fate, dosage of these agents must be carefully adjusted because of the additive central depressant effects.

■ **Neuromuscular Blocking Agents** Excessive neuromuscular blockade has occurred in patients receiving parenteral magnesium sulfate and a neuromuscular blocking agent; these drugs should be administered concomitantly only with caution.

■ **Cardiac Glycosides** Magnesium salts should be administered with extreme caution in digitalized patients, because serious changes in cardiac conduction which can result in heart block may occur if administration of calcium is required to treat magnesium toxicity.

Pharmacology

Magnesium is the fourth most abundant cation in the body and is essential for the function of important enzymes, including those related to the transfer of phosphate groups, all reactions involving ATP, and every step related to the replication and transcription of DNA and the translation of mRNA. Magnesium also is required for cellular energy metabolism and is involved in membrane stabilization, nerve conduction, iron transport, and calcium-channel activity.

When administered parenterally in doses sufficient to produce hypermagnesemia (serum magnesium concentrations greater than 2.5 mEq/L), the drug may depress the CNS and block peripheral neuromuscular transmission, producing anticonvulsant effects. The exact mechanism of this depressant activity is not fully known; however, excess magnesium appears to decrease the amount of acetylcholine liberated by the motor nerve impulse. When serum concentrations of magnesium exceed 4 mEq/L, deep-tendon reflexes may be depressed. At serum concentrations of 10 mEq/L, deep-tendon reflexes may disappear and respiratory paralysis may occur. Serum magnesium concentrations in excess of 12 mEq/L may be fatal. Complete heart block can also occur at high serum concentrations of magnesium (approximately 10 mEq/L). Animal studies suggest that the effect of magnesium ions on cardiac muscle is to slow the rate of the sinoatrial node impulse formation and prolong conduction time. Limited data in patients with no evidence of heart disease indicate that IV infusion of magnesium prolongs PR interval, H(atria-His bundle) interval, antegrade AV nodal effective refractory period, and sinoatrial conduction time. Available data also suggest that magnesium produces systemic and coronary vasodilatation, possesses antiplatelet activity, suppresses automaticity in partially depolarized cells, and protects myocytes against calcium overload under conditions of ischemia by inhibiting calcium influx especially at the time of reperfusion. However, the clinical benefit of administering magnesium in patients with acute myocardial infarction has not been fully determined. (See Uses: Acute Myocardial Infarction.) Magnesium also acts peripherally, producing vasodilation. Moderate doses produce flushing and sweating; and higher doses lower blood pressure. Both the CNS depression and the peripheral neuromuscular transmission blockade produced by hypermagnesemia can be antagonized by administration of excess calcium.

Pharmacokinetics

When magnesium sulfate is administered IV, the onset of action is immediate and the duration of action is about 30 minutes. Following IM administration of the drug, the onset of action occurs in about 1 hour and the duration of action is 3–4 hours. As an anticonvulsant, effective serum concentrations of magnesium have been reported to range from 2.5–7.5 mEq/L.

Magnesium readily crosses the placenta and is distributed into milk following parenteral administration of magnesium sulfate. Milk concentrations of magnesium are increased for only about 24 hours after discontinuance of parenteral magnesium sulfate therapy; the amount of magnesium ingested by a nursing infant during this period is probably too small to be of clinical importance.

Magnesium sulfate is excreted by the kidneys at a rate that varies from one patient to another but that is directly proportional to the serum concentration and glomerular filtration.

Chemistry and Stability

■ **Chemistry** Parenteral magnesium sulfate exhibits anticonvulsant properties. Magnesium sulfate occurs as small, colorless crystals; usually needle-like, with a cooling, saline, bitter taste and is freely soluble in water and sparingly soluble in alcohol. The drug effloresces in warm, dry air. Each gram of magnesium sulfate heptahydrate contains 8.1 mEq of magnesium. The pHs of commercially available magnesium sulfate injection and magnesium sulfate in 5% dextrose injection are adjusted with sodium hydroxide and/or sulfuric acid; the injections have pHs of 3.5–7.

■ **Stability** Magnesium sulfate injection and magnesium sulfate in 5% dextrose injection should be stored at a temperature less than 40°C, preferably between 15–30°C; freezing should be avoided.

Magnesium sulfate is converted to the monohydrate when heated to 150–160°C. Magnesium sulfate is incompatible with alkali hydroxides (forming insoluble magnesium hydroxide), with alkali carbonates (forming basic carbonates), and with salicylates (forming basic salicylates). The drug reacts with arsenates, phosphates, and tartrates, precipitating the corresponding magnesium salts. Lead, barium, strontium, and calcium react with magnesium sulfate resulting in precipitation of the respective sulfates. Specialized references should be consulted for specific compatibility information. Following withdrawal of a dose from one of the solutions which do not contain preservatives, any unused portion should be discarded.

Preparations

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

Magnesium Sulfate

Crystals		
Parenteral		
Injection	50%*	Magnesium Sulfate Injection
Injection, for IV use only	4% (4, 20, and 40 g)*	Magnesium Sulfate Injection
	8% (4 g)*	Magnesium Sulfate Injection

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

Magnesium Sulfate in Dextrose

Parenteral		
Injection, for IV use only	1% (1 g) in 5% Dextrose*	Magnesium Sulfate in 5% Dextrose Injection

*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

Oxcarbazepine

■ Oxcarbazepine is an anticonvulsant agent.

Uses

■ **Seizure Disorders** ***Partial Seizures*** Oxcarbazepine is used as monotherapy or in combination with other anticonvulsants in the management of partial seizures in adults and children 4 years of age and older.

Monotherapy. Efficacy of oxcarbazepine monotherapy in patients with partial seizures has been established in several multicenter, randomized, double-blind clinical trials. These studies have included adults and children 8 years of age or older. In one placebo-controlled, randomized clinical trial in patients with refractory partial seizures (undergoing evaluation for epilepsy surgery) who had been withdrawn from anticonvulsants prior to randomization, oxcarbazepine at dosages up to 2400 mg daily for 10 days was more effective than placebo. Results of another placebo-controlled clinical trial in patients with newly diagnosed or recent-onset partial seizures indicate that oxcarbazepine dosages up to 1200 mg daily for 84 days were more effective than placebo. In addition, therapy with oxcarbazepine 2400 mg daily for up to 126 days was substantially more effective than oxcarbazepine 300 mg daily in 2 other clinical trials in patients with partial seizures who had been withdrawn from therapy with 1 or 2 anticonvulsants because of inadequate control.

Results of several multicenter, randomized, double-blind monotherapy trials in patients with newly diagnosed or previously untreated partial or generalized seizures indicate that oxcarbazepine exhibits anticonvulsant activity similar to carbamazepine, phenytoin, or valproate sodium.

