quently in patients receiving acamprosate than in those receiving placebo (2.4 versus 0.8%). Completed suicide occurred in 0.13% of patients receiving acamprosate in clinical studies and in 0.1% of those receiving placebo. While many of these events occurred in the context of alcohol relapse, a consistent pattern between recovery from alcoholism and the emergence of suicidality was not identified. These studies excluded patients with severe psychiatric impairment, and review of safety data did not show a difference in the incidence of adverse events designated as depression between those receiving acamprosate and those receiving placebo. The existence of a relationship between alcohol dependence, depression, and suicidality is well known.

Closely monitor patients for symptoms of depression and suicidal thinking.

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

Lactation. Acamprosate is distributed into milk in rats; caution if used in nursing women.

Pediatric Use. Safety and efficacy not established in children younger than 18 years of age. Acamprosate has been evaluated in a limited number of adolescents 16–19 years of age.

Geriatric Use. Experience in those 65 years of age or older insufficient to determine whether they respond differently than younger adults.

Pharmacokinetics not evaluated in geriatric individuals. Because geriatric patients frequently have decreased renal function, plasma concentrations of acamprosate are expected to be higher in geriatric individuals than in younger adults. Select drug dosage carefully. Consider monitoring renal function.

Hepatic Impairment. Pharmacokinetics not altered in patients with mild or moderate hepatic impairment (Child-Pugh class A or B). Safety and pharmacokinetics not evaluated in patients with severe hepatic impairment.

Renal Impairment. Acamprosate is eliminated in urine as unchanged drug; clearance depends on renal function. Dosage adjustment recommended in patients with creatinine clearance of 30–50 mL/minute. (See Dosage and Administration: Special Populations.) Contraindicated in patients with creatinine clearance less than 30 mL/minute.

■ **Common Adverse Effects** Adverse effects reported in 5% or more of patients receiving acamprosate and more frequently than placebo include diarrhea and asthenia.

Drug Interactions

Safety profile in patients receiving acamprosate in conjunction with anxiolytics, hypnotics and sedatives (including benzodiazepines), or nonopiate analgesics in clinical studies was similar to that in patients receiving these drugs with placebo.

Alcohol. Pharmacokinetic interaction unlikely.

Antidepressants. Changes in weight (i.e., loss or gain) reported more frequently in patients receiving acamprosate concomitantly with an antidepressant than in patients receiving either agent alone.

No change in the pharmacokinetics of desipramine or imipramine.

Diazepam. Pharmacokinetic interaction unlikely.

Disulfiram. Pharmacokinetic interaction unlikely.

Naltrexone. Pharmacokinetic interaction (increased plasma concentrations of acamprosate; no change in plasma concentrations of naltrexone or its major metabolite, 6-β-naltrexol). No dosage adjustment recommended.

Description

Acamprosate calcium is a synthetic homotaurine derivative and is structurally related to γ-aminobutyric acid (GABA).

While the precise mechanism of action of acamprosate in the maintenance of abstinence from alcohol ingestion remains to be determined, the drug decreases glutamatergic transmission and modulates neuronal hyperexcitability during withdrawal from alcohol. Acamprosate reduces voluntary intake of alcohol in alcohol-dependent animals. Acamprosate did not exhibit anticonvulsant, antidepressant, or anxiolytic activity in animal studies. Administration of acamprosate was not associated with the development of tolerance or dependence in animal studies. Acamprosate is not known to cause alcohol aversion. Ingestion of alcohol by individuals receiving acamprosate therapy does not result in a disulfiram-like reaction.

Acamprosate is eliminated principally in urine as unchanged drug. The drug is not metabolized in the liver. Acamprosate does not induce cytochrome P-450 (CYP) isoenzymes 1A2 or 3A4, nor does it inhibit CYP isoenzymes 1A2, 2C9, 2C19, 2D6, 2E1, or 3A4.

Advice to Patients

Risk of psychomotor impairment; importance of exercising caution while driving or operating hazardous machinery until the effects of the drug on the individual are known.

Importance of continuing acamprosate as directed by their clinician, even in the event of a relapse. Importance of discussing any renewed use of alcohol with their clinician.

Advise patients that acamprosate helps maintain abstinence only when used as part of a treatment program that includes counseling and other supportive measures.

Risk of suicidality; importance of patients, families, and caregivers notifying clinicians of emergence of suicidality or symptoms of depression.

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

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

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.

Acamprosate Calcium

Oral		
Tablets, delayed-release (enteric-coated)	333 mg	Campral®, Forest

Atomoxetine Hydrochloride

■ Atomoxetine is a selective norepinephrine-reuptake inhibitor.

Uses

Atomoxetine hydrochloride is used as an adjunct to psychological, educational, social, and other remedial measures in the treatment of attention-deficit hyperactivity disorder (ADHD).

■ **Attention Deficit Hyperactivity Disorder** Atomoxetine hydrochloride is used as an adjunct to psychological, educational, social, and other remedial measures in the treatment of ADHD (hyperkinetic disorder, hyperkinetic syndrome of childhood, minimal brain dysfunction) in adults and children 6 years of age and older. Efficacy of the drug for this indication was established in short-term (6–9 weeks) controlled clinical studies in children and adolescents 6–18 years of age and also in 10-week controlled clinical studies in adults who met DSM-IV criteria for ADHD. Efficacy of atomoxetine in the treatment of ADHD also was established in one longer-term (12 months) controlled clinical study in children and adolescents 6–15 years of age.

In controlled clinical studies in children 7–13 years of age with ADHD, therapy with atomoxetine (mean final dosage of 1.6 mg/kg daily, administered in 2 divided doses in the morning and late afternoon for 9 weeks) was more effective than placebo in decreasing inattention and hyperactive/impulsive symptoms, as measured by the ADHD Rating Scale-IV-Parent Version (ADHDRS), Clinical Global Impressions-ADHD-Severity (CGI-ADHD-S), and Conners Parent Rating Scale-Revised: Short Form (CPRS-R:S). In another controlled clinical study in children and adolescents 6–16 years of age with ADHD, therapy with atomoxetine (mean final dosage of 1.3 mg/kg once daily in the morning for 6 weeks) was more effective than placebo in decreasing inattention and hyperactive/impulsive symptoms, as measured by the ADHDRS, Conners Parent Rating Scale, and Conners Teacher Rating Scale.

In a randomized, placebo-controlled, dose-response study with atomoxetine (0.5, 1.2, or 1.8 mg/kg daily, administered in 2 divided doses in the morning and late afternoon for 8 weeks) in children and adolescents 8–18 years of age with ADHD, therapy with atomoxetine 1.2 or 1.8 mg/kg daily was more effective than placebo in decreasing inattention and hyperactive/impulsive symptoms, as measured by the ADHDRS, and improving social and family functioning, as measured by the Child Health Questionnaire (CHQ). Patients receiving atomoxetine 0.5 mg/kg daily exhibited responses intermediate to those observed in patients receiving placebo or atomoxetine at higher dosages (1.2 or 1.8 mg/kg daily), but no differences in response were observed between patients receiving dosages of 1.2 versus 1.8 mg/kg daily.

In an open-label, multicenter study in boys 7–15 years of age and girls 7–9 years of age with ADHD, therapy with atomoxetine (up to 2 mg/kg daily, administered in 2 divided doses in the morning and late afternoon) or methylphenidate (up to 60 mg daily, administered once daily or in 2 or 3 divided doses) for 10 weeks produced similar results in the reduction of ADHD symptoms; however, double-blind clinical studies are needed to establish the comparative efficacy and tolerance of these therapies.

In a randomized, double-blind, placebo-controlled maintenance study, 604 children and adolescents 6–15 years of age with ADHD initially received open-label atomoxetine (1.2–1.8 mg/kg daily in 2 divided doses) for 10 weeks. Patients who responded to therapy during the open-label phase were randomized at week 12 to receive either atomoxetine (at the same dosage) or placebo for an additional 9 months. At study end point, relapse (defined as an increase in ADHDRS total score to 90% of baseline score *and* an increase of 2 or more

points on the CGI-S scale) occurred in fewer patients receiving atomoxetine compared with those receiving placebo (22 versus 38%). When the more-sensitive secondary definition of relapse (an increase in ADHDRS total score to 50% of baseline score *and* an increase of 2 or more points on the CGI-S scale) was used, the relapse rate also was substantially lower in atomoxetine-treated patients (28%) than in placebo-treated patients (48%). In addition, patients who continued receiving atomoxetine experienced a longer time to relapse and achieved superior psychosocial functioning compared to those receiving placebo.

In controlled clinical studies in adults with ADHD, therapy with atomoxetine (mean final dosage of 95 mg daily, administered in 2 equally divided doses in the morning and late afternoon/early evening for 10 weeks) was more effective than placebo in decreasing inattention and hyperactive/impulsive symptoms, as measured by the Conners Adult ADHD Rating Scale (CAARS).

Dosage and Administration

■ **Administration** Atomoxetine hydrochloride may be administered orally once daily in the morning or in 2 equally divided doses in the morning and late afternoon/early evening. The drug may be administered without regard to meals.

The manufacturer states that atomoxetine is an ocular irritant; therefore, the capsules should be swallowed whole and should not be broken or opened, nor should the capsule contents be sprinkled on food.

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

The usual initial dosage of atomoxetine in adults or in children and adolescents weighing more than 70 kg is 40 mg daily; dosage may be increased after a minimum of 3 days to a target dosage of approximately 80 mg daily. If an optimum response has not been achieved after 2–4 additional weeks of therapy, dosage may be increased to a maximum of 100 mg daily; dosages exceeding 100 mg daily have not been shown in clinical trials to result in additional therapeutic benefit. In adults or in children and adolescents weighing more than 70 kg, if atomoxetine is used concomitantly with potent inhibitors of the cytochrome P-450 2D6 (CYP2D6) isoenzyme (e.g., paroxetine, fluoxetine, quinidine) or in patients with poor metabolizer phenotypes of the CYP2D6 isoenzyme, the initial atomoxetine dosage should be 40 mg daily and dosage should be increased to the usual target dosage of 80 mg daily only if ADHD symptoms fail to improve after 4 weeks of therapy and the initial dosage is well tolerated. The maximum recommended dosage of atomoxetine in adults or in children and adolescents weighing more than 70 kg is 100 mg daily. The safety of single doses exceeding 120 mg and total daily dosages exceeding 150 mg has not been established.

The usual initial dosage of atomoxetine in children and adolescents weighing 70 kg or less is approximately 0.5 mg/kg daily; dosage may be increased after a minimum of 3 days to a target dosage of approximately 1.2 mg/kg daily. In children and adolescents weighing 70 kg or less, if atomoxetine is used concomitantly with potent CYP2D6 inhibitors (e.g., paroxetine, fluoxetine, quinidine) or in patients with poor metabolizer phenotypes of the CYP2D6 isoenzyme, the initial atomoxetine dosage should be 0.5 mg/kg daily and dosage should be increased to the usual target dosage of 1.2 mg/kg daily only if ADHD symptoms fail to improve after 4 weeks of therapy and the initial dosage is well tolerated. Daily dosage of atomoxetine in children and adolescents weighing 70 kg or less should not exceed 100 mg or 1.4 mg/kg, whichever is less; dosages exceeding 1.2 mg/kg daily have not been shown in clinical trials to result in additional therapeutic benefit.

Because the effectiveness of atomoxetine for long-term use (i.e., more than 12 months in children and adolescents 6–15 years of age, more than 9 weeks in those 16–18 years of age, and more than 10 weeks in adults) has not been established, patients receiving atomoxetine for extended periods should be periodically reevaluated to assess the long-term usefulness of the drug.

Atomoxetine may be discontinued without tapering the dosage.

■ **Special Populations** The manufacturer recommends that usual initial and target dosages of atomoxetine be reduced by 50% in patients with moderate hepatic impairment (Child-Pugh class B) and by 75% in those with severe hepatic impairment (Child-Pugh class C).

Cautions

■ **Contraindications** Known hypersensitivity to atomoxetine or any ingredient in the formulation.

The manufacturer states that atomoxetine is contraindicated in patients currently receiving or having recently received (i.e., within 2 weeks) monoamine oxidase (MAO) inhibitor therapy. In addition, at least 2 weeks should elapse after discontinuing atomoxetine before initiating MAO inhibitor therapy. Severe, potentially fatal, reactions (including hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma) have been reported in patients receiving other drugs that affect brain monoamine concentrations concomitantly with MAO inhibitor therapy.

The manufacturer also states that atomoxetine should not be used in patients with angle-closure glaucoma, since the drug was associated with an increased risk of mydriasis in some patients during controlled clinical trials.

■ **Warnings/Precautions** ***Warnings*** **Suicidality Risk.** Atomoxetine may increase the risk of suicidal ideation in children and adolescents with attention deficit hyperactivity disorder (ADHD). (See Pediatric Use under Warnings/Precautions: Specific Populations, in Cautions.) Pediatric patients should be closely monitored for clinical worsening, suicidality (suicidal ideation or behaviors), or unusual changes in behavior, particularly during the first few months after initiation of therapy and during periods of dosage adjustments. Monitoring should include daily observation by family members and caregivers and frequent contact with the prescribing clinician, particularly if the patient's behavior changes or is a concern. The manufacturer recommends face-to-face contact between clinicians and patients or their family members or caregivers at least weekly during the first 4 weeks of therapy and then every other week for the next 4 weeks, with subsequent face-to-face contact at 12 weeks and as clinically indicated thereafter; additional contact via telephone may be appropriate between visits.

Discontinuance of therapy should be considered in patients with emergent suicidality or manifestations that may be precursors to emerging suicidality (e.g., anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia, hypomania, mania), particularly if such manifestations are severe or abrupt in onset or were not part of the patient's presenting symptoms.

Sensitivity Reactions Allergic reactions, including angioedema, urticaria, and rash, have been reported rarely in patients receiving atomoxetine.

Other Warnings and Precautions **Severe Hepatic Injury.** Severe hepatic injury was reported during postmarketing surveillance in 2 patients (an adolescent and an adult) who had received atomoxetine for several months. In one patient, hepatic injury was manifested by increased hepatic enzymes (up to 40 times the upper limit of normal [ULN]) and jaundice (bilirubin up to 12 times the ULN); manifestations recurred upon rechallenge with atomoxetine and resolved upon discontinuance of the drug, providing evidence that the hepatic injury was caused by atomoxetine. Both patients recovered and did not require liver transplantation. However, the manufacturer notes that severe drug-related hepatic injury may progress to acute hepatic failure resulting in death or requiring liver transplantation in a small percentage of patients. The actual incidence of hepatic injury in patients receiving atomoxetine is unknown because of possible underreporting of postmarketing adverse effects.

