients at risk for heart attacks or strokes who use clopidogrel to prevent blood clots will not get the full effect of this medicine if they are also taking omeprazole. Separating the dose of clopidogrel and omeprazole in time will not reduce this drug interaction.

Other drugs that are expected to have a similar effect and should be avoided in combination with clopidogrel include: cimetidine, fluconazole, ketoconazole, voriconazole, etravirine, felbamate, fluoxetine, fluvoxamine, and ticlopidine.

Recommendations for healthcare professionals are provided in the "Information for Healthcare Professionals" sheet. For more information visit the FDA website at: [Web] and [Web].

Introduction

Fluvoxamine maleate, a selective serotonin-reuptake inhibitor (SSRI), is an antidepressant.[1 7]

Uses

Pending revision, the material in this section should be considered in light of more recently available information in the MEDWATCH notification at the beginning of this monograph.

■ 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.[1 2 4 7 8 9 10 11 12 13 14] Efficacy of fluvoxamine for the management of obsessive-compulsive disorder has been established by controlled studies of 10 weeks' duration principally in outpatient settings.[1 2 14] 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.[1 2 4 7 8 9 10 12] 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.[1 2 14] In these studies, no age- or gender-related differences in efficacy were noted.[1] Results from a limited number of comparative studies suggest that fluvoxamine is as effective as clomipramine in the management of obsessive-compulsive disorder.[2 4 13] Like fluoxetine and clomipramine, fluvoxamine reduces but does not eliminate obsessions and compulsions.[1 2 4 7 12 14] 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.[4 8 9 12 14] The efficacy of fluvoxamine for long-term use (i.e., longer than 10 weeks) has not been established in placebo-controlled studies,[1] 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.[4 14] If fluvoxamine is used for extended periods, the need for continued therapy should be reassessed periodically.[1]

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.[1 4 7 15 16]

■ Bulimia Nervosa

Fluvoxamine has been used in the treatment of bulimia nervosa†.[19 20] 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.[20] 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

Pending revision, the material in this section should be considered in light of more recently available information in the MEDWATCH notification at the beginning of this monograph.

Fluvoxamine maleate is administered orally.[1 5] 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.[1 5] Since food does not appear to affect GI absorption of fluvoxamine maleate, the drug generally can be administered without regard to meals.[1 17]

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.[23 24 25] (See Suicidality Precautions under Dosage and Administration: Dosage.)

Fluvoxamine should *not* be used concomitantly with thioridazine.[1 22 26] 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.[1 34 35 36 42] 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.[1 43 44] Therefore, patients should be cautioned about the potential risk of serotonin syndrome when fluvoxamine is given concurrently with other serotonergic agents.[43] 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).[43 44]

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.[1 44] 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.[1 22]

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.[42 43] In addition, clinicians should assess the potential risks and benefits of concurrent therapy with fluvoxamine and triptans prior to prescribing these drugs concurrently.[43] Concurrent use of SSRIs with serotonin precursors (such as tryptophan supplements) is not recommended.[44] 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

Pending revision, the material in this section should be considered in light of more recently available information in the MEDWATCH notification at the beginning of this monograph.

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.[1] Based on the tolerance and clinical response of the patient, dosage may be increased by increments of 50 mg daily at intervals of 4–7 days up to a maximum of 300 mg daily.[1] Because fluvoxamine clearance may be reduced in geriatric patients and/or such patients may have increased sensitivity to the adverse effects of CNS-active drugs, fluvoxamine maleate therapy may be initiated with a lower dosage (i.e., 25 mg daily)[19] and subsequent dosage adjustments made.[1] While a relationship between dosage and therapeutic effect in obsessive-compulsive disorder has not been established, efficacy of fluvoxamine maleate was demonstrated in clinical trials employing 100–300 mg daily.[1] Although the optimum duration of fluvoxamine therapy has not been established, obsessive-compulsive disorder may require several months of sustained drug therapy.[1] If therapy with the drug is prolonged, the lowest possible dosage should be employed and the need for continued therapy reassessed periodically.[1]