Combination Therapy Efficacy of oxcarbazepine as adjunctive therapy in patients with partial seizures was established in 2 multicenter, placebo-controlled, randomized, double-blind clinical trials in patients with partial seizures (one in adults and one in children 3–17 years of age). In both studies, patients initially were stabilized with optimum dosages of 1–3 anticonvulsants during an 8-week baseline period; those experiencing at least 8 (minimum 1–4 per month) partial seizures during this phase were randomized to receive oxcarbazepine or placebo during a dosage titration period of 2 weeks followed by a 14- or 24-week maintenance period in children or adults, respectively. Efficacy of oxcarbazepine in these studies was evaluated in terms of the change in seizure frequency (i.e., the median decrease [or increase] in average monthly [28-day] seizure rate). Adult patients receiving oxcarbazepine 600, 1200, or 2400 mg daily or placebo experienced a median decrease in seizure frequency of about 26, 40, 50, or 8%, respectively, while pediatric patients receiving oxcarbazepine maintenance dosages ranging from 30–46 mg/kg daily (depending on baseline body weight) or placebo experienced a median decrease in seizure frequency of about 35 or 9%, respectively.

■ **Bipolar Disorder** Oxcarbazepine 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†. Limited data suggest that oxcarbazepine may have equivalent efficacy and better tolerability than carbamazepine for this indication. However, the American Psychiatric Association (APA) currently recommends that oxcarbazepine be reserved for patients unable to tolerate or who had an inadequate therapeutic response to first-line agents such as 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.

Dosage and Administration

■ **General** Oxcarbazepine tablets and suspension are administered orally twice daily without regard to meals.

Oxcarbazepine suspension should be shaken well prior to administration of each dose. The appropriate measured dose of the suspension should be administered using an oral dosing syringe. The oral suspension may be added to a small glass of water or swallowed directly from the syringe. After each use, the oral syringe should be rinsed with warm water and allowed to dry thoroughly.

The manufacturer of Trileptal® states that oral bioavailability of oxcarbazepine tablets appears to be similar to that of the suspension and, therefore, these preparations can be used interchangeably on a mg-for-mg basis.

Patients currently receiving or beginning therapy with oxcarbazepine 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 Suicidality Risk under Warnings/Precautions: Warnings, in Cautions.)

Partial Seizures **Monotherapy.** In adults and children older than 16 years of age with partial seizures being transferred from other anticonvulsant drug therapy to monotherapy with oxcarbazepine, the recommended initial dosage of oxcarbazepine is 600 mg daily given in 2 equally divided doses. Oxcarbazepine dosage may be increased by 600-mg daily increments at approximately weekly intervals to a recommended daily dosage of 2400 mg, usually within 2–4 weeks. As oxcarbazepine replaces the existing anticonvulsant therapeutic regimen, dosage of the other anticonvulsant(s) is simultaneously reduced and discontinued over 3–6 weeks. Patients should be observed during this transition phase.

In adults not receiving anticonvulsant drug therapy, the recommended initial daily dosage of oxcarbazepine as initial monotherapy is 600 mg daily administered in 2 equally divided doses. Dosage should be increased by 300-mg daily increments every third day to a maximum daily dosage of 1200 mg.

In children 4–16 years of age with partial seizures being transferred from other anticonvulsant drug therapy to monotherapy with oxcarbazepine, the recommended initial dosage of oxcarbazepine is 8–10 mg/kg daily given in 2 equally divided doses. Oxcarbazepine dosage may be increased in increments of up to 10 mg/kg daily at weekly intervals to achieve the recommended maintenance dosage. (See Table 1.) As oxcarbazepine replaces the existing anticonvulsant therapeutic regimen, dosage of the other anticonvulsant(s) is simultaneously reduced and discontinued over 3–6 weeks.

Children 4–16 years of age not receiving anticonvulsant drug therapy may initiate therapy with oxcarbazepine at a dosage of 8–10 mg/kg daily given in 2 equally divided doses. Dosage may be increased in increments of 5 mg/kg daily every third day until the recommended maintenance dosage is achieved. (See Table 1.)

Table 1. Recommended Range of Maintenance Dosages in Children Receiving Oxcarbazepine Monotherapy

Weight (kg)	Dosage Range (mg/day)
20	600–900
25	900–1200
30	900–1200
35	900–1500
40	900–1500
45	1200–1500
50	1200–1800
55	1200–1800
60	1200–2100
65	1200–2100
70	1500–2100

Combination Therapy. For adjunctive therapy in the management of partial seizures in adults and children older than 16 years of age, the initial dosage of oxcarbazepine is 600 mg daily administered in 2 equally divided doses. Oxcarbazepine dosage may be increased by 600-mg daily increments at approximately weekly intervals to a recommended daily dosage of 1200 mg. Although efficacy may be somewhat higher in patients receiving oxcarbazepine dosages exceeding 1200 mg daily, most patients cannot tolerate daily dosages of 2400 mg, mainly because of adverse CNS effects. The manufacturers recommend that patients be observed closely and that plasma concentrations of concomitantly administered anticonvulsants be monitored during dosage titration of oxcarbazepine since plasma concentrations of these drugs may be altered when dosage of oxcarbazepine exceeds 1200 mg daily.

For adjunctive therapy in the management of partial seizures in children 4–16 years of age, the recommended initial dosage of oxcarbazepine (administered in 2 equally divided doses) is 8–10 mg/kg daily, generally not exceeding 600 mg daily. The target daily maintenance dosage of 900–1800 mg depends on patient weight (900, 1200, or 1800 mg in children weighing 20–29, 29.1–39, or more than 39 kg, respectively) and should be reached within 2 weeks. Since clearance of the drug appears to be increased (by 30–40%) in children younger than 8 years of age compared with that in adults, such children received the highest maintenance dosage in controlled clinical trials.

■ **Special Populations** The manufacturers state that the initial dosage of oxcarbazepine should be 300 mg daily (one-half of the usual starting dosage) in patients with renal impairment (creatinine clearance less than 30 mL/minute); dosage should be increased slowly to achieve the desired clinical response.

In general, no dosage adjustments are necessary in patients with mild to moderate hepatic impairment.

Cautions

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

■ **Warnings/Precautions** ***Warnings*** **Hyponatremia.** Clinically important hyponatremia (serum sodium concentrations less than 125 mEq/L) has been reported in 2.5% of patients receiving oxcarbazepine in clinical studies, versus 0% in patients receiving placebo or active controls (i.e., carbamazepine, phenobarbital, phenytoin, valproic acid). Generally, hyponatremia occurred during the first 3 months of oxcarbazepine therapy, although this adverse effect was reported in some patients more than 1 year after initiation of such therapy. In clinical studies, most patients with hyponatremia were asymptomatic. However, it should be considered that these patients were monitored frequently, and in some patients dosage of oxcarbazepine was reduced or discontinued or the fluid intake restricted. It is not known whether these measures prevented development of hyponatremia. Symptomatic hyponatremia was reported in some patients during postmarketing surveillance. In clinical trials in patients developing hyponatremia, serum sodium concentrations returned to baseline values a few days after discontinuance of the drug. The manufacturers state that monitoring serum sodium concentrations should be considered during maintenance therapy with oxcarbazepine, particularly in patients concurrently receiving other drugs known to decrease serum sodium concentrations (e.g., drugs associated with inappropriate antidiuretic hormone secretion [SIADH]) or in those with symptoms of hyponatremia (e.g., nausea, malaise, headache, lethargy, confusion, obtundation, increase in seizure frequency or severity).