Adverse hepatic effects may occur several months after initiation of atomoxetine, and laboratory abnormalities may continue to worsen for several weeks after discontinuance of the drug. Hepatic enzyme concentrations should be determined after the first manifestation of hepatic dysfunction (e.g., pruritus, dark urine, jaundice, right upper quadrant tenderness, unexplained flu-like symptoms) in patients receiving atomoxetine. Atomoxetine should be discontinued in patients with jaundice or laboratory evidence of hepatic injury, and therapy with the drug should *not* be reinitiated in such patients.

Sudden Death and Serious Cardiovascular Events. Although a causal relationship to atomoxetine has not been established, sudden unexplained death, stroke, and myocardial infarction have been reported in adults receiving usual dosages of atomoxetine for the treatment of ADHD. Sudden unexplained death also has been reported in children and adolescents with structural cardiac abnormalities or other serious cardiac conditions receiving usual dosages of atomoxetine. Children, adolescents, and adults who are being considered for atomoxetine therapy should undergo a thorough medical history review (including evaluation for a family history of sudden death or ventricular arrhythmia) and physical examination to detect the presence of cardiac disease, and should receive further cardiac evaluation (e.g., ECG, echocardiogram) if initial findings suggest such disease. Although some serious cardiac conditions are independently associated with an increased risk of sudden death, atomoxetine generally should *not* be used in children, adolescents, or adults with known serious structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, coronary artery disease, or other serious cardiac conditions. Patients who develop exertional chest pain, unexplained syncope, or other manifestations suggestive of cardiac disease during atomoxetine therapy should undergo prompt cardiac evaluation.

For further information on screening for cardiac conditions, selecting appropriate candidates for stimulant therapy, and monitoring for treatment-emergent cardiac conditions, see Cardiovascular Precautions under Cautions: Precautions and Contraindications, in the Amphetamines General Statement 28:20.04.

Psychiatric Effects. Atomoxetine should be used with caution in the management of ADHD in patients with comorbid bipolar disorder because of the potential for precipitation of mixed or manic episodes in such patients. Prior to initiating atomoxetine therapy, patients with ADHD and comorbid depressive symptoms should be carefully screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history (e.g., family history of suicide, bipolar disorder, or depression).

Psychotic or manic symptoms (e.g., hallucinations, delusional thinking, mania) have been reported in children and adolescents without prior history of psychotic illness or mania who received usual dosages of atomoxetine. In a pooled analysis of multiple short-term, placebo-controlled studies, such symptoms occurred in about 0.2% of patients receiving usual dosages of atomoxetine compared with 0% of those receiving placebo. If psychotic or manic symptoms occur, a causal relationship to atomoxetine should be considered, and discontinuance of therapy may be appropriate.

Cardiovascular Effects. Increased blood pressure and heart rate were reported in children, adolescents, and adults receiving atomoxetine in controlled clinical studies. The drug should be used with caution in patients with hyper-

tension, tachycardia, or cardiovascular or cerebrovascular disease that might be affected by increases in blood pressure or heart rate. Blood pressure and pulse rate should be measured before initiation of atomoxetine, following any increase in dosage, and periodically during therapy.

Orthostatic hypotension and syncope also were reported in patients receiving atomoxetine in controlled clinical studies. The drug should be used with caution in patients with conditions that would predispose them to hypotension.

Peripheral Vascular Effects. Exacerbation or precipitation of Raynaud's phenomenon was reported during postmarketing surveillance in patients receiving atomoxetine.

Genitourinary Effects. Urinary retention and urinary hesitation were reported in adults receiving atomoxetine in controlled clinical studies.

Growth Effects. Temporary suppression of normal weight and height patterns has been observed in pediatric patients receiving atomoxetine therapy. Gains in weight and height generally lag behind predicted population values for about the first 9–12 months of therapy; however, weight and height gains rebound with continued treatment. Similar growth patterns have been observed regardless of metabolizer phenotype (poor or extensive metabolizer of the drug) or pubertal status upon initiation of treatment. The manufacturer states that growth should be monitored in patients receiving therapy with atomoxetine.

Children and adolescents 6–18 years of age receiving atomoxetine for up to 9 weeks in controlled clinical studies had an average weight loss of 0.4 kg compared with an average weight gain of 1.5 kg in those receiving placebo for the same time period; similar rates of weight loss have been reported in other controlled clinical studies with the drug. In one clinical trial, decreases in body weight of at least 3.5% occurred in 7–29% of patients receiving atomoxetine at various dosages, compared with 1.3% of patients receiving placebo. However, in patients receiving atomoxetine for 3 years, weight increased by an average of 17.9 kg (0.5 kg more than predicted by baseline data) and height increased by an average of 19.4 cm (0.4 cm less than predicted by baseline data) at 3 years. Gain in height stabilized at about 12 months.

Behavioral Effects. Aggressive behavior and hostility frequently are observed in pediatric patients with ADHD and have been reported in patients receiving drug therapy (including atomoxetine) for the disorder. In controlled clinical studies in pediatric patients, aggressive behavior or hostility was reported slightly (overall risk ratio of 1.33), but not significantly, more frequently in those receiving atomoxetine compared with those receiving placebo. Patients beginning treatment for ADHD should be monitored for the onset or worsening of aggressive behavior or hostility.

Priapism. Priapism was reported rarely during postmarketing surveillance in pediatric and adult patients receiving atomoxetine; if priapism is suspected, prompt medical attention is required. (See Advice to Patients.)

Tics. In a controlled study, atomoxetine did not worsen tics in patients with ADHD and comorbid Tourette's disorder.

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

Lactation. Atomoxetine and/or its metabolites are distributed into milk in rats; it is not known whether the drug is distributed into milk in humans. Therefore, atomoxetine should be used with caution in nursing women.

Pediatric Use. Safety and efficacy of atomoxetine have not been established in children younger than 6 years of age.

Atomoxetine may increase the risk of suicidal ideation in children and adolescents with ADHD. In a pooled analysis of 12 short-term controlled clinical studies in pediatric patients with ADHD (11 studies) or enuresis (1 study), the risk of suicidal ideation was about 0.4% in those receiving atomoxetine versus 0% in those receiving placebo. One child receiving the drug attempted suicide; no completed suicides were reported. All events representing suicidal behavior or thinking occurred in children 12 years of age or younger and occurred during the first month of therapy. It is not known whether the risk of suicidal ideation in pediatric patients extends to long-term use of the drug. A similar analysis of data from adults with ADHD or major depressive disorder found no increased risk of suicidal ideation or behavior in those receiving atomoxetine. The potential risks of suicidality should be weighed against the clinical need for the drug prior to initiating atomoxetine therapy in children or adolescents. (See Suicidality Risk under Warnings/Precautions: Warnings, in Cautions.)

Sudden death has been reported in children and adolescents with structural cardiac abnormalities or other serious cardiac conditions receiving usual dosages of stimulants. (See Sudden Death and Serious Cardiovascular Events under Warnings/Precautions: Other Warnings and Precautions, in Cautions.)

Temporary suppression of normal weight and/or height patterns has been reported during the first 9–12 months of atomoxetine therapy; however, weight and height gains have rebounded with continued treatment. (See Growth Effects under Warnings/Precautions: Other Warnings and Precautions, in Cautions.) The growth of pediatric patients receiving atomoxetine should be monitored.

Geriatric Use. Safety and efficacy of atomexetine have not been established in geriatric patients.

Hepatic Impairment. Systemic exposure to atomoxetine concentrations is increased twofold in patients with moderate hepatic impairment (Child-Pugh class B) and fourfold in those with severe hepatic impairment (Child-Pugh class C). (See Dosage and Administration: Special Populations.)

■ **Common Adverse Effects** Abdominal pain, decreased appetite, vomiting, somnolence, hubsea, fatigue, irritability, and dizziness each occurred in 5% or more of children and adolescents receiving atomoxetine in controlled clinical studies and were at least twice as frequent in patients receiving the drug as in those receiving placebo. Dry mouth, nausea, insomnia, decreased appetite, constipation, fatigue, erectile dysfunction, hot flush, urinary disorders (urinary hesitation, urinary retention), and dysmenorrhea each occurred in 5% or more of adults receiving atomoxetine in controlled clinical studies and were at least twice as frequent in patients receiving the drug as in those receiving placebo.

Drug Interactions

■ **Drugs Affecting Hepatic Microsomal Enzymes** Potential pharmacokinetic interaction (decreased metabolism of atomoxetine) when atomoxetine is used concomitantly with drugs that inhibit the activity of the cytochrome P-450 2D6 (CYP2D6) isoenzyme. Inhibitors of CYP2D6 may increase plasma concentrations of atomoxetine in patients with the extensive-metabolizer phenotype to such an extent that plasma concentrations of the drug are similar to those achieved in poor metabolizers. When atomoxetine is used concomitantly with potent CYP2D6 inhibitors (e.g., paroxetine, fluoxetine, quinidine), or in patients with poor-metabolizer phenotypes of the CYP2D6 isoenzyme, the manufacturer states that dosage adjustment of atomoxetine should be considered. (See Dosage and Administration: Dosage.) However, in vitro studies suggest that concomitant use of atomoxetine with CYP2D6 inhibitors will not increase plasma concentrations of atomoxetine in patients with the poor-metabolizer phenotype.

■ **Drugs Metabolized by Hepatic Microsomal Enzymes** Pharmacokinetic interaction unlikely; evidence to date suggests that atomoxetine does not cause clinically important inhibition or induction of cytochrome P-450 enzymes, including CYP1A2, CYP3A, CYP2D6, and CYP2C9.

■ **GI Drugs** No important pharmacokinetic interactions reported with drugs that increase gastric pH (e.g., antacids containing magnesium hydroxide and aluminum hydroxide, omeprazole).

■ **Protein-bound Drugs** Pharmacokinetic interaction unlikely. In vitro studies indicate that atomoxetine is not displaced from binding sites by, and does not displace from binding sites, other highly protein-bound drugs (e.g., warfarin, aspirin, phenytoin, diazepam) in therapeutic concentrations.

■ **Alcohol** No change in the intoxicating effects of alcohol when alcohol was ingested by individuals receiving atomoxetine.

■ **β-Adrenergic Agonists** Potential pharmacologic interaction (increased cardiovascular effects [e.g., increased heart rate and blood pressure]) when atomoxetine is used concomitantly with oral or parenteral β_2-adrenergic agonists (e.g., albuterol). Use with caution.

■ **Cardiovascular Agents** Potential pharmacologic interaction (increased hypertensive effects) with concomitant use of pressor agents (e.g., dopamine, dobutamine) and atomoxetine. Use with caution.

■ **Methylphenidate** No increase in cardiovascular effects with concomitant use of methylphenidate and atomoxetine relative to use of methylphenidate alone.

■ **Monoamine Oxidase Inhibitors** Potential pharmacologic interaction (inhibition of catecholamine metabolism). (See Cautions: Contraindications.)

Description

Atomoxetine is a selective norepinephrine-reuptake inhibitor. Atomoxetine is not considered a stimulant and also is structurally unrelated to other agents used for the treatment of attention deficit hyperactivity disorder (ADHD). The exact mechanism(s) of action of atomoxetine in the management of ADHD has not been fully elucidated but, based on in vitro studies, appears to be related to selective inhibition of the presynaptic norepinephrine transporter; the drug appears to have minimal affinity for other noradrenergic receptors or for other neurotransmitter transporters or receptors.

Atomoxetine is readily absorbed following oral administration. The drug is approximately 98% bound to plasma proteins, principally albumin, at therapeutic concentrations. Atomoxetine is metabolized principally via oxidation by the cytochrome P-450 2D6 (CYP2D6) isoenzyme and subsequent glucuronidation. Individuals who extensively metabolize atomoxetine via the CYP2D6 pathway exhibit the extensive-metabolizer phenotype, while those who have an impaired ability to metabolize the drug by this pathway exhibit the poor-metabolizer phenotype. In patients with the poor-metabolizer phenotype (about 7% of Caucasians and 2% of African-Americans), metabolic clearance of atomoxetine may be decreased; a fivefold increase in peak plasma concentrations of atomoxetine and a tenfold increase in area under the plasma concentration-time curve (AUC) have been reported in individuals with the poor-metabolizer phenotype relative to those with the extensive-metabolizer phenotype. The mean elimination half-life of atomoxetine is 5.2 or 21.6 hours in extensive or poor metabolizers, respectively. Atomoxetine does not inhibit or induce CYP2D6.

Advice to Patients

Importance of providing patient or caregiver with a copy of the manufacturer's patient information (medication guide); discuss and answer questions about its contents (e.g., benefits and risks of atomoxetine therapy, appropriate use) as needed. Importance of instructing the patient or caregiver to read and

understand the contents of the medication guide before initiating therapy and each time the prescription is refilled.

Risk of suicidal thinking. Importance of patients, caregivers, and family members immediately informing clinician if clinical worsening, anxiety, agitation; panic attacks, insomnia, irritability, aggressive behaviors, hostility, impulsivity, restlessness, mania, depression, suicidal ideation or behaviors, or unusual changes in behavior occur, particularly during the first few months after initiation of therapy or following dosage adjustments.

Patients and/or caregivers should be advised that hepatic dysfunction may develop rarely. Importance of informing clinician immediately if symptoms of hepatic injury occur (e.g., pruritus, jaundice, dark urine, upper right-sided abdominal tenderness, unexplained flu-like symptoms).

Importance of informing clinician immediately if adverse cardiovascular effects (e.g., chest pain, shortness of breath, fainting) occur.

Importance of informing clinician immediately if precipitation of psychotic (e.g., hallucinations, delusional thinking) or manic symptoms occurs.

Importance of exercising caution when driving or operating machinery until the effects of the drug on the individual are known.

Risk of priapism. Importance of seeking immediate medical attention if an erection persists for more than 4 hours.

Importance of taking atomoxetine exactly as prescribed. If a patient misses a dose of the drug, the missed dose should be taken as soon as it is remembered, but the amount of atomoxetine taken within a 24-hour period should not exceed the prescribed total daily dosage of the drug.

Importance of advising patient and/or caregivers that atomoxetine capsules should not be opened because the drug is an ocular irritant; if eye contact occurs, flush the affected eye(s) with water immediately, obtain medical advice, and wash hands and potentially contaminated surfaces as soon as possible.

Importance of informing clinician of any history of physical or mental disorders (e.g., cardiovascular disease, liver disease, depression).