Pediatric Dosage. For the management of obsessive-compulsive disorder in pediatric patients 8–17 years of age, the recommended initial dosage of fluvoxamine maleate is 25 mg at bedtime.[1] This dosage may be increased in increments of 25 mg every 4–7 days, as tolerated, until maximum therapeutic benefit is achieved.[1] In one clinical study, dosages for pediatric patients 8–17 years of age were titrated within a range of 50–200 mg daily.[1 21] However, in a multiple-dose, pharmacokinetic study, steady-state plasma fluvoxamine concentrations were found to be twofold to threefold higher in children 6–11 years of age than in adolescents 12–17 years of age, and the area under the plasma concentration-time curve (AUC) and peak plasma concentrations were 1.5-2.7 times higher in children than in adolescents.[1 37] Both children and adolescents exhibited nonlinear pharmacokinetics, and female children exhibited higher AUC values and peak plasma concentrations compared with male children.[1 37] Steady-state plasma concentrations were similar in adults and adolescents receiving 300 mg of fluvoxamine daily, suggesting that fluvoxamine exposure was similar in these two groups.[1 37] Clinicians should consider both age and gender differences when selecting a fluvoxamine dosage in pediatric patients.[1 37] The maximum dosage of fluvoxamine in children up to 11 years of age should not exceed 200 mg daily, and therapeutic effects of the drug in female children may be achieved with a lower dosage than in male children.[1 37] In adolescents, fluvoxamine dosage adjustment up to the maximum daily dosage of 300 mg daily used in adults may be necessary to achieve optimal therapeutic benefit.[1 37]

The optimum duration of fluvoxamine therapy in pediatric patients has not been established.[22] If therapy with the drug is prolonged (i.e., longer than 10 weeks), the lowest possible dosage should be employed and the need for continued therapy reassessed periodically.[22] (See Pediatric Precautions under Dosage and Administration: Dosage.)

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: Dosage) patients with major depressive disorder or other psychiatric disorders, whether or not they

are taking antidepressants.[23 24 25 45] This risk may persist until clinically important remission occurs.[23] Suicide is a known risk of depression and certain other psychiatric disorders, and these disorders themselves are the strongest predictors of suicide.[23 24 25] 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.[23] 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.[23 24] 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.[23 24]

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 duringinitiation of therapy (i.e., the first few months) and during periods of dosage adjustments.[23 24 25] Families and caregivers of patients being treated with antidepressants for major depressive disorder or other indications, both psychiatric and nonpsychiatric, 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.[23 25 47]

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.[1 23 25] 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.[23] If a decision is made to discontinue therapy, fluvoxamine dosage should be tapered as rapidly as is feasible but with recognition of the risks of abrupt discontinuance.[23] 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.[23]

Bipolar Disorder Precautions. 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.[23] 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).[23] Fluvoxamine is *not* approved for use in treating bipolar depression.[23]

Pediatric Precautions. Safety and efficacy of fluvoxamine for the treatment of obsessive-compulsive disorder in children younger than 8 years of age have not been established.[22] In addition, the safety and efficacy of fluvoxamine in the management of pediatric patients with conditions other than obsessive-compulsive disorder have not been established.[1]

The safety and efficacy of fluvoxamine in pediatric patients with obsessive-compulsive disorder were established in a 10-week, placebo-controlled trial in children and adolescents 8–17 years of age.[1 21] The majority of these patients continued receiving fluvoxamine therapy for up to 1–3 years longer in an open-label extension of the initial study.[1] Adverse effects generally were similar to those reported in adults.[1 21] Agitation, depression, dysmenorrhea, flatulence, hyperkinesia, and rash were reported in at least 5% of the pediatric patients and with an incidence at least twice that reported with placebo.[1] In addition, abnormal thinking, increased cough, ecchymosis, emotional lability, epistaxis, hyperkinesia, infection, manic reaction, rash, sinusitis, and weight loss were reported in 2 or more of the 57 pediatric patients receiving fluvoxamine and more frequently than among the patients receiving placebo.[1]

The risks, if any, that may be associated with extended use of fluvoxamine in children and adolescents with obsessive-compulsive disorder have not been systematically evaluated.[1] The evidence relied upon to conclude that fluvoxamine is safe for use in children and adolescents was derived from relatively short-term clinical studies and from extrapolation of experience gained with adult patients.[1] In addition, the effects of long-term fluvoxamine use on the growth, development, and maturation of children and adolescents have not been established.[1] Regular monitoring of weight and growth is recommended if treatment of a child with an SSRI is to be continued long term.[1]

FDA has determined that antidepressants increase the risk of suicidal thinking and behavior (suicidality) in children and adolescents with major depressive disorder and other psychiatric disorders.[23 24] However, FDA also states that depression and certain other psychiatric disorders are themselves associated with an increased risk of suicide.[23 25 45] (See Cautions: Pediatric Precautions, in Fluoxetine Hydrochloride 28:16.04.20.) Anyone considering the use of fluvoxamine in a child or adolescent for any clinical use must therefore balance the potential risks with the clinical need.[23 25] (See Suicidality Precautions under Dosage and Administration: Dosage.)