Suicidality Risk. The US Food and Drug Administration (FDA) has alerted healthcare professionals about an increased risk of suicidality (suicidal behavior or ideation) observed in an analysis of studies using various anticonvulsants, including oxcarbazepine, compared with placebo. The analysis of suicidality reports from placebo-controlled studies involving 11 anticonvulsants (i.e., carbamazepine, felbamate, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, pregabalin, tiagabine, topiramate, valproate, zonisamide) in patients with epilepsy, psychiatric disorders (e.g., bipolar disorder, depression, anxiety), and other conditions (e.g., migraine, neuropathic pain) found that patients receiving anticonvulsants had approximately twice the risk of suicidal behavior or ideation (0.43%) compared with patients receiving placebo (0.24%). This increased suicidality risk was observed as early as one week after beginning therapy and continued through 24 weeks. Although patients treated with an anticonvulsant for epilepsy, psychiatric disorders, and other conditions were all found to have an increased suicidality risk compared with those receiving placebo, the relative suicidality risk was higher for patients with epilepsy compared with those receiving anticonvulsants for other conditions.

Based on the current analysis of the available data, FDA recommends that clinicians inform patients, their families, and caregivers about the potential for an increase in the risk of suicidality with anticonvulsant therapy and that all patients 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, hypomania, and mania may be precursors to emerging suicidality. Clinicians who prescribe oxcarbazepine or any other anticonvulsant should 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 should consider whether these symptoms may be related to the illness being treated. (See Advice to Patients.)

Discontinuance of Oxcarbazepine. Because of the possibility of increased seizure frequency, anticonvulsant drugs, including oxcarbazepine, should be withdrawn gradually. If a hypersensitivity reaction occurs, discontinue oxcarbazepine and initiate alternative therapy.

Sensitivity Reactions **History of Carbamazepine Hypersensitivity.** Approximately 25–30% of patients with a history of carbamazepine hypersensitivity will develop hypersensitivity to oxcarbazepine. Therefore, oxcarbazepine should only be used in patients with a history of such hypersensitivity if the potential benefits justify the potential risk to the patient. If a hypersensitivity reaction develops, oxcarbazepine should be discontinued immediately.

Dermatologic and Hypersensitivity Reactions. Serious dermatologic reactions, including Stevens-Johnson syndrome and toxic epidermal necrolysis, have been reported in adults and children receiving oxcarbazepine; reactions have been life-threatening, have required hospitalization, and rarely have been fatal. The incidence of Stevens-Johnson syndrome and toxic epidermal necrolysis reported in patients receiving oxcarbazepine exceeds the rate in the general population by threefold to tenfold. The median time to onset of these reactions was 19 days. Recurrence of serious dermatologic reactions following rechallenge with oxcarbazepine has occurred.

If a skin reaction develops in a patient receiving oxcarbazepine, consider discontinuance of the drug and initiation of therapy with another anticonvulsant agent.

Multiorgan hypersensitivity reactions occurring days to weeks or months (range 4–60 days) after initiation of oxcarbazepine therapy have been reported in adults and pediatric patients. Although these reactions have been reported rarely, many of these patients required hospitalization, and some reactions were considered life-threatening. Manifestations may include (but are not limited to) fever, rash, lymphadenopathy, hepatitis, abnormal liver function test results, eosinophilia, thrombocytopenia, neutropenia, pruritus, nephritis, oliguria, hepatorenal syndrome, arthralgia, and asthenia.

If a multiorgan hypersensitivity reaction is suspected, discontinue oxcarbazepine and initiate alternative therapy.

Possibility of cross-sensitivity with other drugs that produce multiorgan hypersensitivity reactions exists.

General Precautions **Nervous System Effects.** Neuropsychiatric effects reported during oxcarbazepine treatment are classified into 3 categories: impaired cognitive or psychomotor performance including difficulties in concentrating, language, and speech; somnolence or fatigue; and coordination difficulties (e.g., ataxia, gait disturbances). (See Suicidality Risk under Warnings/Precautions: Warnings, in Cautions.)

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

North American Antiepileptic Drug (NAAED) Pregnancy Registry at 888-233-2334 (for patients); registry information also available on the website http://www.aedpregnancyregistry.org.

The effect of oxcarbazepine on labor and delivery is unknown.

Lactation. Both oxcarbazepine and its active 10-monohydroxy metabolite (MHD) are distributed into milk in humans. Discontinue nursing or the drug, taking into account the importance of the drug to the woman.

Pediatric Use. Safety and efficacy of oxcarbazepine as monotherapy or adjunctive therapy for partial seizures in children younger than 4 years of age have not been established.

Efficacy of oxcarbazepine as adjunctive therapy for partial seizures in children 4–16 years of age established in clinical studies. Efficacy as monotherapy for partial seizures in children 4–16 years of age based on clinical studies and pharmacokinetic and pharmacodynamic considerations.

Oxcarbazepine has not been evaluated in clinical studies in children younger than 2 years of age.

Severe dermatologic and other sensitivity reactions have been reported in pediatric patients. (See Dermatologic and Hypersensitivity Reactions under Warnings/Precautions: Sensitivity Reactions, in Cautions.)

Geriatric Use. Although peak plasma concentrations of MHD and the area under the plasma concentration-time curve (AUC) may be 30–60% higher in adults 60 years of age or older than in younger adults (possibly related to decreases in renal function with age), the manufacturers do not make specific recommendations for dosage adjustment in such patients.

■ **Common Adverse Effects** Adverse effects occurring in 5% or more of patients and more frequently than placebo include dizziness, somnolence, diplopia, fatigue, nausea, vomiting, ataxia, abnormal vision, abdominal pain, tremor, dyspepsia, abnormal gait.

Drug Interactions

■ **Drugs Affecting Hepatic Microsomal Enzymes**

Anticonvulsants Oxcarbazepine may inhibit metabolism of other anticonvulsants (e.g., phenobarbital, phenytoin), possibly via inhibition of the cytochrome P-450 (CYP) isoenzyme 2C19, resulting in increased plasma concentrations of these drugs. Oxcarbazepine dosages exceeding 1200 mg daily may increase plasma phenytoin concentrations by 40% and, therefore, when such dosages of oxcarbazepine are used concomitantly with phenytoin, dosage reduction of phenytoin may be required.

Potent inducers of CYP isoenzymes (e.g., carbamazepine, phenytoin, phenobarbital) may decrease plasma concentrations of oxcarbazepine and its active 10-monohydroxy metabolite (MHD).

Oral Contraceptives Oxcarbazepine may induce metabolism of oral estrogen-progestin contraceptives, possibly via induction of CYP3A4 and CYP3A5, resulting in decreased area under the plasma concentration-time curve (AUC) and consequent decreased efficacy of the contraceptives.

Calcium-channel Blocking Agents Oxcarbazepine may induce metabolism of some calcium-channel blocking agents (e.g., felodipine, verapamil), possibly via induction of CYP3A4 and CYP3A5 isoenzymes, resulting in decreased AUC of the calcium-channel blocking agents.