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

Importance of informing clinicians of existing or contemplated concomitant therapy, including prescription and OTC drugs, dietary supplements, and herbal products, as well as any concomitant illnesses/conditions (e.g., glaucoma, suicidal ideation or behaviors, cardiac/cardiovascular disease, mental/psychiatric disorder, hepatic disease).

Importance of informing patients and/or caregivers of other important precautionary information. (See Cautions.)

Overview[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.

Atomoxetine Hydrochloride

Oral

Capsules	10 mg (of atomoxetine)	Strattera®, Lilly
	18 mg (of atomoxetine)	Strattera®, Lilly
	25 mg (of atomoxetine)	Strattera®, Lilly
	40 mg (of atomoxetine)	Strattera®, Lilly
	60 mg (of atomoxetine)	Strattera®, Lilly
	80 mg (of atomoxetine)	Strattera®, Lilly
	100 mg (of atomoxetine)	Strattera®, Lilly

Flumazenil

■ Flumazenil, a 1,4-imidazobenzodiazepine derivative, is a benzodiazepine antagonist.

Uses

Flumazenil is used in adults for the complete or partial reversal of benzodiazepine-induced sedation when benzodiazepines are used for induction or maintenance of general anesthesia or for diagnostic or therapeutic procedures (i.e., conscious sedation) and for the management of benzodiazepine intoxication. Flumazenil also is used in children 1–17 years of age for the reversal of benzodiazepine-induced sedation when benzodiazepines are used for diagnostic or therapeutic procedures. The manufacturer states that the safety and efficacy of flumazenil have *not* been established in pediatric patients for reversal of benzodiazepine-induced sedation when benzodiazepines are used for induction of general anesthesia, for the management of benzodiazepine intoxication, nor for the resuscitation of neonates. (See Special Populations: Pediatric Use.)

■ **Reversal of General Anesthesia** Flumazenil has been shown to be effective in reversing sedation and restoring psychomotor function in adults who received midazolam for induction or maintenance of general anesthesia. Efficacy was established in 4 clinical studies in adults who received 5–80 mg of midazolam alone or in conjunction with skeletal muscle relaxants, nitrous oxide, regional or local anesthetics, opiates, and/or inhalational anesthetics. A 0.2-mg dose of flumazenil was administered, followed by additional 0.2-mg doses as needed to reach a complete response (up to a maximum of 1 mg). In these studies, 81% of patients became completely alert or remained only slightly drowsy following total flumazenil doses of 0.4–0.6 mg (36%) or 0.8–1 mg (64%). However, resedation occurred in 10–15% of patients who responded to flumazenil. (See Warnings: Resedation.) Flumazenil failed to restore memory completely as tested by picture recall. In addition, flumazenil was not as effective in the reversal of sedation in patients who received multiple anesthetic agents in addition to benzodiazepines.

■ **Reversal of Conscious Sedation** Flumazenil has been shown to be effective in reversing the sedative and psychomotor effects of benzodiazepines when these drugs are used for diagnostic or therapeutic procedures but was less effective in completely and consistently reversing benzodiazepine-induced amnesia. Efficacy was established in 4 clinical studies in adults who received an average of 30 mg of diazepam or 10 mg of midazolam for sedation (with or without an opiate) for both inpatient and outpatient diagnostic or surgical procedures. Flumazenil was administered as an initial dose of 0.4 mg (2 doses of 0.2 mg each), with additional 0.2-mg doses administered as needed to achieve complete awakening, up to a maximum of 1 mg. In these studies, 78% of patients receiving flumazenil achieved complete consciousness, but approximately 50% of these patients required 2–3 additional doses of the drug in order to achieve this level of consciousness. In addition, while most patients remained alert throughout the 3-hour postprocedure observation period, resedation occurred in 3–9% of these patients.

Pediatric Considerations The safety and efficacy of flumazenil for the reversal of benzodiazepine-induced conscious sedation have been established in children 1 year of age and older. In one uncontrolled clinical trial involving 107 children 1–17 years of age who had received midazolam for conscious sedation, flumazenil was administered at doses of 0.01 mg/kg (maximum of 0.2 mg) up to a maximum of 5 doses or a total dose of 1 mg. In this study, 56% of the children achieved complete consciousness within 10 minutes of flumazenil administration, but 51% of them required the maximum number of doses of the drug allowed for initial treatment in order to achieve this level of consciousness. In addition, approximately 12% of the patients (all of whom were 1–5 years of age) who achieved complete consciousness following flumazenil administration experienced resedation within 19–50 minutes of initial administration of the drug. Episodes of resedation were reversed by additional doses of flumazenil. However, the manufacturer states that the safety and efficacy of repeated flumazenil administration in pediatric patients experiencing resedation have *not* been established.

■ **Benzodiazepine Overdosage** Flumazenil is used in adults for the management of benzodiazepine overdosage. The drug is an adjunct to, not a replacement for, appropriate supportive and symptomatic measures (e.g., ventilatory and circulatory support) in the management of benzodiazepine overdosage. Because patients admitted to hospitals for drug overdoses may have ingested multiple substances and/or are being treated for concomitant illnesses (e.g., depression, substance abuse), the presence of contraindications or precautions, which may limit the use of flumazenil therapy, should be considered. (See Contraindications under Warnings/Precautions, in Cautions.) Flumazenil has no known benefit other than reversal of benzodiazepine-induced sedation in seriously ill patients with multiple-drug overdosage, and the drug should *not* be used in cases where seizures (from any cause) are likely. In addition, the manufacturer warns that flumazenil should *not* be used in patients with serious cyclic depressant overdosage. (See Drug Interactions: Cyclic Antidepressants.) For information on the pathogenesis, manifestations, and treatment of benzodiazepine overdosage, see Acute Toxicity in the Benzodiazepines General Statement 28:24.08.

Efficacy of flumazenil has been established in 2 studies in patients who were presumed to have taken an overdose of a benzodiazepine, either alone or in combination with a variety of other agents. In these studies, of patients who were proven to have taken a benzodiazepine, 80% of those who received flumazenil responded with an improvement in level of consciousness. Of those who responded to flumazenil, 75% responded to a total dose of 1–3 mg. However, reversal of sedation was associated with an increased frequency of symptoms of CNS excitation, and 1–3% of patients who received flumazenil were treated for agitation or anxiety.

■ **Other Uses** The manufacturer states that the safety and efficacy of flumazenil for the treatment of benzodiazepine dependence or for the management of protracted benzodiazepine abstinence syndrome have not been established and therefore such use currently is not recommended.

Dosage and Administration

■ **General** Flumazenil is administered by rapid (over 15–30 seconds) IV injection through a freely flowing IV infusion into a large vein. Because of the risk of local irritation, the drug is recommended for IV use only, and extravasation into perivascular tissues should be avoided. Patients should have a secure airway and established IV access prior to administration of the drug.

Phenytoin appears to be distributed into milk in small amounts.

■ **Elimination** Following oral administration, the plasma half-life of phenytoin averages about 22 hours, although the half-life has ranged from 7–42 hours in individual patients. The plasma half-life of phenytoin in humans following IV administration ranges from 10–15 hours.

The major route of metabolism of phenytoin is oxidation by the liver to the inactive metabolite 5-(*p*-hydroxyphenyl)-5-phenylhydantoin (HPPH). Because this metabolism is a saturable process, small increases in dosage may produce substantial increases in plasma phenytoin concentrations; the steady-state plasma concentration may double or triple from a 10% or more increase in dosage, possibly resulting in toxicity. HPPH undergoes enterohepatic circulation and is excreted in urine via glomerular filtration and tubular secretion, mainly as the glucuronide. Approximately 60–75% of the daily dose of the drug is excreted in this form. Other minor metabolites also appear in urine. In therapeutic doses, approximately 1% is excreted unchanged in urine; in toxic doses, up to 10% of the ingested drug may be excreted unchanged by the kidneys.

Following equal doses of phenytoin, total plasma phenytoin concentrations are lower in chronic uremic patients than in non-uremic patients which suggests an altered metabolic disposition of the drug in patients with uremia.

Chemistry and Stability

■ **Chemistry** Phenytoin is a hydantoin-derivative anticonvulsant. Phenytoin occurs as a white powder and is practically insoluble in water, soluble in hot alcohol, and slightly soluble in cold alcohol. The drug has an apparent pK_a of 8.06–8.33. Phenytoin sodium occurs as a white, hygroscopic powder and is freely soluble in water, soluble in alcohol, and freely soluble in warm propylene glycol.

Aqueous solutions of phenytoin sodium gradually absorb carbon dioxide, and the drug undergoes partial hydrolysis to phenytoin, resulting in turbid solutions. The drug is more stable in propylene glycol. Commercially available phenytoin sodium injection is a sterile solution of the drug containing 40% propylene glycol and 10% alcohol in water for injection. Sodium hydroxide is added during manufacture of the injection to adjust the pH to 12. Each 100-mg phenytoin sodium capsule contains approximately 0.35 mEq of sodium, and phenytoin sodium injection contains about 0.2 mEq of sodium per mL.

Extended phenytoin sodium capsules are formulated so that they undergo slower dissolution with more prolonged absorption than prompt phenytoin sodium capsules.

■ **Stability** Commercially available phenytoin oral suspension and tablets, and extended and prompt phenytoin sodium capsules generally should be stored in tight containers at a room temperature less than 30°C, although one manufacturer recommends storage of their extended phenytoin sodium capsules (Phenytek®) at controlled room temperatures of 15–30°C; the extended capsules should be protected from light and moisture and the oral suspension should be protected from freezing and light. Phenytoin sodium injection should be stored at 15–30°C; freezing should be avoided. A precipitate may form if the injection is refrigerated or frozen; however, this will dissolve after warming to room temperature. Slight yellowish discoloration of the injection will not affect potency or efficacy, but the injection should not be used if the solution is not clear or if a precipitate is present. Precipitation of free phenytoin will occur at a pH of 11.5 or less.

Phenytoin sodium injection is physically and/or chemically incompatible with some drugs, but the compatibility depends on several factors (e.g., concentrations of the drugs, specific diluents used, resulting pH, temperature). Specialized references should be consulted for specific compatibility information.

For further information on chemistry and stability, pharmacology, pharmacokinetics, uses, cautions, acute toxicity, drug interactions, and dosage and administration of phenytoin, see the Anticonvulsants General Statement 28:12.

Preparations

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

Phenytoin

Oral		
Suspension	125 mg/5 mL*	Dilantin-125®, Pfizer
		Phenytoin Oral Suspension
Tablets, chewable	50 mg	Dilantin® Infatabs®, Pfizer

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

Phenytoin Sodium

Parenteral		
Injection	50 mg/mL*	Phenytoin Sodium Injection

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

Phenytoin Sodium, Extended

Oral		
Capsules	30 mg	Dilantin® Kapseals®, Pfizer
	100 mg*	Dilantin® Kapseals®, Pfizer
		Phenytoin Sodium Extended Capsules
	200 mg*	Phenytek®, Mylan
	300 mg*	Phenytek®, Mylan

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

Phenytoin Sodium, Prompt

Oral		
Capsules	100 mg*	Phenytoin Sodium Prompt Capsules

*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

ANTICONVULSANTS, MISCELLANEOUS 28:12.92

Carbamazepine

■ Carbamazepine is an iminostilbene derivative that is used as both an anticonvulsant and for the relief of pain associated with trigeminal neuralgia (tic douloureux) as well as for various psychiatric disorders.

Uses

■ **Seizure Disorders** Carbamazepine is used in adults and children in the prophylactic management of partial seizures with complex symptomatology (psychomotor or temporal lobe seizures), generalized tonic-clonic (grand mal) seizures, and mixed seizure patterns that include partial seizures with complex symptomatology, generalized tonic-clonic seizures, or other partial or generalized seizures. Patients with partial seizures with complex symptomatology appear to show greater improvement during carbamazepine therapy than patients with other types of seizures. Although the drug is useful in the management of mixed seizures, the response in patients with mixed seizures may be variable. The drug is ineffective in the management of absence (petit mal) seizures or myoclonic and akinetic seizures.

Carbamazepine may be administered concomitantly with other anticonvulsants such as phenytoin, phenobarbital, or primidone. However, the drug should be administered with caution in conjunction with those anticonvulsants that produce toxic effects similar to carbamazepine such as phenacemide (no longer commercially available in the US), mephenytoin, or trimethadione or paramethadione (both no longer commercially available in the US).

■ **Neuropathic Pain** Carbamazepine is used in the symptomatic treatment of pain associated with true trigeminal neuralgia. *Carbamazepine is not a simple analgesic and should not be administered casually for relief of trivial facial pain.* Although some patients with glossopharyngeal neuralgia may respond to carbamazepine, the drug usually does not provide relief in facial pain from causes other than trigeminal neuralgia. Some patients with trigeminal neuralgia who did not respond to carbamazepine have been successfully treated with combined carbamazepine-phenytoin therapy.

Like certain other anticonvulsants, carbamazepine also has been used for the symptomatic treatment of chronic pain arising from other peripheral neuropathic syndromes†, including pain of diabetic neuropathy†. (See Uses: Neuropathic Pain, in the Anticonvulsants General Statement 28:12.)

■ **Schizophrenia** Carbamazepine has been used in the symptomatic management of the acute phase of schizophrenia† as an adjunct to therapy with an antipsychotic agent in patients who fail to respond to an adequate trial of the antipsychotic agent alone. For adjunctive therapy with an antipsychotic agent, carbamazepine generally is administered at the same range in dosage and therapeutic plasma concentrations as in the management of seizure disorders and bipolar disorder. The American Psychiatric Association (APA) states that, with the exception of schizophrenic patients whose illness has strong affective components, carbamazepine therapy *alone* (i.e., monotherapy rather than adjunctive therapy) has not been shown to be substantially effective in the long-term treatment of schizophrenia. For additional information on the management of schizophrenia, see Uses: Psychotic Disorders, in the Phenothiazines General Statement 28:16.08.24.

■ **Bipolar Disorder** Carbamazepine has been used alone or in combination with other drugs (e.g., antipsychotic agents) for the treatment and prevention of acute manic or mixed episodes in patients with bipolar disorder. However, results of clinical studies of the drug in the management of bipolar disorder have been inconsistent, and the APA currently recommends that carbamazepine be reserved for patients unable to tolerate or who had an inadequate therapeutic response to lithium and valproate (e.g., valproic acid, divalproex). For further information on the management of bipolar disorder, see Uses: Bipolar Disorder, in Lithium Salts 28:28.