For further information on use of SSRIs in the treatment of major depressive disorder and considerations in choosing the most appropriate antidepressant agent for a particular patient, see Uses: Major Depressive Disorder, in Fluoxetine Hydrochloride 28:16.04.20.

Other Considerations

Pending revision, the material in this section should be considered in light of more recently available information in the MEDWATCH notification at the beginning of this monograph.

Concomitant use of fluvoxamine is contraindicated in patients receiving astemizole (no longer commercially available in the US), cisapride, pimozide, or terfenadine (no longer commercially available in the US), since fluvoxamine may inhibit metabolism of these drugs and increase the potential for serious adverse cardiac effects.[1]

Since mean AUCs of alosetron were increased approximately sixfold and the elimination half-life was increased approximately

threefold during concurrent fluvoxamine administration in one pharmacokinetic study, concurrent use of these drugs is contraindicated.[1 34]

In a limited number of male patients with schizophrenia, concomitant use of thioridazine and low-dosage fluvoxamine (25 mg twice daily for 1 week) resulted in a threefold increase in plasma concentrations of thioridazine and its two active metabolites (mesoridazine and sulforidazine).[1 26] Thioridazine produces a dose-related prolongation of the QT_C interval, which is associated with serious ventricular arrhythmias (e.g., torsades de pointes) and sudden death. [1] The possible effects of combining higher dosages of thioridazine and/or fluvoxamine are not yet known, but may be even more pronounced. [1] Therefore, concurrent administration of fluvoxamine and thioridazine is contraindicated.[1]

In a limited number of healthy individuals, concurrent administration of fluvoxamine (100 mg daily for 4 days) and tizanidine (single 4-mg dose) resulted in a 12-fold increase in peak plasma tizanidine concentrations, a threefold increase in elimination half-life of tizanidine, and a 33-fold increase in the AUC of tizanidine.[1 35 42] The mean cardiovascular effects observed in this study were a decrease in systolic blood pressure of 35 mm Hg, a decrease in diastolic blood pressure of 20 mm Hg, and a decrease in heart rate of 4 beats/minute.[1 35] In addition, drowsiness was substantially increased and psychomotor performance was substantially impaired during concurrent therapy.[1 35] Since fluvoxamine has been shown to markedly affect the pharmacokinetics of tizanidine and to increase the risk of adverse cardiovascular (including substantial hypotension) and CNS (e.g., drowsiness, psychomotor impairment) effects associated with tizanidine use,[1 35 42] concomitant use of tizanidine and fluvoxamine is contraindicated.[1 35 36 42]

Caution should be exercised if fluvoxamine is used concomitantly with benzodiazepines that are metabolized by hepatic oxidation (e.g., alprazolam, midazolam, triazolam).[1] Concomitant use of diazepam and fluvoxamine generally should be avoided.[1] The clearance of diazepam was reduced by 65% and that of its active metabolite *N*-desmethyldiazepam could not be determined during concomitant administration with fluvoxamine in one study.[1] Concomitant use of fluvoxamine (100 mg daily) and alprazolam (1 mg 4 times daily) resulted in plasma alprazolam concentrations that were approximately twice those observed when alprazolam was administered alone.[1] The initial dosage of alprazolam should be reduced by at least 50% if the drugs are administered concomitantly, with subsequent alprazolam dosages titrated to the lowest effective dosage; modification of fluvoxamine maleate is not necessary.[1] The clearance of benzodiazepines that are metabolized by glucuronidation (e.g., lorazepam, oxazepam, temazepam) is unlikely to be affected by fluvoxamine.[1]

Fluvoxamine (50 mg twice daily for 7 days) reduced the clearance of mexiletine (administered as a single dose of 200 mg) by 38% in a limited number of healthy Japanese males in one pharmacokinetic study.[1 38] Pending further accumulation of data, close patient monitoring and monitoring of serum mexiletine concentrations are recommended when fluvoxamine and mexiletine are given concurrently.[1 38]

Since fluvoxamine coadministration decreased theophylline clearance by approximately threefold, the theophylline dosage should be reduced to approximately one-third of the usual daily maintenance dosage and plasma theophylline concentrations should be monitored if the drugs are administered concomitantly.[1]

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.[1 39 41] Although these studies focused on upper GI bleeding, there is some evidence suggesting that bleeding at other sites may be similarly potentiated.[1] 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.[1 40 41] Patients receiving fluvoxamine should be cautioned about the concomitant use of drugs that interfere with hemostasis, including aspirin and other nonsteroidal anti-inflammatory agents.[1]