Description

Oxcarbazepine is an anticonvulsant agent that is structurally and chemically related to carbamazepine. Although the exact mechanism of action of oxcarbazepine is unknown, in vitro electrophysiologic studies indicate that the drug may stabilize excitatory neuronal membranes, inhibit repetitive neuronal firing, and decrease propagation of synaptic impulses by blocking voltage-sensitive sodium channels, actions that may prevent spread of epileptic seizures. Increased potassium conductance and modulation of high-voltage activated calcium channels also may contribute to the anticonvulsant activity of oxcarbazepine. No substantial interactions between the drug and neurotransmitter receptors in the brain have been observed to date.

Oxcarbazepine and its active 10-monohydroxy metabolite (MHD) exhibit anticonvulsant activity in several animal seizure models. Oxcarbazepine protects against electrically induced tonic extension seizures and, to a lesser degree, chemically induced clonic seizures and may abolish or reduce frequency of chronically recurring focal seizures.

Following oral administration, oxcarbazepine is completely absorbed and extensively metabolized in the liver by cytosolic enzymes to MHD (10,11-dihydro-10-hydroxy-5*H*-dibenz[*b*, *f*]azepine-5-carboxamide), which is believed to be responsible for the pharmacologic activity of oxcarbazepine. The oral bioavailabilities of oxcarbazepine tablets and suspension appear to be similar. More than 95% of an oral dose of oxcarbazepine is excreted in urine, mainly as metabolites with less than 1% as unchanged drug; less than 4% is excreted in feces.

Advice to Patients

Importance of providing copy of written patient information (medication guide) each time oxcarbazepine is dispensed.

Risk of hypersensitivity reaction; patients who have had previous hypersensitivity reaction to carbamazepine at increased risk. Importance of immediately reporting hypersensitivity reactions, skin reactions, or fever accompanied by signs and/or symptoms of other organ system involvement (e.g., rash, lymphadenopathy).

Risk of dizziness and somnolence; avoid driving or operating machinery while taking oxcarbazepine until effects of the drug on the individual are known.

Risk of low sodium concentrations in the blood; manifestations may include nausea, extreme drowsiness and/or fatigue, discomfort, headache, confusion, increase in seizure frequency or severity, or dullness.

Importance of patients, family members, and caregivers being aware that anticonvulsants, including oxcarbazepine, may increase the risk of having suicidal thoughts or actions in a very small number of people (about 1 in 500). Advise patients, family members, and caregivers to pay close attention to any day-to-day changes in mood, behavior, and actions; these changes can happen very quickly. They should also 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). Advise patients, family members, and caregivers to contact the responsible clinician immediately if these or any new and worrisome behaviors occur.

Caution if alcohol is used concomitantly because additive sedative effects may occur.

Importance of not abruptly discontinuing therapy.

Importance of women informing clinicians if they are or plan to become pregnant or plan to breast-feed. Importance of informing women of childbearing age that concomitant use of oxcarbazepine with oral contraceptives may result in decreased efficacy of the contraceptives.

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

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

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

Preparations

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

Oxcarbazepine

Oral		
Suspension	300 mg/5 mL	**Trileptal®**, Novartis
Tablets, film-coated	150 mg*	**Oxcarbazepine Tablets**
		Trileptal® (scored), Novartis
	300 mg*	**Oxcarbazepine Tablets**
		Trileptal® (scored), Novartis
	600 mg*	**Oxcarbazepine Tablets**
		Trileptal® (scored), 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

Chemistry and Stability

■ **Chemistry** Dextroamphetamine is the dextrorotatory isomer of amphetamine. Dextroamphetamine sulfate occurs as a white, odorless, crystalline powder and has a bitter taste. Dextroamphetamine sulfate is freely soluble in water (about 1:10) and slightly soluble in alcohol (about 1:800). Dextroamphetamine sulfate also is commercially available as fixed-combination preparations with dextroamphetamine saccharate, amphetamine aspartate, and amphetamine sulfate.

■ **Stability** Preparations containing dextroamphetamine sulfate should be stored in tight, light-resistant containers at 15–30°C.

Preparations

Dextroamphetamine and dextroamphetamine sulfate preparations are subject to control under the Federal Controlled Substances Act of 1970 as schedule II (C-II) drugs.

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

Dextroamphetamine Sulfate

Oral		
Capsules, extended-release	5 mg*	**Dexedrine* Spansule*** (C-II), GlaxoSmithKline
		Dextroamphetamine Sulfate Capsules SR (C-II)
	10 mg*	**Dexedrine* Spansule*** (C-II), GlaxoSmithKline
		Dextroamphetamine Sulfate Capsules SR (C-II)
	15 mg*	**Dexedrine* Spansule*** (C-II), GlaxoSmithKline
		Dextroamphetamine Sulfate Capsules SR (C-II)
Tablets	5 mg*	**Dexedrine*** (C-II; scored), GlaxoSmithKline
		Dextroamphetamine Sulfate Tablets (C-II; scored)
		DextroStat* (C-II; scored), Shire
	10 mg*	**Dextroamphetamine Sulfate Tablets** (C-II; scored)
		DextroStat* (C-II; double-scored), Shire