■ **Other Uses** Carbamazepine has been used for the management of aggression (e.g., uncontrolled rage outbursts) and/or loss of control (dyscontrol) in patients with or without an underlying seizure disorder (e.g., as features of intermittent explosive disorder, conduct disorder, antisocial personality disorder, borderline personality disorder, dementia)†, alcohol withdrawal syndrome†, relief of neurogenic pain and/or control of seizures in a variety of conditions including "lightning" pains of tabes dorsalis†, pain and control of paroxysmal symptoms of multiple sclerosis†, paroxysmal kinesigenic choreoathetosis†, Klüver-Bucy syndrome†, post-hypoxic action myoclonus†, acute idiopathic polyneuritis (Landry-Guillain-Barré syndrome)†, pain of posttraumatic paresthesia†, and, in children, hemifacial spasm† and dystonia†. The drug also has been used for its antidiuretic effects in the management of neurohypophyseal diabetes insipidus†; however, other less toxic agents are available, and patients with primary polydipsia and polyuria have shown signs of water intoxication during carbamazepine therapy.

Dosage and Administration

■ **Administration** Carbamazepine conventional tablets and suspension are administered orally with meals. The oral suspension should be shaken well before administration. To minimize loss of carbamazepine oral suspension during oral administration via a nasogastric tube (secondary to adherence to PVC tubing), the suspension can be diluted with an equal volume of diluent (e.g., sterile water, 5% dextrose, 0.9% sodium chloride) prior to administration, combined with flushing of the tube with 100 mL of the diluent after administration.

Because a rubbery, orange substance was noticed in the stool of a patient who ingested chlorpromazine oral solution immediately after ingesting carbamazepine oral suspension and subsequent testing has shown that mixing carbamazepine oral suspension with chlorpromazine or thioridazine oral solution results in a rubbery, orange precipitate, the manufacturer recommends that carbamazepine oral suspension not be administered with other liquid preparations. In addition, it is not known whether the development of this precipitate results in decreased bioavailability of carbamazepine or the other drugs.

Extended-release tablets of carbamazepine (Tegretol®-XR) should be swallowed whole and not be broken or chewed. The manufacturer states that the extended-release tablets should be inspected visually for chips or cracks and that damaged tablets should not be used. Because the coating of the extended-release tablet is not absorbed, it may be noticeable in the stools. The extended-release tablet formulation of carbamazepine is administered twice daily. When patients are switched from conventional dosage forms to the extended-release tablets of carbamazepine, the same total daily dosage is then administered in 2 divided doses.

Extended-release capsules of carbamazepine (Carbatrol®) may be opened and the beads sprinkled over food (e.g., a teaspoonful of applesauce). Extended-release capsules of carbamazepine and their contents should not be chewed or crushed. In addition, the extended-release capsules of carbamazepine may be taken without regard to meals. Patients receiving total daily carbamazepine dosages of 400 mg or greater in other preparations may be switched to the extended-release capsules; the same total daily dosage is then administered in 2 divided doses.

Patients who are currently receiving or beginning therapy with carbamazepine 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: Nervous System Effects and see Cautions: Precautions and Contraindications.)

Dispensing and Administration Precautions Because of similarity in spelling between Tegretol® or Tegretol®-XR (trade names for carbamazepine) and Toprol-XL® (a trade name for metoprolol succinate, a β-adrenergic blocking agent), the potential exists for dispensing errors involving these drugs. According to medication error reports, the overlapping tablet strengths (100 and 200 mg) between Tegretol® or Tegretol®-XR and Toprol-XL® and the fact that these drugs were stored closely together in pharmacies also may have been contributing factors in causing these errors. Therefore, extra care should be exercised to ensure the accuracy of both oral and written prescriptions for these drugs. The manufacturer of Toprol-XL® also recommends that pharmacists assess various measures of avoiding dispensing errors and implement them as appropriate (e.g., by verifying all orders for these drugs by citing both the trade and generic names to prescribers, attaching reminders to pharmacy shelves, separating the drugs on pharmacy shelves, counseling patients). (See Cautions: Precautions and Contraindications.)

■ **Dosage** Dosage of carbamazepine must be carefully and slowly adjusted according to individual requirements and response. It is important to begin therapy with a low dosage and to proceed slowly when increasing or decreasing the dosage of the drug. When carbamazepine is added to an anticonvulsant therapeutic regimen, the drug should usually be added gradually while the other anticonvulsant(s) is maintained or gradually decreased. Carbamazepine should be withdrawn slowly to avoid precipitating seizures or status epilepticus.

Because a given dose of carbamazepine administered as the oral suspension will produce higher peak concentrations of the drug than when administered as tablets, therapy with the oral suspension should be initiated with low, frequent doses (e.g., 50 mg 4 times daily for children 6–12 years of age) and increased slowly to reduce the risk of adverse effects (e.g., sedation). Alternatively, if rapid achievement of therapeutic plasma concentrations and control of seizures is necessary, an oral loading-dose regimen with carbamazepine oral suspension can be employed. When transferring patients from therapy with oral tablets to the oral suspension, the total daily dose administered as tablets should be divided into smaller, more frequent doses of the suspension (e.g., transfer from twice-daily divided dosing of tablets to thrice [3 times]-daily divided dosing of the suspension).

Seizure Disorders The usual initial dosage of carbamazepine for the management of seizure disorders in adults and children older than 12 years of age is 200 mg twice daily as tablets or 100 mg 4 times daily as the oral suspension. Dosage is increased by up to 200 mg daily at weekly intervals using a 3 or 4 times daily divided dosing regimen until the optimum response is obtained. Dosage generally should not exceed 1 g daily in children 12–15 years of age and 1.2 g daily in patients older than 15 years of age; however, some patients have required up to 1.6–2.4 g daily. When adequate seizure control is achieved, dosage should be adjusted to the minimum effective level, which is usually 800 mg to 1.2 g daily in adults and children older than 12 years of age.

In children 6–12 years of age, the usual initial dosage of carbamazepine is 100 mg twice daily as tablets or 50 mg 4 times daily as the oral suspension. Dosage is increased by up to 100 mg daily at weekly intervals using a 3 or 4 times daily divided dosing regimen until the optimum response is obtained. Dosage generally should not exceed 1 g daily in children 6–12 years of age. When adequate seizure control is achieved, dosage should be adjusted to the minimum effective level, which is usually 400–800 mg daily in children 6–12 years of age.

In children younger than 6 years of age, the initial daily dosage of carbamazepine given as conventional tablets or oral suspension is 10–20 mg/kg in 2 or 3 divided doses (as tablets) or 4 divided doses (as the oral suspension). Optimal clinical response in children younger than 6 years of age generally is achieved at daily maintenance dosages of less than 35 mg/kg. If satisfactory clinical response has not been achieved, plasma carbamazepine concentrations should be obtained to determine whether they are in the therapeutic range. The manufacturers state that safety of carbamazepine dosages exceeding 35 mg/kg in 24 hours in children younger than 6 years of age has not been established.

Therapeutic serum carbamazepine concentrations can be achieved more rapidly (in about 2 hours) by the use of an oral loading-dose regimen with the oral suspension, preferably in a clinic or hospital setting where plasma concentrations and the patient can be monitored closely. In this regimen, an initial oral loading dose (as the oral suspension) of 8 mg/kg in children 12 years of age and older or 10 mg/kg in children younger than 12 years of age is administered for the rapid control of seizures.

Neuropathic Pain For the symptomatic treatment of pain associated with trigeminal neuralgia, the usual initial adult dosage of carbamazepine on the first day of therapy is 100 mg twice daily as tablets or 50 mg 4 times daily as the oral suspension. Dosage may be increased gradually by up to 200 mg daily using 100-mg increments every 12 hours for tablets or by using 50-mg increments 4 times daily for the oral suspension until pain is relieved. The dosage necessary to relieve pain may range from 200 mg to 1.2 g daily; daily dosage should not exceed 1.2 g. After control of pain is achieved, maintenance dosages of 400–800 mg daily usually are adequate; however, some patients may require as little as 200 mg daily while others may require 1.2 g daily. At least once every 3 months throughout carbamazepine therapy for trigeminal neuralgia, an attempt should be made to decrease dosage to the minimum effective level or to discontinue the drug.

Bipolar Disorder Although dosage of carbamazepine for the management of bipolar disorder has not been established, experts generally recommend administering the drug at the same range in dosage and therapeutic plasma concentrations as in the management of seizure disorders. In patients older than 12 years of age, the usual initial dosage of carbamazepine for the management of bipolar disorder is 200–600 mg daily, given in 3 or 4 divided doses. Dosage may be titrated upward according to patient response and tolerability. In hospitalized patients with acute mania, dosages may be increased as tolerated in 200-mg daily increments up to 800 mg to 1 g daily, with slower increases thereafter as indicated. However, dosages should *not* exceed 1.6 g daily. In less acutely ill outpatients, dosage adjustments should be slower because rapid increases may cause patients to develop adverse GI (e.g., nausea, vomiting) or nervous system (e.g., drowsiness, dizziness, ataxia, clumsiness, diplopia) effects. If such adverse effects occur, temporary dosage reductions should be considered. Dosage may be increased again more slowly once these adverse effects have been resolved. Maintenance dosages of carbamazepine average about 1 g daily but may range from 200 mg to 1.6 g daily in routine clinical practice.

Cautions

■ **Hematologic Effects** Although transient or persistent, minor hematologic changes (e.g., decreased leukocyte counts) are not uncommon, the risk of serious carbamazepine-induced hematologic toxicity appears to be low. Deaths from aplastic anemia have occurred rarely following carbamazepine therapy. Other hematopoietic complications associated with the drug include leukopenia, agranulocytosis, eosinophilia, leukocytosis, thrombocytopenia, pancytopenia, bone marrow depression, and purpura. Although data from a population-based, case-control study indicate that the risk of developing aplastic anemia or agranulocytosis in patients receiving carbamazepine is 5–8 times greater than that in the general population, the overall risk of these reactions in the untreated general population is low (about 6 cases per million population per year for agranulocytosis and about 2 cases per million population per year for aplastic anemia). Transient or persistent decreases in platelet or leukocyte counts are not uncommonly associated with carbamazepine use, but currently available data do not permit accurate estimates of the incidence or outcome of

these effects; however, the vast majority of cases of leukopenia reportedly have not progressed to aplastic anemia or agranulocytosis. In addition, because the apparent frequency of minor hematologic changes progressing to agranulocytosis and aplastic anemia is very low, the vast majority of such changes observed during routine, periodic hematologic monitoring of carbamazepine-treated patients are unlikely to be signaling the impending development of either abnormality. Nonetheless, determination of baseline hematologic function should be performed prior to initiation of carbamazepine therapy, and patients exhibiting abnormalities during therapy with the drug should be monitored closely. (See Cautions: Precautions and Contraindications.)

■ **Dermatologic and Sensitivity Reactions** Serious and sometimes fatal dermatologic reactions, including toxic epidermal necrolysis and Stevens-Johnson syndrome, have been reported in patients receiving carbamazepine therapy. These reactions are estimated to occur in 1–6 per 10,000 new users of the drug in countries with mainly Caucasian populations; however, the risk in some Asian countries is estimated to be approximately 10 times higher. Retrospective, case-control studies in patients of Asian ancestry have demonstrated a strong association between the risk of developing Stevens-Johnson syndrome and toxic epidermal necrolysis with carbamazepine therapy and the presence of human leukocyte antigen (HLA)-B*1502, an inherited allelic variant of the HLA-B gene. The HLA-B*1502 allele is found almost exclusively in patients with ancestry across broad areas of Asia (including Han Chinese, Filipinos, Malaysians, South Asian Indians, and Thais), although marked variation exists in its prevalence among various Asian populations. Greater than 15% of the population is reportedly HLA-B*1502-positive in Hong Kong, Thailand, Malaysia, and parts of the Philippines compared with about 10% in Taiwan and 4% in North China. South Asians, including Indians, appear to have an intermediate prevalence of HLA-B*1502, which averages about 2–4% but may be higher in some groups. HLA-B*1502 is present in less than 1% of the population in Japan and Korea and is largely absent in individuals not of Asian origin (e.g., Caucasians, African-Americans, Hispanics, Native Americans).

The US Food and Drug Administration (FDA) and the manufacturers of carbamazepine recommend that patients with ancestry in genetically at-risk populations be screened for the presence of the HLA-B*1502 allele prior to initiating carbamazepine therapy. In deciding which patients to screen, the rates provided above for the prevalence of the HLA-B*1502 allele may provide a rough guide; however, clinicians should keep in mind the limitations of these figures because of the wide variability in rates even within ethnic groups, the difficulty in ascertaining ethnic ancestry, and the likelihood of mixed ancestry. High-resolution HLA-B*1502 typing is recommended in genetically at-risk patients; the test is considered positive if 1 or 2 HLA-B*1502 alleles are detected and negative if no HLA-B*1502 alleles are detected. Patients testing positive for this allele should not receive carbamazepine therapy unless the benefit clearly outweighs the risk. Patients who are found to be negative for the allele are thought to have a low risk of developing Stevens-Johnson syndrome and toxic epidermal necrolysis. In addition, over 90% of carbamazepine-treated patients who will experience Stevens-Johnson syndrome and toxic epidermal necrolysis develop these reactions within the first few months of therapy; this information may be considered in determining the need for screening genetically at-risk patients currently receiving the drug.

The HLA-B*1502 allele has not been found to predict risk of less severe adverse dermatologic reactions associated with carbamazepine (e.g., multiple-organ hypersensitivity reactions, non-serious rash such as maculopapular eruption). However, limited evidence suggests that HLA-B*1502 may be a risk factor for the development of Stevens-Johnson syndrome and toxic epidermal necrolysis in patients of Asian ancestry who are receiving other anticonvulsants associated with these reactions (e.g., lamotrigine, fosphenytoin, phenytoin). Avoidance of such drugs should therefore be considered in HLA-B*1502-positive patients when alternative therapies are otherwise equally acceptable.

FDA and the manufacturers caution that application of HLA-B*1502 genotyping as a screening tool has important limitations and must never substitute for appropriate clinical vigilance and patient management. Many HLA-B*1502-positive Asian patients treated with carbamazepine will never develop Stevens-Johnson syndrome and toxic epidermal necrolysis, and such reactions may develop infrequently in HLA-B*1502-negative patients of any ethnicity. The role of other possible factors, such as anticonvulsant drug dosage, compliance, concomitant medications and illnesses, in the development of, and morbidity from, these reactions and the level of dermatologic monitoring has not been adequately studied to date.