Patients receiving fluvoxamine concomitantly with oral anticoagulants (e.g., warfarin) should have close monitoring of prothrombin times and adjustment of their anticoagulant dosage if indicated.[1] Prothrombin times were prolonged and plasma warfarin concentrations were increased when the drug was administered concomitantly with fluvoxamine.[1]

■ **Dosage in Renal and Hepatic Impairment**

Because patients with hepatic impairment have reduced fluvoxamine clearance, reduction of the initial dosage and modification of subsequent dosage titration may be appropriate; subsequent dosage adjustments generally should be made in smaller increments and at longer intervals in such patients.[1 19] Limited evidence indicates that dosage modification is not necessary in patients with renal impairment.[1 18 19]

■ **Treatment of Pregnant Women during the Third Trimester**

Some neonates exposed to fluvoxamine and other selective serotonin-reuptake inhibitors or selective serotonin- and norepinephrine-reuptake inhibitors (SNRIs) late in the third trimester of pregnancy have developed complications, which have sometimes been severe and required prolonged hospitalization, respiratory support, enteral nutrition, and other forms of supportive care in special-care nurseries.[1 27 28 29 30 31 32 33] Therefore, the clinician should carefully consider the potential risks and benefits of treating a pregnant woman with fluvoxamine during the third trimester of pregnancy.[1 28 29 30 33] In addition, consideration may be given to cautiously tapering fluvoxamine therapy in the third trimester prior to delivery if the drug is administered during pregnancy.[1 30] For additional information on use of selective serotonin-reuptake inhibitors during pregnancy, see Pregnancy, under Cautions: Pregnancy, Fertility, and Lactation, in Fluoxetine Hydrochloride 28:16.04.20.

Description

Fluvoxamine maleate, a selective serotonin-reuptake inhibitor (SSRI), is an aralkylketone-derivative antidepressant agent.[1 7] The drug differs structurally from other SSRIs (e.g., citalopram, escitalopram, fluoxetine, paroxetine, sertraline) and also differs structurally from other currently available antidepressant agents (e.g., monoamine oxidase inhibitors, and tricyclic and tetracyclic antidepressants).[1 3 4 6 46] The exact mechanism of action of fluvoxamine has not been fully elucidated but appears to involve inhibition of reuptake of serotonin (5-hydroxytryptamine [5-HT]) at the presynaptic membrane.[1 3 4 8 9] Data from in vitro studies suggest that fluvoxamine is more potent than clomipramine, fluoxetine, and desipramine as a serotonin-reuptake inhibitor.[3 4 6 7] Although not clearly established, it has been suggested that the mechanism of action of fluvoxamine and other drugs (e.g., clomipramine, fluoxetine, sertraline) used in the management of obsessive compulsive disorder may be related to their

serotonergic activity.[1 2 7 9 47] Fluvoxamine appears to have little or no effect on reuptake of other neurotransmitters such as norepinephrine and dopamine.[3 4 6] In addition, the selectivity of fluvoxamine in inhibiting serotonin versus norepinephrine reuptake appears to be substantially greater than that of other SSRIs (e.g., fluoxetine, paroxetine, sertraline) and tricyclic antidepressants, including clomipramine.[3 4 6 9] In vitro studies have demonstrated that fluvoxamine possesses virtually no affinity for α_1- or α_2-adrenergic, β-adrenergic, muscarinic, dopamine D_2, histamine H_1, GABA-benzodiazepine, opiate, 5-HT_1, or 5-HT_2 receptors.[1 3 4 6]

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.

Preparations

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

Fluvoxamine Maleate

Routes	Forms	Strengths	Brand Names	Manufacturer
Oral	Tablets, film-coated	25 mg*	Fluvoxamine Maleate Tablets	
		50 mg*	Fluvoxamine Maleate Tablets	
		100 mg*	Fluvoxamine Maleate Tablets	

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

■ Comparative Pricing

This pricing information is subject to change at the sole discretion of DS Pharmacy. This pricing information was updated 03/2010. For the most current and up-to-date pricing information, please visit www.drugstore.com. Actual costs to patients will vary depending on the use of specific retail or mail-order locations and health insurance copays.

Fluvoxamine Maleate 100MG Tablets (TEVA PHARMACEUTICALS USA): 50/$104 or 100/$194.98

Fluvoxamine Maleate 25MG Tablets (IVAX PHARMACEUTICALS INC.): 30/$53.99 or 90/$155.98

Fluvoxamine Maleate 50MG Tablets (BAY PHARMA): 100/$166.77 or 200/$332.5

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

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