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

Dextroamphetamine Sulfate Combinations

Oral		
Capsules, extended-release	5 mg total amphetamine (as 1.25 mg with Amphetamine Sulfate 1.25 mg, Amphetamine Aspartate 1.25 mg, and Dextroamphetamine Saccharate 1.25 mg)	**Adderall XR*** (C-II), Shire
	10 mg total amphetamine (as 2.5 mg with Amphetamine Sulfate 2.5 mg, Amphetamine Aspartate 2.5 mg, and Dextroamphetamine Saccharate 2.5 mg)	**Adderall XR*** (C-II), Shire
	15 mg total amphetamine (as 3.75 mg with Amphetamine Sulfate 3.75 mg, Amphetamine Aspartate 3.75 mg, and Dextroamphetamine Saccharate 3.75 mg)	**Adderall XR*** (C-II), Shire
	20 mg total amphetamine (as 5 mg with Amphetamine Sulfate 5 mg, Amphetamine Aspartate 5 mg, and Dextroamphetamine Saccharate 5 mg)	**Adderall XR*** (C-II), Shire
	25 mg total amphetamine (as 6.25 mg with Amphetamine Sulfate 6.25 mg, Amphetamine Aspartate 6.25 mg, and Dextroamphetamine Saccharate 6.25 mg)	**Adderall XR*** (C-II), Shire
	30 mg total amphetamine (as 7.5 mg with Amphetamine Sulfate 7.5 mg, Amphetamine Aspartate 7.5 mg, and Dextroamphetamine Saccharate 7.5 mg)	**Adderall XR*** (C-II), Shire
Tablets	5 mg total amphetamine (as 1.25 mg with Amphetamine Aspartate 1.25 mg, Amphetamine Sulfate 1.25 mg, and Dextroamphetamine Saccharate 1.25 mg)*	**Adderall*** (C-II; double-scored), Shire
		Dextroamphetamine Saccharate, Amphetamine Aspartate, Dextroamphetamine Sulfate, and Amphetamine Sulfate Tablets (C-II; double-scored)
	7.5 mg total amphetamine (as 1.875 mg with Amphetamine Aspartate 1.875 mg, Amphetamine Sulfate 1.875 mg, and Dextroamphetamine Saccharate 1.875 mg)*	**Adderall*** (C-II; double-scored), Shire
		Dextroamphetamine Saccharate, Amphetamine Aspartate, Dextroamphetamine Sulfate, and Amphetamine Sulfate Tablets (C-II; double-scored)
	10 mg total amphetamine (as 2.5 mg with Amphetamine Aspartate 2.5 mg, Amphetamine Sulfate 2.5 mg, and Dextroamphetamine Saccharate 2.5 mg)*	**Adderall*** (C-II; double-scored), Shire
		Dextroamphetamine Saccharate, Amphetamine Aspartate, Dextroamphetamine Sulfate, and Amphetamine Sulfate Tablets (C-II; double-scored)
	12.5 mg total amphetamine (as 3.125 mg with Amphetamine Aspartate 3.125 mg, Amphetamine Sulfate 3.125 mg, and Dextroamphetamine Saccharate 3.125 mg)*	**Adderall*** (C-II; double-scored), Shire
		Dextroamphetamine Saccharate, Amphetamine Aspartate, Dextroamphetamine Sulfate, and Amphetamine Sulfate Tablets (C-II; double-scored)
	15 mg total amphetamine (as 3.75 mg with Amphetamine Aspartate 3.75 mg, Amphetamine Sulfate 3.75 mg, and Dextroamphetamine Saccharate 3.75 mg)*	**Adderall*** (C-II; double-scored), Shire
		Dextroamphetamine Saccharate, Amphetamine Aspartate, Dextroamphetamine Sulfate, and Amphetamine Sulfate Tablets (C-II; double-scored)
	20 mg total amphetamine (as 5 mg with Amphetamine Aspartate 5 mg, Amphetamine Sulfate 5 mg, and Dextroamphetamine Saccharate 5 mg)*	**Adderall*** (C-II; double-scored), Shire
		Dextroamphetamine Saccharate, Amphetamine Aspartate, Dextroamphetamine Sulfate, and Amphetamine Sulfate Tablets (C-II; double-scored)
	30 mg total amphetamine (as 7.5 mg with Amphetamine Aspartate 7.5 mg, Amphetamine Sulfate 7.5 mg, and Dextroamphetamine Saccharate 7.5 mg)*	**Adderall*** (C-II; double-scored), Shire
		Dextroamphetamine Saccharate, Amphetamine Aspartate, Dextroamphetamine Sulfate and Amphetamine Sulfate Tablets (C-II; double-scored)

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

Lisdexamfetamine Dimesylate

■ Prodrug of dextroamphetamine; noncatechol, sympathomimetic amine with CNS-stimulating activity.

Uses

■ **Attention-Deficit Hyperactivity Disorder** Lisdexamfetamine dimesylate is used as an adjunct to psychological, educational, social, and other remedial measures in the treatment of attention deficit hyperactivity disorder (ADHD) (hyperkinetic disorder, hyperkinetic syndrome of childhood, minimal brain dysfunction). Safety and efficacy for this indication have been established in controlled clinical trials in children 6–12 years of age and in adults.

Safety and efficacy of lisdexamfetamine dimesylate in the treatment of ADHD in children 6–12 years of age who met DSM-IV-TR criteria for ADHD (combined type or predominantly hyperactive-impulsive type) have been evaluated in 2 randomized, double-blind, placebo-controlled clinical studies (one phase 2 and one phase 3). The phase 2 crossover study was conducted in an analog classroom environment. In this study, dosage of amphetamines was titrated over a 3-week period using an extended-release formulation of mixed amphetamine salts (Adderall XR®) to a final dosage of 10, 20, or 30 mg daily; the children then were assigned to receive, in randomly determined sequence, 1 week each of treatment with extended-release mixed amphetamine salts (continued at the same dosage), lisdexamfetamine dimesylate (30, 50, or 70 mg

daily, respectively, depending on the titrated amphetamines dosage), and placebo. The primary measure of efficacy was the Swanson, Kotkin, Agler, M-Flynn, and Pelham (SKAMP) deportment score. Assessments performed on day 7 of each treatment period (at various intervals from 2–12 hours after dosing) suggested that behavioral and symptomatic improvements observed with lisdexamfetamine were superior to those observed with placebo and not substantially different from those observed with mixed amphetamine salts. In the phase 3 parallel-group study, improvement in symptom scores, as measured using the ADHD Rating Scale version IV (ADHD-RS-IV), the revised Conners' Parent Rating Scale (CPRS-R), and the Cognitive Global Impression of Improvement (CGI-I) scale, from baseline to study end (4 weeks) was greater in children receiving lisdexamfetamine dimesylate titrated to a fixed, final dosage of 30, 50, or 70 mg daily than in those receiving placebo. Mean changes in symptom scores generally were similar for all 3 lisdexamfetamine dosage levels; however, changes in ADHD-RS-IV scores were numerically greater with the 70-mg dose than with the 30- and 50-mg doses. Symptom control in patients receiving the drug was maintained throughout the day up to 6 p.m.

Safety and efficacy of lisdexamfetamine in adults have been established in one phase 3 forced-titration, double-blind, randomized, placebo-controlled clinical study of 4 weeks' duration in 420 adults who met DSM-IV-TR criteria for ADHD. After a washout period, patients were randomized to receive 30, 50, or 70 mg of lisdexamfetamine dimesylate daily or placebo. All patients receiving lisdexamfetamine initially received 30 mg daily for the first week, with subsequent dosage titrations occurring in 20-mg increments at weekly intervals for those randomized to receive 50 or 70 mg of the drug daily. The primary measure of efficacy was the ADHD Rating Scale (ADHD-RS) score. At study end point (4 weeks), patients randomized to receive lisdexamfetamine demonstrated significant improvements in ADHD symptoms compared with placebo recipients. Significant improvements in ADHD symptoms were evident within the first week of treatment in all lisdexamfetamine groups. Patients randomized to receive lisdexamfetamine dimesylate 70 mg daily showed a greater reduction in ADHD-RS total score at weeks 3 and 4 compared with patients receiving lisdexamfetamine dimesylate 30 mg daily.

For further information on the management of ADHD, including the use of stimulants such as amphetamines, see Uses: Attention Deficit Hyperactivity Disorder in the Amphetamines General Statement 28:20.04, and also in Methylphenidate 28:20.92.

Dosage and Administration

■ **Administration** ***Oral Administration*** Administer once daily in the morning without regard to meals. Because of potential for insomnia, avoid administering in the afternoon.

Capsule may be swallowed whole or may be opened and the entire contents dissolved in water immediately prior to administration; resulting solution should *not* be stored for use at a later time.

Do *not* subdivide capsule contents; do *not* administer a dose less than the entire contents of one capsule.

■ **Dosage** Available as lisdexamfetamine dimesylate; dosage expressed in terms of the salt.