Other adverse dermatologic effects of carbamazepine include pruritic, erythematous, and maculopapular rashes (e.g., maculopapular eruption); urticaria; photosensitivity reactions; alterations in skin pigmentation; and exfoliative dermatitis. In addition, erythema multiforme and nodosum and development of a lupus erythematosus-like syndrome or aggravation of systemic lupus erythematosus have been reported. Alopecia also may occur. Although a causal relationship has not been established, hirsutism has been reported rarely in patients receiving carbamazepine.

Multiple-organ hypersensitivity reactions occurring days to weeks or months after initiation of carbamazepine therapy have been reported rarely. Manifestations may include (but are not limited to) fever, rashes, vasculitis, lymphadenopathy, disorders mimicking lymphoma, arthralgia, leukopenia, eosinophilia, hepatosplenomegaly, and abnormal liver function test results. These manifestations may initially be mild and may occur in various combinations and not necessarily concurrently. Various organs, including but not limited to, liver, skin, immune system, lungs, kidneys, pancreas, myocardium, and colon, may be affected.

Other hypersensitivity reactions, including fever, rash, peripheral eosinophilia, and reversible aseptic meningitis (manifested by confusion, myoclonus, and CSF pleocytosis), have been reported rarely in patients receiving carbamazepine.

■ **Cardiovascular Effects** Adverse cardiovascular effects (some of which may be fatal), including congestive heart failure, aggravation of hypertension, hypotension, syncope and collapse, edema, thrombophlebitis, thromboembolism, aggravation of coronary artery disease, arrhythmias, and AV block, have been reported. Myocardial infarction has been associated with tricyclic compounds.

■ **Hepatic Effects** Hepatic complications associated with the long-term administration of carbamazepine include abnormalities in liver function test results, cholestatic and hepatocellular jaundice, hepatitis, and very rare cases of hepatic failure.

■ **Genitourinary Effects** Genitourinary complications associated with carbamazepine include urinary frequency, acute urinary retention, oliguria with elevated blood pressure, azotemia, renal failure, and impotence. Albuminuria, glycosuria, elevated BUN concentrations, and microscopic deposits in the urine also have been reported.

■ **Nervous System Effects** Adverse neurologic and sensory effects of carbamazepine include dizziness, vertigo, drowsiness, fatigue, ataxia, disturbances of coordination, confusion, headache, nystagmus, blurred vision, transient diplopia, visual hallucinations, hyperacusis, oculomotor disturbances, speech disturbances, and abnormal involuntary movements. Rarely, peripheral neuritis and paresthesia, depression with agitation, talkativeness, and tinnitus may occur. Reports of associated paralysis and other symptoms of cerebral arterial insufficiency have been made, but the exact relationship of these reactions to the administration of carbamazepine has not been established.

The US Food and Drug Administration (FDA) has analyzed suicidality reports from placebo-controlled studies involving 11 anticonvulsants, including carbamazepine, 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%). 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 or (e.g., bipolar disorder, depression, anxiety), and other conditions (e.g., migraine, neuropathic pain). 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. (See Cautions: Precautions and Contraindications.)

Initiation of carbamazepine for the management of complex partial seizures has been associated with exacerbation of seizures, principally atypical absence and/or generalized convulsive seizures, in some children with mixed seizure disorders. In one group of children, video-EEG monitoring revealed a generalized paroxysmal spike-and-wave discharge in all of the children in whom exacerbation of seizures occurred during carbamazepine therapy. Children who developed frequent generalized convulsive seizures had a pattern of spikes and slow waves with a frequency of 1–2 cycles/second, and those who developed more frequent and severe atypical absence seizures had a generalized spike-and-wave discharge of 2.5–3 cycles/second. Although the mechanism is not known, it was suggested that exacerbation of seizures in these children may result from carbamazepine-induced activation of epileptiform discharges. It has been suggested that carbamazepine be used with caution for the management of complex partial seizures in children with mixed seizure disorders; particularly those who have a generalized absence or atypical absence component, and that the drug be avoided when there is generalized, synchronous, spike-and-wave discharges of 2.5–3 cycles/second in association with clinical seizures regardless of their clinical manifestation. The possibility that a worsening of atypical absence and/or generalized convulsive seizures following initiation of carbamazepine therapy may be drug induced rather than the natural history of the child's epilepsy should be considered.

■ **GI Effects** Adverse GI effects of carbamazepine include nausea, vomiting, gastric distress, abdominal pain, diarrhea, constipation, anorexia, dryness of the mouth and pharynx, glossitis, and stomatitis.

■ **Other Adverse Effects** Other adverse effects reported during carbamazepine therapy include diaphoresis, fever and chills, adenopathy or lymphadenopathy, acute intermittent porphyria, aching joints and muscles, leg cramps, and conjunctivitis. Decreased plasma calcium concentrations and hyponatremia have been reported. Syndrome of inappropriate antidiuretic hormone secretion (SIADH) and cases of frank water intoxication, with hyponatremia and confusion, have also been reported. Pulmonary hypersensitivity, characterized by fever, dyspnea, pneumonitis, or pneumonia, also has occurred. Isolated cases of neuroleptic malignant syndrome have been reported with concomitant use of carbamazepine and psychotropic drugs.

Although scattered, punctate lens opacities have occurred only rarely in patients receiving carbamazepine, other drugs such as the phenothiazines have caused various ocular changes.

■ **Precautions and Contraindications** Carbamazepine may produce dangerous and alarming adverse effects, principally consisting of hematopoietic, dermatologic, cardiovascular, hepatic, and renal disturbances. The drug also shares the toxic potentials of the hydantoin-derivative anticonvulsants, and the usual precautions of anticonvulsant administration should be observed. When serious adverse effects occur requiring discontinuance of the drug, it is important to remember that abrupt withdrawal of any anticonvulsant drug in a responsive epileptic patient may precipitate seizures or status epilepticus. Carbamazepine therapy should be withdrawn gradually, whenever possible, to minimize the potential for increased seizure frequency. Patients must be carefully examined prior to initiation of carbamazepine therapy and should remain under close medical supervision throughout therapy with the drug. Carbamazepine should be prescribed only after careful benefit-to-risk evaluation in patients with a history of cardiac conduction disturbances; cardiac, hepatic, or renal damage; or adverse hematologic or hypersensitivity reaction to other drugs (e.g., other anticonvulsants) or who have had interrupted therapy with carbamazepine.

Serious and sometimes fatal dermatologic reactions, including toxic epidermal necrolysis and Stevens-Johnson syndrome, have been reported in patients receiving carbamazepine therapy. These reactions are estimated to occur in 1–6 per 10,000 new users of the drug in countries with mainly Caucasian populations; however, the risk in some Asian countries is estimated to be about 10 times higher. Carbamazepine should be discontinued at the first sign of a skin rash, unless the rash is clearly not drug-related. If signs or symptoms suggest Stevens-Johnson syndrome or toxic epidermal necrolysis, carbamazepine therapy should not be resumed and alternative therapy should be considered. Retrospective case-control studies in patients of Asian ancestry have demonstrated a strong association between the risk of developing Stevens-Johnson syndrome and toxic epidermal necrolysis and the presence of human leukocyte antigen (HLA)-B*1502, an inherited allelic variant of the HLA-B gene; this allele is found almost exclusively in patients with ancestry across broad areas of Asia. Therefore, the US Food and Drug Administration (FDA) and the manufacturers of carbamazepine recommend that patients with ancestry in genetically at-risk populations be screened for the presence of the HLA-B*1502 allele prior to initiating carbamazepine therapy. Patients testing positive for this allele should not receive carbamazepine therapy unless the benefit clearly outweighs the risk. (See Cautions: Dermatologic and Sensitivity Reactions.)

Multiple-organ hypersensitivity reactions occurring days to weeks or months following initiation of carbamazepine have been reported rarely. (See Cautions: Dermatologic and Sensitivity Reactions.) Discontinuance of carbamazepine should be considered if any evidence of hypersensitivity develops. Because hypersensitivity reactions to carbamazepine have been reported in patients with a history of hypersensitivity reactions to other anticonvulsants (e.g., phenytoin, phenobarbital), a detailed drug history should be obtained from patients and their immediate family members. Carbamazepine should be used with caution in patients with a history of hypersensitivity reactions to other anticonvulsants. Approximately 25–30% of patients who demonstrated hypersensitivity reactions to carbamazepine also may experience hypersensitivity reactions to oxcarbazepine.

Close attention by the patient and clinician to signs and symptoms of the possible development of adverse hematologic, dermatologic, or hypersensitivity reactions is important in patients receiving carbamazepine. Patients should be informed of the early signs and symptoms of these potential problems, such as fever, sore throat, infection, rash, mouth ulcers, easy bruising, lymphadenopathy, and petechial or purpuric hemorrhage, and should be instructed to report to their physician immediately if any such sign or symptom occurs. In addition, patients should be advised that these manifestations should be reported even if they are mild in severity or if they occur after extended use.

Although the manufacturers previously recommended initial frequent (possibly weekly during the first 3 months of therapy) and then less frequent, periodic (monthly for at least 2–3 years) testing of hematologic function in any patient receiving carbamazepine, they currently state that, because the frequency of minor hematologic changes progressing to aplastic anemia and agranulocytosis is very low, the vast majority of such changes observed during routine, periodic monitoring are unlikely to be signaling the impending development of either abnormality. Therefore, the manufacturers currently recommend that complete blood counts, including platelet and possibly reticulocyte counts and serum iron determinations, be performed prior to initiating carbamazepine therapy and that subsequent monitoring be individualized by the clinician. Guidelines for periodic monitoring of hematologic function have been suggested by some clinicians, and clinicians experienced in the use of carbamazepine and knowledgeable about the drug's potential toxicity can be consulted for more specific information. Patients exhibiting baseline abnormalities and those receiving other potentially myelotoxic drugs or with a history of adverse hematologic reactions to any drug should be considered at special risk, and carbamazepine therapy should be monitored closely or avoided in these patients. The manufacturers recommend that patients with a history of bone marrow depression *not* receive the drug. Patients who exhibit low or decreased leukocyte or platelet counts during the course of carbamazepine therapy should be monitored closely. Discontinuance of carbamazepine therapy should be considered if any evidence of significant bone marrow depression develops. In addition, if such evidence develops, particularly if it occurs as a result of overdosage, it has been suggested that complete blood counts, platelet counts, and reticulocyte counts be performed daily and bone marrow aspiration and trephine biopsy be done immediately and repeated as often as necessary to monitor recovery. Alternatively, one manufacturer suggests that the frequency of this monitoring in patients who develop evidence of significant bone marrow depression during the usual course of carbamazepine therapy (i.e., not resulting from overdosage) may be individualized by the clinician. Other special periodic hematologic studies may also be helpful in patients with evidence of significant bone marrow depression. Fully developed aplastic anemia requires appropriate, intensive monitoring and therapy for which specialized consultation should be sought. Some clinicians also advise hematologic consultation if neutropenia and depressed platelet and reticulocyte counts occur during therapy with the drug.

Adverse hepatic effects, ranging from slight elevations in hepatic enzymes to rare cases of hepatic failure, have been reported. In some cases, hepatic effects may progress despite discontinuance of the drug. Liver function tests should be performed prior to carbamazepine therapy, particularly in patients with a history of liver disease, and periodically thereafter. Carbamazepine should be immediately discontinued if evidence of liver dysfunction or active liver disease is observed. In addition, patients should be advised of the early manifestations of adverse hepatic effects (e.g., anorexia, nausea/vomiting, jaundice) and instructed to report such symptoms to their clinician immediately, even if the symptoms are mild or occur after extended use. Complete urinalysis and BUN determinations also should be performed prior to and periodically during carbamazepine therapy.

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. (See Cautions: Nervous System Effects.) 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 medication 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 carbamazepine or any other anticonvulsant balance the risk of 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.

Carbamazepine may exacerbate seizures in some children with mixed seizure disorders. Some clinicians recommend that prolonged video-EEG monitoring be performed prior to initiating carbamazepine therapy in children with mixed seizure disorders in an attempt to identify those children who may be at risk for carbamazepine-induced exacerbation of seizures. (See Cautions: Nervous System Effects.)

Persons who perform hazardous tasks requiring mental alertness or physical coordination should be warned about the possible adverse neurologic and sensory effects of carbamazepine. Patients receiving carbamazepine also should be advised that there is a potential for additive CNS effects if alcohol is used concomitantly with carbamazepine. Because of the relationship of carbamazepine to other tricyclic compounds, the possibility of activation of a latent psychosis or, in geriatric patients, confusion or agitation should be kept in mind.

Baseline and periodic eye examinations including slit-lamp, funduscopy, and tonometry are recommended in patients receiving carbamazepine. Carbamazepine has shown mild anticholinergic activity; therefore, patients with increased intraocular pressure should be closely observed during carbamazepine therapy.

Because of similarity in spelling between Tegretol® or Tegretol®-XR (trade names for carbamazepine) and Toprol-XL® (metoprolol succinate, a β-adrenergic blocking agent), the potential exists for dispensing errors involving these drugs. These medication errors have been associated with serious adverse events sometimes requiring hospitalization as a result of either lack of the intended medication (e.g., seizure recurrence, return of hallucinations, suicide attempt, hypertension recurrence) or exposure to the wrong drug (e.g., bradycardia in a patient erroneously receiving metoprolol). Therefore, extra care should be exercised to ensure the accuracy of both oral and written prescriptions for these drugs. (See Dispensing and Administration Precautions under Dosage and Administration: Administration.) Dispensing errors involving Tegretol® or Tegretol®-XR (carbamazepine) and Toprol-XL® (metoprolol succinate) should be reported to the manufacturers, the USP/ISMP (Institute for Safe Medication Practices) Medication Errors Reporting Program by phone (800-233-7767), or directly to the FDA MedWatch program by phone (800-FDA-1088), fax (800-FDA-0178), or internet (http://www.fda.gov/Safety/MedWatch).

Carbamazepine is contraindicated in patients with a history of previous bone marrow depression, acute intermittent porphyria, and/or hypersensitivity to the drug or in patients who have demonstrated sensitivity to any of the tricyclic antidepressants (e.g., amitriptyline, desipramine, imipramine, nortriptyline, protriptyline). The drug also is contraindicated in patients currently re-

ceiving, or having recently received (i.e., within 2 weeks), monoamine oxidase (MAO) inhibitor therapy. (See Drug Interactions: Monoamine Oxidase Inhibitors.) Concomitant use of carbamazepine and nefazodone is contraindicated. (See Drug Interactions: Nefazodone.) In addition, the manufacturer of voriconazole states that concomitant use of carbamazepine and voriconazole is contraindicated. (See Drug Interactions: Azole Antifungal Agents.)