Adjust dosage according to individual response and tolerance; the smallest dose required to produce the desired response should always be used.

When possible, therapy should be interrupted occasionally to determine if there is a recurrence of behavioral symptoms sufficient to require continued treatment.

Pediatric Patients **Attention Deficit Hyperactivity Disorder.** *Oral*: Children 6–12 years of age: Initially, 30 mg once daily (as initial treatment for ADHD or in patients being switched to lisdexamfetamine from other drugs); dosage may be adjusted in 10- or 20-mg increments at weekly intervals up to a maximum dosage of 70 mg daily.

If the initial 30-mg daily dosage is not tolerated, dosage can be decreased to 20 mg daily.

Long-term use (i.e., exceeding 4 weeks) has not been studied systematically. If used for long-term therapy, periodically reevaluate the usefulness of the drug.

Adults **Attention Deficit Hyperactivity Disorder.** *Oral*: Initially, 30 mg once daily (as initial treatment for ADHD or in patients being switched to lisdexamfetamine from other drugs); dosage may be adjusted in 10- or 20-mg increments at weekly intervals up to a maximum dosage of 70 mg daily.

If the initial 30-mg daily dosage is not tolerated, dosage can be decreased to 20 mg daily.

Long-term use (i.e., exceeding 4 weeks) has not been studied systematically. If used for long-term therapy, periodically reevaluate the usefulness of the drug.

■ **Special Populations** No special population dosage recommendations at this time.

Cautions

■ **Contraindications** Contraindicated in patients with advanced arteriosclerosis, symptomatic cardiovascular disease, moderate to severe hypertension, hyperthyroidism, known hypersensitivity or idiosyncrasy to sympathomimetic amines, glaucoma, or a history of drug abuse; within 14 days of monoamine oxidase (MAO) inhibitor therapy; and in agitated patients.

Although amphetamines generally should not be used in patients with a history of drug abuse, some experts state that this is not an absolute contraindication, provided the patient can be monitored more carefully than would otherwise be indicated.

■ **Warnings/Precautions** ***Warnings*** **Abuse Potential.** Amphetamines have a high potential for abuse. Administration of amphetamines for prolonged periods of time may lead to drug dependence.

Particular attention should be paid to the possibility of individuals obtaining amphetamines for nontherapeutic use or distribution to others, and the drugs should be prescribed or dispensed sparingly. The possibility that family members may abuse the patient's medication should be considered.

Sudden Death and Serious Cardiovascular Events. Possible sudden death and serious cardiovascular events, particularly in individuals who abuse amphetamines.

Sudden unexplained death, stroke, and myocardial infarction have been reported in adults with ADHD receiving usual dosages of stimulants; sudden death also has been reported in children and adolescents with structural cardiac abnormalities or other serious cardiac conditions receiving usual dosages of the drugs. A small number of cases of sudden unexplained death also has been reported in children without structural cardiac abnormalities receiving amphetamine combinations; however, confounding factors were present in some of these incidents.

Results of one retrospective, case-control epidemiologic study showed a possible association between use of stimulant medications (amphetamine, dextroamphetamine, methamphetamine, methylphenidate, or their derivatives) and sudden unexplained death in healthy children and adolescents. (See Pediatric Use under Warnings/Precautions: Specific Populations, in Cautions.) Given the study limitations, the US Food and Drug Administration (FDA) is unable to conclude that these data affect the overall risk and benefit profile of stimulant medications used to treat ADHD in children and adolescents. Amphetamines or other stimulants should not be discontinued by parents of children or patients receiving these medications for ADHD before consulting with their clinician. Because of postmarketing reports and results of this and other epidemiologic studies, FDA is conducting an ongoing review of safety of amphetamines and other stimulants to evaluate a possible link between use of these agents and sudden death in children. To determine whether there is a direct causal relationship between use of stimulants and serious adverse cardiovascular events, the Agency for Healthcare Research and Quality (AHRQ) and FDA announced in 2007 that they are collaborating on a large study evaluating clinical data on approximately 500,000 adults and children who received these drugs for management of ADHD during a 7-year period ending in 2005; data collection for the study is expected to be completed in 2009.

Thoroughly review medical history (including evaluation for family history of sudden death or ventricular arrhythmia) *and* perform physical examination in all children, adolescents, and adults being considered for stimulant therapy; if initial findings suggest presence of cardiac disease, perform further cardiac evaluation (e.g., ECG, echocardiogram).

In general, *avoid* use of CNS stimulants in patients with known serious structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, coronary artery disease, or other serious cardiac conditions. (See Contraindications under Cautions.)

Patients who develop exertional chest pain, unexplained syncope, or other manifestations suggestive of cardiac disease during stimulant 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.

Other Warnings and Precautions Least amount of lisdexamfetamine feasible should be prescribed or dispensed at one time in order to minimize possible overdosage.

Effects on Blood Pressure and Heart Rate. Possible modest increases in average blood pressure (i.e., by about 2–4 mm Hg) and heart rate (i.e., by about 3–6 beats/minute); larger increases may occur. Modest increases not expected to have short-term sequelae; however, monitor all patients for *larger* changes in blood pressure and heart rate.

Caution advised in patients with underlying medical conditions that might be affected by increases in blood pressure or heart rate (e.g., hypertension, heart failure, recent myocardial infarction, ventricular arrhythmia).

Exacerbation or Precipitation of Psychotic Symptoms. May exacerbate symptoms of behavior disturbance and thought disorder in patients with preexisting psychotic disorder.

Psychotic symptoms (e.g., hallucinations, delusional thinking) may occur with usual dosages in children and adolescents without prior history of psychotic illness. If psychotic symptoms occur, consider causal relationship to stimulants, and discontinue therapy as appropriate.

Precipitation of Manic Symptoms. May precipitate mixed or manic episodes in ADHD patients with comorbid bipolar disorder; use with caution in these patients. Prior to initiating therapy, carefully screen patients with ADHD and comorbid depressive symptoms to identify risk for bipolar disorder; screening should include a detailed psychiatric history (e.g., family history of suicide, bipolar disorder, or depression).

Manic symptoms may occur with usual dosages in children and adolescents

without prior history of mania. If manic symptoms occur, consider causal relationship to stimulants, and discontinue therapy as appropriate.

Aggression. Aggressive behavior and hostility (frequently observed in children and adolescents with ADHD) reported in patients receiving drug therapy for ADHD. No systematic evidence that stimulants cause these adverse effects; however, monitor patients beginning treatment for ADHD for onset or worsening of aggressive behavior or hostility.

Growth Suppression. Long-term (i.e., exceeding 12 months) administration expected to cause at least a temporary suppression of normal weight and/or height patterns in some children and adolescents. Dose-related weight loss reported in children during 4 weeks of therapy with lisdexamfetamine.

Manufacturer recommends monitoring growth during treatment; patients not growing or gaining weight as expected may require temporary discontinuance of treatment. However, the American Academy of Pediatrics states that studies of stimulants in children found little or no decrease in expected height, with any decrease in growth early in treatment being compensated for later on.

Seizures. Possible lowering of seizure threshold in patients with history of seizures, in those with prior EEG abnormalities but no history of seizures, and, very rarely, in those without history of seizures and with no prior evidence of EEG abnormalities. If seizures occur, discontinue therapy.

Visual Effects. Visual disturbances (e.g., difficulty with accommodation, blurred vision) reported with stimulants.

Tics. Amphetamines reported to exacerbate motor and phonic tics and Tourette's syndrome. However, a history of tics or their development during therapy is *not* an absolute contraindication to continued use. Nevertheless, evaluate for presence of tics and Tourette's syndrome in children and their families prior to initiating stimulant therapy.

Other CNS Effects. Amphetamines may impair the ability to engage in potentially hazardous activities (e.g., operating machinery or vehicles).

Specific Populations **Pregnancy.** Category C.

Risk of prematurity, low birth weight, and withdrawal symptoms (e.g., dysphoria, lassitude, agitation) in infants born to dependent women.

Lactation. Distributed into milk; discontinue nursing or the drug.

Pediatric Use. Safety and efficacy of lisdexamfetamine not established in children 3–5 years of age. Amphetamines not recommended for ADHD in children younger than 3 years of age. Not studied to date in adolescents.

Aggressive behavior, hostility, and psychotic (e.g., hallucinations, delusional thinking) or manic symptoms reported in children and adolescents receiving stimulants for management of ADHD. (See Warnings under Cautions.)

Sudden death reported in children and adolescents with structural cardiac abnormalities or other serious cardiac conditions receiving usual dosages of stimulants. Sudden unexplained death also reported in a small number of children without structural cardiac abnormalities receiving amphetamine combinations. Results of one retrospective, case-control epidemiologic study suggested a possible association between use of stimulant medications and sudden unexplained death in healthy children and adolescents. (See Sudden Death and Serious Cardiovascular Events under Warnings/Precautions, in Cautions.)

Long-term administration expected to cause at least a temporary suppression of normal weight and/or height patterns in some children and adolescents. (See Growth Suppression under Cautions.)

Geriatric Use. Lisdexamfetamine has not been studied in this population.

Hepatic Impairment. Not specifically studied in hepatic impairment.

Renal Impairment. Not specifically studied in renal impairment.

■ **Common Adverse Effects** Children 6–12 years of age: Decreased appetite, insomnia, upper abdominal pain, irritability, vomiting, weight loss, nausea, dry mouth, dizziness, affect lability, rash, tic, pyrexia, somnolence.

Adults: Decreased appetite, insomnia, dry mouth, diarrhea, nausea, anxiety, anorexia, jitteriness, increased blood pressure, agitation, restlessness, hyperhidrosis, increased heart rate, tremor, dyspnea.

Drug Interactions

Active metabolite (dextroamphetamine) inhibits monoamine oxidase (MAO).

Lisdexamfetamine is not metabolized by cytochrome P-450 (CYP) isoenzymes. In vitro studies suggest only minor inhibition of CYP isoenzymes 1A2, 2D6, and 3A4 by amphetamine and/or its metabolites.

■ **Urinary Acidifying Agents** Increased urinary excretion and decreased serum concentrations and efficacy of amphetamines with concomitant use of urinary acidifying agents (ammonium chloride, sodium acid phosphate, cranberry juice).

■ **Adrenergic Blockers** Potential inhibition of adrenergic blockade.

■ **Alkalinizing Agents** Decreased urinary excretion of amphetamines with concomitant use of alkalinizing agents (carbonic anhydrase inhibitors, sodium bicarbonate).

■ **Tricyclic Antidepressants** Enhanced activity of tricyclic antidepressants; desipramine or protriptyline cause striking and sustained increases in the concentration of dextroamphetamine in the brain; cardiovascular effects can be potentiated.

■ **Antihistamines** Amphetamines may counteract the sedative effects of antihistamines.

■ **Antihypertensives** Amphetamines may antagonize the hypotensive effects of antihypertensives.

■ **Chlorpromazine** Chlorpromazine inhibits the central stimulant effects of amphetamines by blocking dopamine and norepinephrine receptors. Can be used to treat amphetamine poisoning.

■ **Ethosuximide** Intestinal absorption of ethosuximide may be delayed.

■ **Haloperidol** Haloperidol inhibits the central stimulant effects of amphetamines by blocking dopamine receptors.

■ **Lithium Carbonate** Lithium may inhibit the anorectic and stimulatory effects of amphetamine.

■ **MAO Inhibitors** MAO inhibitors slow the metabolism of amphetamines, increasing their effect on the release of norepinephrine and other monoamines leading to headaches and other signs of hypertensive crisis. Toxic neurologic effects, hypertensive crisis, and malignant hyperpyrexia can occur, sometimes with fatal results. Amphetamines contraindicated in patients currently or recently (within 14 days) receiving MAO inhibitor.

■ **Meperidine** Amphetamines potentiate the analgesic effect of meperidine.

■ **Methenamine** Acidifying agents used with methenamine increase urinary excretion and decrease efficacy of amphetamines.

■ **Norepinephrine** Amphetamines enhance the adrenergic effects of norepinephrine.

■ **Phenobarbital** Amphetamines may delay absorption of phenobarbital; concomitant use may produce a synergistic anticonvulsant action.

■ **Phenytoin** Amphetamines may delay absorption of phenytoin; concomitant use may produce a synergistic anticonvulsant action.

■ **Propoxyphene** In propoxyphene overdosage, amphetamine-induced CNS stimulation is potentiated and fatal convulsions can occur.

■ **Sympathomimetic Agents** Enhanced activity of sympathomimetic agents. Use with caution.

■ **Tests for Plasma Corticosteroids** Elevated plasma corticosteroid concentrations; this increase is greatest in the evening.

■ **Tests for Urinary Steroids** Possible interference with urinary steroid determinations.

■ **Veratrum Alkaloids** Amphetamines inhibit the hypotensive effect of veratrum.

Description

Lisdexamfetamine, a prodrug of dextroamphetamine, is a CNS stimulant. Lisdexamfetamine is inactive until hydrolyzed in vivo to *l*-lysine, a naturally occurring essential amino acid, and dextroamphetamine, which is responsible for the drug's activity. For information on the pharmacology of amphetamines, see Pharmacology in the Amphetamines General Statement 28:20.04.

Lisdexamfetamine is rapidly absorbed from the GI tract; following oral administration, the onset of action occurs within 2 hours. Conversion of lisdexamfetamine to *l*-lysine and dextroamphetamine is thought to occur by first-pass intestinal and/or hepatic metabolism. Lisdexamfetamine is not metabolized by the cytochrome P-450 (CYP) enzyme system, and the ability of dextroamphetamine to inhibit this enzyme pathway has not been fully elucidated. In vitro studies with human microsomes indicate minor inhibition of CYP isoenzymes 1A2, 2D6, and 3A4 by amphetamine and/or its metabolites. The plasma half-lives of lisdexamfetamine and dextroamphetamine are less than 1 hour and 9.4–9.7 hours, respectively. Approximately 96% of a radiolabeled dose of lisdexamfetamine is excreted in urine, with the parent drug accounting for only about 2% of the recovered radioactivity.