■ **Pediatric Precautions** Efficacy of carbamazepine for management of seizures in children is based on extrapolation of the demonstrated efficacy of carbamazepine in adults and also on in vitro studies that confirmed that the pathogenetic mechanisms associated with seizure propagation in adults are essentially the same as those in children; in addition, mechanism of action of carbamazepine in the treatment of seizures is the same in adults and children. The therapeutic range for plasma carbamazepine concentrations (i.e., 4–12 mcg/mL) is the same in children and adults. Safety of carbamazepine in children is based on clinical studies in which the drug was administered for up to 6 months. Data from long-term clinical studies in children are not available.

■ **Mutagenicity and Carcinogenicity** Bacterial and mammalian mutagenicity studies using carbamazepine have shown no evidence of mutagenicity. Carbamazepine has produced dose-related increases in the incidence of hepatocellular tumors in female rats and benign interstitial cell adenomas in male rats. The clinical importance of these findings is not known.

■ **Pregnancy and Lactation** Safe use of carbamazepine during pregnancy has not been established. Adverse fetal effects have been observed in reproduction studies in rats. Although several reports suggest an association between use of anticonvulsants in pregnant, epileptic women and an increased incidence of birth defects in children born to these women, a causal relationship to many of these drugs has not been established. However, epidemiologic data do suggest that an association between carbamazepine use during pregnancy and certain congenital abnormalities such as spina bifida may exist. Other congenital anomalies and developmental disorders (e.g., craniofacial defects, cardiovascular malformations, anomalies involving various body systems) also have been reported in association with carbamazepine use. Anticonvulsants should *not* be discontinued in pregnant women in whom the drugs are administered to prevent major seizures because of the strong possibility of precipitating status epilepticus with attendant hypoxia and threat to life. In individual cases, when the severity and frequency of the seizure disorder are such that discontinuance of therapy does not pose a serious threat to the patient, discontinuance of the drugs may be considered prior to and during pregnancy; however, it cannot be said with any certainty that even minor seizures do not pose some hazard to the fetus. Clinicians should carefully weigh these considerations in treating or counseling epileptic women of childbearing potential. Because carbamazepine can cause fetal harm when administered to pregnant women, the benefits of therapy must be weighed against the risks in women of childbearing potential. If carbamazepine is used during pregnancy, or if the patient becomes pregnant while receiving the drug, the patient should be apprised of the potential hazard to the fetus. Tests to detect fetal abnormalities using currently accepted procedures should be considered part of routine prenatal care in women of childbearing potential receiving carbamazepine.

There have been a few cases of seizures and/or respiratory depression in neonates born to women receiving carbamazepine concomitantly with other anticonvulsant agents. A few cases of vomiting, diarrhea, and/or decreased feeding also have been reported in neonates born to women receiving carbamazepine; these symptoms may represent a neonatal withdrawal syndrome.

To provide information regarding the effects of in utero exposure to carbamazepine, clinicians are advised to recommend that pregnant patients receiving carbamazepine enroll themselves in the North American Antiepileptic Drug (NAAED) Pregnancy Registry by calling 888-233-2334.

Carbamazepine and its epoxide metabolite (CBZ-E) are distributed into milk. Safe use of carbamazepine during lactation has not been established. Because of the potential for serious adverse reactions from carbamazepine 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. Following daily oral administration of carbamazepine in nursing women, the milk-to-maternal plasma ratio of carbamazepine is about 0.4 and that of CBZ-E is about 0.5; it is estimated that neonates may receive about 2–5 and 1–2 mg of carbamazepine and CBZ-E, respectively, daily.

Drug Interactions

■ **Alcohol** Because of the risk of additive sedative effects, caution should be exercised if carbamazepine is used concomitantly with alcohol.

■ **Anticonvulsants** Because carbamazepine is an inducer of the cytochrome P-450 (CYP) 3A4 isoenzyme, concomitant use with certain other anticonvulsants (e.g., clonazepam, ethosuximide, lamotrigine, methsuximide, phensuximide [not commercially available in the US], phenytoin, tiagabine, topiramate, valproic acid, zonisamide) has been shown, or would be expected, to decrease plasma concentrations of the other anticonvulsant. It may be desirable to monitor serum concentrations of concomitantly administered anticonvulsants, making dosage adjustments as necessary.

Concomitant use of carbamazepine with other anticonvulsants that induce (e.g., methsuximide, phenobarbital, phenytoin, primidone) or inhibit (e.g., acetazolamide) CYP3A4 has been shown, or would be expected, to decrease or increase plasma carbamazepine concentrations, respectively. In addition, carbamazepine may decrease the half-life of phenytoin. Increased plasma concentrations of phenytoin and primidone have been reported following concomitant use with carbamazepine.

Felbamate and valproic acid apparently can affect both plasma carbamazepine and carbamazepine 10,11-epoxide (CBZ-E, an active metabolite) concentrations, but the interactions appear to be complex and resultant changes may be unpredictable. The effect of valproic acid on concentrations of the drug may depend principally on increases in plasma CBZ-E concentrations relative to parent drug (possibly secondary to inhibition of epoxide hydrolase activity), but other mechanisms (e.g., displacement of carbamazepine from protein binding sites) also have been suggested and may contribute to the overall effect. The importance of determining CBZ-E concentrations in patients exhibiting toxicity during concomitant carbamazepine and valproic acid therapy should be considered.

Recent evidence suggests that the human leukocyte antigen (HLA)-B *1502 allele, which is found almost exclusively in patients with ancestry across broad areas of Asia, may be a risk factor for the development of Stevens-Johnson syndrome and toxic epidermal necrolysis in patients of Asian ancestry who are receiving carbamazepine and some other anticonvulsants associated with these reactions (e.g., lamotrigine, fosphenytoin, phenytoin). Avoidance of such drugs should therefore be considered in HLA-B *1502-positive patients when alternative therapies are otherwise equally acceptable. The role of other possible factors, such as concomitant medications, anticonvulsant dosage, compliance, and illnesses, in the development of, and morbidity from, these reactions, and the level of dermatologic monitoring have not been adequately studied to date. (See Cautions: Dermatologic and Sensitivity Reactions and see Cautions: Precautions and Contraindications.)

Alterations of thyroid function have been reported with concomitant use of carbamazepine and other anticonvulsants.

■ **Lithium** Concomitant use of carbamazepine with lithium may increase the risk of adverse neurologic effects.

■ **Calcium-channel Blocking Agents** Concomitant use of carbamazepine and diltiazem or verapamil may result in increased plasma carbamazepine concentrations and subsequent toxicity. In several patients receiving 1–2 g of carbamazepine daily, initiation of 360 mg of verapamil hydrochloride daily resulted in development of neurologic manifestations (e.g., dizziness, ataxia, nystagmus) of carbamazepine toxicity within 36–96 hours. Plasma total and unbound carbamazepine concentrations increased by a mean of 46 and 33%, respectively, but returned to baseline values within 1 week after discontinuance of verapamil; manifestations of toxicity also resolved during this period. The ratio of plasma carbamazepine 10,11-epoxide to unchanged drug decreased during verapamil therapy but returned toward pretreatment levels following discontinuance of verapamil. Limited experience suggests that a similar interaction also may occur when diltiazem, but not nifedipine, is administered concomitantly with carbamazepine. It appears that verapamil and diltiazem inhibit hepatic metabolism of carbamazepine via the CYP3A4 isoenzyme.

If verapamil is initiated in patients receiving carbamazepine, a 40–50% reduction in carbamazepine dosage may be necessary during concomitant therapy. Patients should be monitored closely for manifestations of carbamazepine toxicity and for alterations in the pharmacokinetics of carbamazepine during concomitant therapy, adjusting carbamazepine dosage accordingly. If verapamil is discontinued, dosage of carbamazepine should be increased to avoid loss of seizure control.

Because carbamazepine is an inducer of the CYP3A4 isoenzyme, concomitant use with dihydropyridine calcium-channel blocking agents (e.g., felodipine) has been shown, or would be expected, to decrease plasma concentrations of the dihydropyridine calcium-channel blocking agent.

■ **Macrolides** Concomitant use of carbamazepine with certain macrolide antibiotics that inhibit CYP3A4 (e.g., clarithromycin, erythromycin, troleandomycin) has been shown, or would be expected, to increase plasma carbamazepine concentrations. Increased plasma concentrations of carbamazepine and subsequent signs of carbamazepine toxicity (e.g., ataxia, dizziness, drowsiness, vomiting) have occurred in adults or children following concomitant use of carbamazepine and erythromycin. Studies in adults indicate that erythromycin can substantially decrease serum clearance of carbamazepine, presumably by inhibiting hepatic metabolism of the drug. Patients receiving carbamazepine and erythromycin concomitantly should be monitored for evidence of carbamazepine toxicity; carbamazepine dosage should be reduced when necessary. Some clinicians suggest that use of an alternative anti-infective agent, instead of erythromycin, may be necessary in patients receiving carbamazepine.

■ **Doxycycline** Preliminary studies indicate that carbamazepine may decrease the half-life of doxycycline, probably by inducing hepatic microsomal enzymes that metabolize the antibiotic. Concomitant administration of doxycycline and carbamazepine should be avoided if possible. If concomitant therapy is necessary, doxycycline probably should be administered at 12-hour intervals and/or serum doxycycline concentrations should be closely monitored.

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

Concomitant use of carbamazepine with fluvoxamine, an inhibitor of CYP3A4, has been shown, or would be expected, to increase plasma carbamazepine concentrations.

■ **Antipsychotic Agents** Because carbamazepine is an inducer of the CYP3A4 isoenzyme, concomitant use with some antipsychotic agents (e.g., aripiprazole, clozapine, haloperidol, risperidone, ziprasidone) has been shown, or would be expected, to decrease plasma concentrations of the antipsychotic agent. Reductions in antipsychotic efficacy with reemergence of symptoms has occurred in some, but not all, such patients. If carbamazepine therapy is added in patients receiving aripiprazole, the dosage of aripiprazole should be doubled and additional increases in aripiprazole dosage should be made based on clinical evaluation; if carbamazepine is withdrawn from combination therapy with aripiprazole, the dosage of aripiprazole should be reduced accordingly. Patients receiving carbamazepine and haloperidol concomitantly should be monitored carefully for loss of antipsychotic control and, if an interaction is suspected, haloperidol dosage adjusted accordingly. The possibility that haloperidol toxicity may occur following discontinuance of carbamazepine also should be considered.

Clozapine Concomitant use of carbamazepine and clozapine has been shown to decrease clozapine concentrations by about 40–50%. Both carbamazepine and clozapine also have the potential to cause adverse hematologic effects, including agranulocytosis. In addition, neuroleptic malignant syndrome (NMS) has been reported rarely during concomitant therapy with these drugs. Therefore, the manufacturers of clozapine and the American Psychiatric Association (APA) state that concomitant use of carbamazepine and clozapine generally is not recommended. However, if carbamazepine and clozapine are used concomitantly, it should be considered that discontinuance of carbamazepine may result in increased plasma concentrations of clozapine.

■ **Monoamine Oxidase Inhibitors** Combined therapy using carbamazepine and monoamine oxidase (MAO) inhibitors is contraindicated. A medication-free period of at least 14 days should be observed when transferring patients from MAO inhibitors to carbamazepine. Therapy with carbamazepine should then be initiated cautiously with gradual increases in dosage to obtain the desired response.

■ **Anticoagulants** Because carbamazepine is an inducer of the CYP3A4 isoenzyme, concomitant use with dicumarol or warfarin has been shown, or would be expected, to decrease plasma concentrations of the anticoagulant. In one study when carbamazepine was administered to patients being treated with warfarin, the serum concentration of warfarin decreased after about 10 days of carbamazepine therapy. Carbamazepine also shortened the half-life of warfarin in some patients. If warfarin and carbamazepine must be used together, the patient should be closely monitored and the dosage of both drugs adjusted as required.

■ **Theophylline** It has been suggested that concomitant administration of carbamazepine and theophylline may induce each other's metabolism, with resultant changes in elimination half-life and plasma concentrations. If carbamazepine and theophylline are used concomitantly, the patient and plasma concentrations of the drugs should be monitored and dosage adjusted accordingly.

■ **Hormonal Contraceptives** Concomitant use of carbamazepine and hormonal contraceptives (e.g., oral contraceptives, levonorgesterol subdermal implant contraceptives [no longer commercially available]) may cause increased metabolism of the contraceptive resulting from induction of hepatic microsomal enzymes. Breakthrough bleeding and unintended pregnancies have been reported in patients receiving carbamazepine and hormonal contraceptives. Because the reliability of hormonal contraceptive therapy may be adversely affected during concomitant administration of carbamazepine, a nonhormonal method of birth control should be considered.

■ **Antihistamines** Concomitant use of carbamazepine with antihistamines that inhibit CYP3A4 (e.g., loratadine, terfenadine [no longer commercially available]) has been shown, or would be expected, to increase plasma carbamazepine concentrations.

■ **Antituberculosis Agents** Concomitant use of carbamazepine with antituberculosis agents that inhibit CYP3A4 (e.g., isoniazid) has been shown, or would be expected, to increase plasma carbamazepine concentrations. Conversely, concomitant use of carbamazepine with antituberculosis agents that induce CYP3A4 (e.g., rifampin) has been shown, or would be expected, to decrease plasma carbamazepine concentrations.

■ **Antineoplastic Agents** Concomitant use of carbamazepine with antineoplastic agents that induce CYP3A4 (e.g., cisplatin, doxorubicin) has been shown, or would be expected, to decrease plasma carbamazepine concentrations.

■ **Azole Antifungal Agents** Concomitant use of carbamazepine with azole antifungal agents that inhibit CYP3A4 (e.g., fluconazole, itraconazole, ketoconazole, voriconazole) has been shown, or would be expected, to increase plasma carbamazepine concentrations.

Concomitant use of carbamazepine and fluconazole has resulted in increased carbamazepine concentrations and associated toxicity, presumably as the result of fluconazole inhibiting CYP isoenzymes involved in metabolism of the anticonvulsant. It has been suggested that carbamazepine concentrations be monitored in patients receiving fluconazole concomitantly.

Because carbamazepine also is an inducer of the CYP3A4 isoenzyme, concomitant use with itraconazole has been shown, or would be expected, to decrease plasma concentrations of itraconazole.

Although the interaction has not been specifically studied to date, carbamazepine would be expected to substantially decrease plasma voriconazole concentrations due to potent induction of CYP enzymes; therefore, the manufacturer of voriconazole states that concomitant use of carbamazepine and voriconazole is contraindicated.

■ **Corticosteroids** Because carbamazepine is an inducer of the CYP3A4 isoenzyme, concomitant use with corticosteroids metabolized by CYP3A4 (e.g., dexamethasone, prednisolone) has been shown, or would be expected, to decrease plasma concentrations of the corticosteroid.

■ **HIV Protease Inhibitors** Concomitant use of carbamazepine with HIV protease inhibitors that inhibit CYP3A4 has been shown, or would be expected, to increase plasma carbamazepine concentrations. Because carbamazepine is an inducer of CYP3A4, concomitant use with HIV protease inhibitors that are metabolized by CYP3A4 has been shown, or would be expected, to decrease plasma concentrations of the HIV protease inhibitor.

■ **Tricyclic Antidepressants** Because carbamazepine is an inducer of the CYP3A4 isoenzyme, concomitant use with tricyclic antidepressants metabolized by CYP3A4 (e.g., amitriptyline, imipramine, nortriptyline) has been shown, or would be expected, to decrease plasma concentrations of the tricyclic antidepressant.

■ **Nefazodone** Concomitant use of carbamazepine and nefazodone is contraindicated since this may reduce plasma concentrations of nefazodone and its active metabolite, hydroxynefazodone, by 95% resulting in levels insufficient to achieve an antidepressant effect.

■ **Trazodone** Because carbamazepine is an inducer of the CYP3A4 isoenzyme, concomitant use with trazodone has been shown to decrease plasma concentrations of trazodone. Concomitant use of carbamazepine (400 mg daily) with trazodone (100–300 mg daily) decreased plasma concentrations of trazodone and an active metabolite, *m*-chlorophenylpiperazine, by 76 and 60%, respectively. Patients receiving carbamazepine and trazodone concomitantly should be closely monitored and dosage of trazodone increased if necessary.

■ **Other Drugs** Concomitant use of carbamazepine with drugs or foods that inhibit CYP3A4 (e.g., cimetidine, danazol, grapefruit juice, niacinamide, propoxyphene) has been shown, or would be expected, to increase plasma carbamazepine concentrations. In addition, because carbamazepine is an inducer of the CYP3A4 isoenzyme, concomitant use with drugs metabolized by CYP3A4 (e.g., acetaminophen, alprazolam, cyclosporine, levothyroxine, methadone, midazolam, praziquantel, tramadol) has been shown, or would be expected, to decrease plasma concentrations of the other drug.

Laboratory Test Interferences

■ **Pregnancy Tests** Carbamazepine interferes with some pregnancy tests.

Acute Toxicity

■ **Pathogenesis** The lowest known lethal dose of carbamazepine is 3.2 and 1.6 g in adults and children, respectively.

■ **Manifestations** Carbamazepine overdosage produces dizziness, ataxia, drowsiness, stupor, nausea, vomiting, opisthotonos, restlessness, agitation, disorientation, tremor, involuntary movements, adiadochokinesis, abnormal reflexes (hypoactive or hyperactive), mydriasis, nystagmus, flushing, cyanosis, and urinary retention. Hypotension or hypertension may develop. Coma may follow. Laboratory findings in some cases of overdosage have included leukocytosis, reduced leukocyte count, glycosuria, and acetonuria. EEG may show dysrhythmias.

A 24-year-old woman who ingested 3.2 g of carbamazepine died of cardiac arrest, and a 24-year-old man died of pneumonia and hypoxic encephalopathy ingesting the same dose. A 14-year-old girl who ingested 4 g of carbamazepine died of cardiac arrest, and a 3-year-old girl who ingested 1.6 g of carbamazepine died of aspiration pneumonia.

■ **Treatment** Treatment of carbamazepine overdosage consists of inducing emesis or gastric lavage and general supportive therapy. Because of the relationship of carbamazepine to the tricyclic antidepressants, the ECG should be monitored, especially in children, to detect cardiac dysfunction.

Pharmacology

The pharmacologic actions of carbamazepine appear to be qualitatively similar to those of the hydantoin-derivative anticonvulsants. The anticonvulsant activity of carbamazepine, like phenytoin, principally involves limitation of seizure propagation by reduction of posttetanic potentiation (PTP) of synaptic transmission. Carbamazepine appears to provide relief of pain in trigeminal neuralgia by reducing synaptic transmission within the trigeminal nucleus. The drug has also demonstrated sedative, anticholinergic, antidepressant, muscle relaxant, antiarrhythmic, antidiuretic, and neuromuscular transmission-inhibitory actions. Carbamazepine has only slight analgesic properties.

Pharmacokinetics

The pharmacokinetic parameters of carbamazepine disposition are similar in children and in adults; however, there is a poor correlation between dosage and plasma concentrations of carbamazepine in children. The effects of race and gender on carbamazepine pharmacokinetics have not been systematically evaluated. However, retrospective, case-control studies in patients of Chinese ancestry have demonstrated a strong pharmacogenomic association between the risk of developing Stevens-Johnson syndrome and toxic epidermal necrolysis and the presence of HLA-B*1502, an inherited allelic variant of the HLA-B gene. (See Cautions: Dermatologic and Sensitivity Reactions.)

■ **Absorption** Carbamazepine is slowly absorbed from the GI tract. Following chronic oral administration of carbamazepine tablets, suspension, extended-release tablets, or extended-release capsules, peak plasma concentra-

tions are reached in 4.5, 1.5, 3–12, or 4.1–7.7 hours, respectively. The oral bioavailabilities of carbamazepine tablets and suspension reportedly are equivalent, although the rate of absorption is faster for the suspension. The bioavailability of the extended-release tablets is reportedly 89% of that of the suspension, and the absorption of the extended-release tablets is slightly slower than that of the conventional tablets. Peak plasma concentrations of the drug are higher and trough concentrations are lower for the suspension compared with tablets when the drug is administered once or twice daily, but steady-state concentrations reportedly are comparable when the suspension is administered in 3 divided doses daily and the tablets are administered in 2 divided doses daily. Following oral administration of carbamazepine extended-release capsules or tablets every 12 hours, steady-state plasma carbamazepine concentrations were comparable to those achieved with corresponding dosages of the conventional (immediate-release) tablets every 6 hours. Although one manufacturer states that peak plasma concentrations may be higher with chewable tablets than with conventional tablets, a crossover study employing this manufacturer's tablets in adults with seizure disorders showed no such difference. In this study, the oral pharmacokinetics, including bioavailability, and peak and trough plasma concentrations, were comparable for conventional and chewable tablets of the drug, although individual patients may have achieved somewhat higher concentrations for one or the other tablet formulation.

Two to 4 days of therapy may be required to achieve steady-state plasma concentrations. Although optimal therapeutic plasma concentrations suitable for all patients have not yet been determined, therapeutic plasma concentrations of carbamazepine (for both anticonvulsant effects and relief of pain of trigeminal neuralgia) are usually 3–14 mcg/mL. Some investigators have noted that nystagmus frequently occurs when plasma concentrations are greater than 4 mcg/mL and that ataxia, dizziness, and anorexia often occur when plasma concentrations are 10 mcg/mL or greater. There appears to be a wide variation in steady-state plasma concentrations produced by specific daily dosages of carbamazepine (e.g., daily dosages of 800 mg, 1.2 g, or 1.6 g may produce plasma concentrations of 2–10 mcg/mL).

In one study, when carbamazepine extended-release capsules (Carbatrol®) were administered as a single 400-mg dose with a high-fat meal, the rate, but not the extent, of carbamazepine absorption was increased when compared with administration of the capsules in the fasting state. Results of a multiple-dose study of the extended-release capsules indicate that when these capsules are administered after a meal, peak steady-state plasma concentrations are within the therapeutic range. When the extended-release capsules of carbamazepine (Carbatrol®) are broken and the beads sprinkled over applesauce prior to administration, the pharmacokinetic profile of the drug is similar to that following oral administration of the intact capsule to fasting individuals. The manufacturer of carbamazepine extended-release capsules states that the elimination half-life of the drug does not differ substantially between fasted and nonfasted conditions of administration.

■ **Distribution** Carbamazepine is widely distributed in the body; the drug has been detected in CSF (approximately 15–22% of serum concentrations), the brain (at autopsy), duodenal fluids, bile, and saliva. A major metabolite, carbamazepine 10,11-epoxide, has also been detected in CSF. Carbamazepine rapidly crosses the placenta (i.e., 30–60 minutes) and accumulates in fetal tissues, with higher concentrations in the liver and kidney than in brain and lungs. Carbamazepine and its epoxide metabolite are distributed in breast milk. The ratio of the concentration in breast milk to that in plasma is approximately 0.4 for the drug and 0.5 for the epoxide metabolite.

In vitro studies indicate that at plasma concentrations of 1–50 mcg/mL, 75–90% of the drug is bound to plasma proteins.

■ **Elimination** Carbamazepine has a relatively long plasma half-life, variously reported to be 8–72 hours. The variability results in part because carbamazepine can induce its own metabolism; autoinduction of metabolism usually is completed after 3–5 weeks of a fixed dosing regimen. The plasma half-life generally ranges from 25–65 hours initially and from 12–17 hours with multiple dosing.

The metabolic fate of carbamazepine has not been completely elucidated. A major metabolic pathway appears to be oxidation by microsomal enzymes in the liver (principally cytochrome P-450 isoform 3A4) to form carbamazepine 10,11-epoxide (CBZ-E), which is almost completely metabolized to *trans*-10,11-dihydroxy-10,11-dihydrocarbamazepine (*trans*-CBZ-diol) and excreted in urine mainly unconjugated. CBZ-E has anticonvulsant activity in animals and potent analgesic activity in patients with trigeminal neuralgia. CBZ-E also has been implicated as contributing to adverse neurologic effects of the drug. Carbamazepine is more rapidly metabolized to CBZ-E in children than in adults. In children younger than 15 years of age, there is an inverse relationship between the CBZ-E/CBZ ratio and increasing age; this ratio was reported to be 0.44 in children younger than 1 year old and 0.18 in children 10–15 years of age. Carbamazepine also undergoes aromatic hydroxylation to form 2-hydroxycarbamazepine and 3-hydroxycarbamazepine. The pathway is not clearly determined, but the drug also undergoes metabolism to form 9-hydroxymethyl-10-carbamoyl-acridan. Carbamazepine and its metabolites are excreted in urine. Only about 1–3% of the drug is excreted in urine unchanged. Carbamazepine induces liver microsomal enzymes and thus may accelerate its own metabolism and that of other concomitantly administered drugs that are metabolized by these enzymes. (See Drug Interactions.)

Chemistry and Stability

■ **Chemistry** Carbamazepine is an iminostilbene derivative that is used as both an anticonvulsant and for the relief of pain associated with trigeminal neuralgia (tic douloureux). Carbamazepine is structurally related to the tricyclic antidepressants such as amitriptyline and imipramine. Carbamazepine occurs as a white to off-white powder and is practically insoluble in water and soluble in alcohol and in acetone.

The multi-compartment, extended-release capsule formulation of carbamazepine (Carbatrol®) contains 3 different types of beads: immediate-, extended-, and enteric-release beads. The 3 bead types are combined in a specific ratio to allow for twice-daily dosing.

■ **Stability** Carbamazepine tablets, extended-release tablets, and chewable tablets should be stored in tight, light-resistant containers at temperatures not exceeding 30°C. Carbamazepine extended-release capsules should be stored in tight, light-resistant containers at 15–25°C. Because dissolution characteristics and associated oral bioavailability of carbamazepine tablets may be affected substantially by moisture, patients should be cautioned to keep containers of the tablets tightly closed and in a dry location; away from areas with excessive moisture (e.g., showers, bathrooms, humidifiers). Carbamazepine tablets may lose one-third or more of their oral bioavailability when exposed to excessive moisture. Tablets continuously exposed to 97% relative humidity at room temperature for 2 weeks become hardened and dissolve poorly.

Carbamazepine oral suspension should be stored in tight, light-resistant containers at temperatures not exceeding 30°C; freezing of the oral suspension should be avoided.

Testing has shown that mixing carbamazepine oral suspension either with chlorpromazine oral solution or with liquid thioridazine preparations results in a rubbery, orange precipitate. It is not known whether the development of this precipitate results in decreased bioavailability of either carbamazepine or the other drugs. The extent to which this interaction occurs with other liquid preparations also is not known. Therefore, the manufacturer recommends that carbamazepine oral suspension not be administered simultaneously with other liquid preparations.

For further information on pharmacology, cautions, and dosage and administration of carbamazepine, see the Anticonvulsants General Statement 28:12.

Preparations

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

Carbamazepine

Oral		
Capsules, extended-release	100 mg	**Carbatrol®, Shire**
	200 mg	**Carbatrol®, Shire**
	300 mg	**Carbatrol®, Shire**
Suspension	100 mg/5 mL*	**Carbamazepine Suspension**
		Tegretol®, Novartis
Tablets	200 mg*	**Carbamazepine Tablets**
		Epitol® (scored), Teva
		Tegretol® (scored), Novartis
Tablets, chewable	100 mg*	**Carbamazepine Chewable Tablets**
		Tegretol® (scored), Novartis
Tablets, extended-release	100 mg	**Tegretol®-XR, Novartis**
	200 mg	**Tegretol®-XR, Novartis**
	400 mg	**Tegretol®-XR, Novartis**

*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

Felbamate

■ Felbamate, a dicarbamate, is an anticonvulsant.

Uses

In July 1993, felbamate (Felbatol®) originally was approved by the US Food and Drug Administration (FDA) for use as monotherapy or in combination with other anticonvulsant agents in the management of partial seizures with or without secondary generalization in adults. Felbamate also was approved by FDA at that time for use in combination with other anticonvulsant agents in the management of partial and generalized seizures associated with Lennox-Gastaut syndrome in children and has been designated an orphan drug by FDA for the treatment of this latter syndrome. However, because use of the drug has since been associated with marked increases in the incidences of **aplastic anemia** and **acute hepatic failure**, the manufacturer in conjunction with FDA warns that the drug should *only* be initiated or continued in the management

The US Food and Drug Administration (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. However, FDA also states that depression and certain other psychiatric disorders are themselves associated with an increased risk of suicide. Anyone considering the use of doxepin in a child or adolescent for any clinical use must therefore balance the potential risk of therapy with the clinical need. (See Cautions: Precautions and Contraindications and Cautions: Pediatric Precautions, in the Tricyclic Antidepressants General Statement 28:16.04.28.)

■ **Lactation** Limited data indicate that doxepin and its active *N*-demethylated metabolite are distributed into milk. Sedation and serious respiratory depression were reported in a nursing infant whose mother was receiving 75 mg of doxepin daily; substantial concentrations of the active metabolite of the drug were detected in the infant's serum and urine. In addition, poor sucking and swallowing while nursing, drowsiness, muscle hypotonia, and vomiting were reported in a nursing infant whose mother was receiving 35 mg of doxepin daily. Because of the potential for serious adverse reactions to doxepin and/or its active metabolite 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.

Pharmacokinetics

■ **Absorption** The pharmacokinetics of doxepin have not been extensively studied, but the drug is well absorbed from the GI tract in animals. Peak plasma concentrations usually occur within 2 hours after oral administration of the drug.

■ **Distribution** Doxepin is highly bound to plasma proteins.

Limited data indicate that doxepin and its active *N*-demethylated metabolite are distributed into milk in concentrations reportedly ranging from about 30–140% and 10–115%, respectively, of those in maternal serum and that substantial concentrations of the active metabolite have been detected in the serum and urine of nursing infants whose mothers were receiving 75–150 mg of doxepin daily.

■ **Elimination** The plasma half-life of doxepin is 6–24.5 hours. The drug appears to be metabolized via the same pathways as are other tricyclic antidepressants; its *N*-demethylated metabolite is pharmacologically active.

Chemistry and Stability

■ **Chemistry** Doxepin hydrochloride is a dibenzoxepin-derivative tricyclic antidepressant. The drug occurs as a white powder, is freely soluble in water and in alcohol, and has a pK_a of 8. Doxepin hydrochloride oral concentrate has a pH of 4–7.

■ **Stability** Doxepin hydrochloride capsules should be stored in tight, light-resistant containers at a temperature between 15–30°C and the oral concentrate should be stored at a temperature between 20–25°C. Commercially available doxepin hydrochloride capsules have an expiration date of 36 months and the oral concentrate has an expiration date of 24 months following the date of manufacture.

Doxepin hydrochloride oral concentrate is physically incompatible with many carbonated beverages, but is compatible with some other beverages. (See Dosage and Administration: Administration.) Bulk preparation and storage of dilutions of the commercially available oral concentrate are not recommended by the manufacturers.

For further information on chemistry, pharmacology, pharmacokinetics, uses, cautions, acute toxicity, drug interactions, and dosage and administration of doxepin, see the Tricyclic Antidepressants General Statement 28:16.04.28.

Preparations

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

Doxepin Hydrochloride

Oral		
Capsules	10 mg (of doxepin)*	**Doxepin Hydrochloride Capsules**
		Sinequan*, Pfizer
	25 mg (of doxepin)*	**Doxepin Hydrochloride Capsules**
		Sinequan*, Pfizer
	50 mg (of doxepin)*	**Doxepin Hydrochloride Capsules**
		Sinequan*, Pfizer
	75 mg (of doxepin)*	**Doxepin Hydrochloride Capsules**
		Sinequan*, Pfizer
	100 mg (of doxepin)*	**Doxepin Hydrochloride Capsules**
		Sinequan*, Pfizer
	150 mg (of doxepin)*	**Doxepin Hydrochloride Capsules**
		Sinequan*, Pfizer
Solution, concentrate	10 mg (of doxepin) per mL*	**Doxepin Hydrochloride Oral Solution (Concentrate)**
		Sinequan* Oral Concentrate, Pfizer

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

Imipramine Hydrochloride Imipramine Pamoate

■ Imipramine is a dibenzazepine-derivative tricyclic antidepressant.

Dosage and Administration

■ **Administration** Imipramine hydrochloride and imipramine pamoate are administered orally. Although imipramine hydrochloride has been administered in up to 4 divided doses throughout the day, it is long-acting and the entire oral daily dose may be administered at one time. Imipramine pamoate may also be used to administer the daily oral dose of imipramine, but it has no advantages over the hydrochloride. Administration of the entire daily dose at bedtime may reduce daytime sedation; patients who experience insomnia and stimulation may be given the entire daily dose in the morning.

■ **Dosage** Dosage of imipramine salts is expressed in terms of imipramine hydrochloride.

Patients should be monitored for possible worsening of depression, suicidality, or unusual changes in behavior, especially at the beginning of therapy or during periods of dosage adjustment. (See Cautions: Precautions and Contraindications, in the Tricyclic Antidepressants General Statement 28:16.04.28.)

Major Depressive Disorder There is a wide range of oral dosage requirements, and dosage must be carefully individualized. Initial dosages of imipramine should be low and generally range from 75–100 mg daily, depending on the severity of the condition being treated. Dosage may be gradually adjusted to the level that produces maximal therapeutic effect with minimal toxicity and may range up to 300 mg daily. Hospitalized patients under close supervision may generally be given higher dosages than outpatients, and manufacturers state that dosages of greater than 200 mg daily are not recommended for outpatients. Geriatric patients should usually be given lower than average dosages. Manufacturers state that therapy should be initiated with 25–50 mg daily as imipramine hydrochloride (e.g., Tofranil®) in these patients and that optimal dosage rarely exceeds 100 mg daily. If the daily dosage is established at 75 mg or more, imipramine pamoate (e.g., Tofranil®-PM) may be administered. Maximum antidepressant effects may not occur for 2 or more weeks after therapy is begun.

After symptoms are controlled, dosage should be gradually reduced to the lowest level that will maintain relief of symptoms. If maintenance therapy is necessary, manufacturers recommend an adult dosage of 50–150 mg daily. To avoid the possibility of precipitating withdrawal symptoms, imipramine should not be terminated abruptly in patients who have received high dosage for prolonged periods.

Functional Enuresis in Children For the treatment of functional enuresis in children who are at least 6 years of age, the usual initial oral dosage of imipramine hydrochloride is 25 mg daily, administered 1 hour prior to bedtime. If a satisfactory response is not obtained within 1 week, dosage may be increased to 50 mg nightly for children younger than 12 years of age or 75 mg nightly for children 12 years of age and older. Dosages higher than 75 mg daily do not improve results and may increase the risk of adverse reactions. For children who are early-night bedwetters, better results may be obtained by administering 25 mg in midafternoon and again at bedtime. Dosage of imipramine hydrochloride for the treatment of functional enuresis in children should not exceed 2.5 mg/kg daily. Long-term effects of the drug in children have not been determined; therefore, after a satisfactory response has been maintained, imipramine hydrochloride should be gradually withdrawn. If dosage is gradually reduced after a favorable response of many weeks, relapses may be less frequent; children who relapse may not respond to subsequent treatment with imipramine. (See Cautions: Pediatric Precautions.)

Cautions

Imipramine shares the pharmacologic actions, uses, and toxic potentials of the tricyclic antidepressants, and the usual precautions of tricyclic antidepressant administration should be observed. Patients should be fully advised about the risks, especially suicidal thinking and behavior (suicidality), associated with tricyclic antidepressant therapy. For a complete discussion, see Cautions: Precautions and Contraindications and Cautions: Pediatric Precautions, in the Tricyclic Antidepressants General Statement 28:16.04.28.

Although the clinical importance is not known, ECG changes have been reported in pediatric patients receiving twice the recommended maximum daily dosage.

■ **Pediatric Precautions** Imipramine hydrochloride is used for the treatment of enuresis in children 6 years of age or older, but safety and efficacy of the drug for the treatment of this condition in younger children or for the treatment of any other condition in pediatric patients have not been established. The manufacturer of imipramine *pamoate* states that the drug should not be used in children of any age because of the high potency and risk of acute overdose.

The US Food and Drug Administration (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. However, FDA also states that depression and certain other psychiatric disorders are themselves associated with an increased risk of suicide. Anyone considering the use of imipramine in a child or adolescent for any clinical use must therefore balance the potential risk of therapy with the clinical need. (See Cautions: Precautions and Contraindications and Cautions: Pediatric Precautions, in the Tricyclic Antidepressants General Statement 28:16.04.28.)

Pharmacokinetics

■ **Absorption** In studies with radiolabeled imipramine, the drug was completely absorbed from the GI tract. Peak plasma concentrations of imipramine occur within 1–2 hours after oral administration and 30 minutes after IM administration (no longer commercially available in the US).

■ **Distribution** Limited data indicate that imipramine and its active metabolite, desipramine, are distributed into milk in concentrations similar to those present in maternal plasma.

■ **Elimination** The plasma half-life of imipramine ranges from 8–16 hours. Imipramine is metabolized via the same pathways as are other tricyclic antidepressants; desipramine, its *N*-monodemethylated metabolite, is pharmacologically active. Approximately 40% of a dose of imipramine is excreted in urine as inactive metabolites within 24 hours and 70% within 72 hours; small amounts are excreted in feces via biliary elimination.

Chemistry and Stability

■ **Chemistry** Imipramine is a dibenzazepine-derivative tricyclic antidepressant. The drug is commercially available as the hydrochloride and pamoate salts.

Imipramine hydrochloride occurs as a white to off-white, odorless or practically odorless, crystalline powder and is freely soluble in water and in alcohol. Imipramine pamoate occurs as a fine yellow powder and is insoluble in water and soluble in alcohol. Imipramine hydrochloride has a pK_a of 9.5.

■ **Stability** Imipramine hydrochloride turns yellowish or reddish on exposure to light; slight discoloration does not affect potency, but marked discoloration is associated with loss of potency. Solutions of imipramine hydrochloride are stable at pH 4–5. During storage, minute crystals may form in imipramine hydrochloride injection (no longer commercially available in the US); the efficacy of the preparation is unaltered if the crystals are redissolved by immersing the ampul in hot water for 1 minute.

Imipramine hydrochloride tablets and impramine pamoate capsules should be stored in tight containers at a temperature between 15–30°C. Commercially available oral imipramine hydrochloride preparations have expiration dates of 3–5 years (depending on the manufacturer) following the date of manufacture. Commercially available imipramine pamoate capsules have an expiration date of 3 years following the date of manufacture.

For further information on chemistry, pharmacology, pharmacokinetics, uses, cautions, acute toxicity, drug interactions, and dosage and administration of imipramine, see the Tricyclic Antidepressants General Statement 28:16.04.28.

Preparations

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

Imipramine Hydrochloride

Oral		
Tablets	10 mg*	Imipramine Hydrochloride Tablets
		Tofranil®, Mallinckrodt
	25 mg*	Imipramine Hydrochloride Tablets
		Tofranil®, Mallinckrodt
	50 mg*	Imipramine Hydrochloride Tablets
		Tofranil®, Mallinckrodt
Tablets, film-coated	10 mg*	Imipramine Hydrochloride Film-coated Tablets
	25 mg*	Imipramine Hydrochloride Film-coated Tablets
	50 mg*	Imipramine Hydrochloride Film-coated Tablets

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

Imipramine Pamoate

Oral		
Capsules	equivalent to Imipramine Hydrochloride 75 mg	Tofranil-PM®, Mallinckrodt
	equivalent to Imipramine Hydrochloride 100 mg	Tofranil-PM®, Mallinckrodt
	equivalent to Imipramine Hydrochloride 125 mg	Tofranil-PM®, Mallinckrodt
	equivalent to Imipramine Hydrochloride 150 mg	Tofranil-PM®, Mallinckrodt

Maprotiline Hydrochloride

■ Maprotiline hydrochloride is a tetracyclic antidepressant that is pharmacologically similar to the tricyclic antidepressants.

Uses

Maprotiline hydrochloride is used in the treatment of depressive affective (mood) disorders, including dysthymic disorder (depressive neurosis) and major depressive disorder. The drug has been used for the depressive phase of bipolar disorder; however, hypomanic or manic episodes may occur when the drug is given to patients with this disorder and other antidepressants (e.g., bupropion, selective serotonin-reuptake inhibitors) generally are preferred when an antidepressant is considered necessary in such patients. (See Considerations in Choosing Therapy for Depressive Episodes under Uses: Bipolar Disorder, in Lithium Salts 28:28.) Maprotiline is effective for the relief of anxiety associated with depression. Most studies comparing maprotiline with amitriptyline or imipramine in the treatment of patients with various types of depression have not demonstrated superiority of maprotiline over these tricyclic antidepressants. Although maprotiline has been reported to have a slightly more rapid onset of action than either amitriptyline or imipramine in some studies, this finding has not been adequately established.

For further information on treatment of major depressive disorder and considerations in choosing the most appropriate antidepressant for a particular patient, including considerations related to patient tolerance, patient age, and cardiovascular, sedative, and suicidal risks, see Considerations in Choosing Antidepressants under Uses: Major Depressive Disorder, in the Tricyclic Antidepressants General Statement 28:16.04.28.

Dosage and Administration

■ **Administration** Maprotiline hydrochloride is administered orally. Although maprotiline has been administered in 3 divided doses throughout the day, it is long-acting and the entire daily dose may be administered at one time.

Dispensing and Administration Precautions Dispensing errors have occurred because of the similarity in spelling between Ludiomil® (the former trade name for maprotiline hydrochloride; no longer commercially available under this trade name in the US) and Lamictal® (the trade name for lamotrigine, an anticonvulsant). Therefore, extra care should be exercised in ensuring the accuracy of both oral and written prescriptions for Ludiomil® and Lamictal®. The manufacturer of Lamictal® (GlaxoSmithKline) 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 of Lamictal® 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.)

■ **Dosage** There is a wide range of dosage requirements, and dosage of maprotiline hydrochloride must be carefully individualized. The manufacturer suggests that the risk of seizures may be decreased by initiating therapy with low dosages of the drug. Initial dosages should be low, generally 75 mg daily in outpatients with mild to moderate depression, although a lower initial dosage may be used in some patients (e.g., geriatric patients). Because of the long elimination half-life of maprotiline, the initial dosage should be maintained for 2 weeks. Depending on tolerance and response, the daily dose may then be gradually increased in 25-mg increments. In most outpatients, a maximum dosage of 150 mg daily will be effective; it is recommended that this dosage be exceeded only in very severely depressed patients. Severely depressed hospitalized patients under close supervision may generally be given higher dosages than outpatients; such patients may be given an initial dosage of 100–150 mg daily which may be increased cautiously. Most hospitalized patients with moderate to severe depression will respond to a dosage of 150 mg daily, but dosages as high as 225 mg daily may be necessary in some patients; dosage should not exceed 225 mg daily. Geriatric patients (i.e., patients older than 60 years of age) should usually be given lower than average dosages; 50–75 mg daily is generally satisfactory for these patients. Antidepressant effects usually occur within 2–3 weeks in most patients who respond to maprotiline therapy and may occur within 3–7 days.