Advice to Patients

Provide patient or caregiver with a copy of the manufacturer's patient information (medication guide); discuss and answer questions about its contents as needed. Instruct patient or caregiver to read and understand contents of medication guide before initiating therapy and each time the prescription is refilled.

Advise parents with concerns about long-term effects (e.g., effects on weight) and the need for continued therapy that drug holidays can be considered in consultation with the patient's clinician. However, the benefits versus risks of such interruptions in therapy have not been established.

Question about possible substance abuse, including in other family members (since they may abuse the patient's medication supply).

Advise to take drug in the morning to minimize insomnia.

Advise that appetite suppression may occur. Giving the morning dose with a meal and providing a high-caloric drink or snack late in the evening when the stimulant effects have subsided may be helpful.

Advise to inform clinician immediately if adverse cardiovascular (e.g., chest pain, shortness of breath, fainting) or psychiatric effects (e.g., hallucinations, delusional thinking, mania) occur.

Instruct about the potential for amphetamines to impair patient's ability to perform potentially hazardous activities, such as driving or operating heavy machinery.

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., cardiac/cardiovascular disease, thyroid disease, glaucoma, suicidal ideation or behaviors, mental/psychiatric disorder, seizures).

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

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

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

Preparations

Subject to control under the Federal Controlled Substances Act of 1970 as a schedule II (C-II) drug.

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

Lisdexamfetamine Dimesylate

Oral

Capsules	20 mg	Vyvanse® (C-II), Shire
	30 mg	Vyvanse® (C-II), Shire
	40 mg	Vyvanse® (C-II), Shire
	50 mg	Vyvanse® (C-II), Shire
	60 mg	Vyvanse® (C-II), Shire
	70 mg	Vyvanse® (C-II), Shire

Methamphetamine Hydrochloride

Desoxyephedrine Hydrochloride

■ Methamphetamine hydrochloride, the dextrorotatory isomer of phenylmethylamine, has pharmacologic actions that are qualitatively similar to those of amphetamine and ephedrine.

Uses

Methamphetamine has been used as an adjunct to caloric restriction in the short-term (i.e., a few weeks) treatment of exogenous obesity. However, short-term or intermittent therapy with methamphetamine is unlikely to maintain a long-term benefit, and prolonged administration of methamphetamine for the treatment of obesity is not indicated. Methamphetamine also is used as an adjunct to psychological, educational, social, and other remedial measures in the treatment of attention deficit hyperactivity disorder (ADHD). Methamphetamine also has been misused and abused for its CNS stimulatory effects.

■ **Exogenous Obesity** Methamphetamine has been used as an adjunct to caloric restriction in the short-term (i.e., a few weeks) treatment of exogenous obesity. The anorexigenic effect of sympathomimetic compounds used in the treatment of obesity is temporary, seldom lasting more than a few weeks, and tolerance may occur. However, obesity usually is a chronic disease, and short-term or intermittent therapy with these drugs is unlikely to maintain a long-term benefit; therefore, short-term use of anorexigenic agents, including methamphetamine, is not recommended. Furthermore, prolonged administration of methamphetamine in the treatment of obesity is not indicated. (See Cautions: Precautions and Contraindications.) To help bring about and maintain loss of weight, the patient must be taught to curtail overeating and to consume a suitable diet. For further information on the treatment of exogenous obesity, see Uses: Exogenous Obesity, in the Amphetamines General Statement 28:20.04.

■ **Attention Deficit Hyperactivity Disorder** Methamphetamine also 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 children older than 6 years of age.

Methamphetamine should not be used to combat fatigue or exhaustion or to replace sleep in normal persons.

ADHD usually is characterized by developmentally inappropriate symptoms (e.g., moderate to severe distractibility, short attention span, hyperactivity, emotional lability, impulsivity). The final diagnosis of this disorder should not be made if these symptoms are of only comparatively recent origin. Nonlocalizing (soft) neurologic signs, learning disability, and abnormal EEG may or may not be present, and a diagnosis of CNS dysfunction may or may not be warranted. Drug therapy is not indicated in all children with ADHD, and such therapy should be considered only after a complete evaluation including medical history has been performed. The decision to use amphetamines should depend on the age of the child and the physician's assessment of the severity and duration of symptoms and should not depend solely on one or more behavioral characteristics. When symptoms of ADHD are associated with acute stress reactions, use of amphetamines usually is not recommended. For a more detailed discussion on the management of ADHD, including the use of stimulants such as methamphetamine, see Uses: Attention Deficit Hyperactivity Disorder, in Methylphenidate 28:20.92.

■ **Misuse and Abuse** Misuse and abuse of amphetamines, especially methamphetamine, for CNS stimulatory effects have experienced a resurgence. In large part, this resurgence has resulted from the relative ease with which methamphetamine can be synthesized clandestinely from readily available chemicals such as ephedrine, phenylpropanolamine (no longer commercially available in the US), or pseudoephedrine. (See Chronic Toxicity, in the Amphetamines General Statement 28:20.04.) Legal restrictions, including enactment of the US Comprehensive Methamphetamine Control Act of 1996 and later the Methamphetamine Anti-Proliferation Act of 2000 and the Combat Methamphetamine Epidemic Act of 2005, on the availability of these compounds have been enacted in an effort to reverse this resurgence in misuse and abuse.

Dosage and Administration

■ **Administration** Methamphetamine hydrochloride is administered orally. Because of the potential for insomnia, administration of methamphetamine in the late evening should be avoided.

■ **Dosage** Dosage and potency of methamphetamine hydrochloride are expressed in terms of the hydrochloride. (See Chemistry and Stability: Chemistry.)

Dosage of methamphetamine hydrochloride should be adjusted according to individual response and tolerance; the smallest dose required to produce the desired response should always be used.

Exogenous Obesity As an adjunct in the treatment of exogenous obesity, the usual adult dosage of methamphetamine hydrochloride is 2.5–5 mg 2 or 3 times daily, given one-half hour before meals. Treatment should not exceed a duration of a few weeks.

Attention Deficit Hyperactivity Disorder As an adjunct in the treatment of attention deficit hyperactivity disorder (ADHD) in children 6 years of age and older, the usual initial dosage of methamphetamine hydrochloride is 5 mg once or twice daily. Daily dosage may be increased by 5 mg at weekly intervals until an optimum clinical response is achieved. The usual effective dosage is 20–25 mg daily. The total daily dose may be given as conventional tablets in 2 divided doses daily.

When possible, therapy should be interrupted occasionally to determine if there is a recurrence of behavioral symptoms sufficient to require continued treatment.

Cautions

Methamphetamine shares the toxic potentials of amphetamines, and the usual cautions, precautions, and contraindications of amphetamine therapy should be observed. (See Cautions, in the Amphetamines General Statement 28:20.04.)

■ **Cardiovascular Effects** Sudden death, stroke, myocardial infarction, hypertension or hypotension, tachycardia, palpitation, or cardiac arrhythmias may occur in patients receiving stimulants, including methamphetamine. (See Cardiovascular Precautions under Cautions: Precautions and Contraindications, in the Amphetamines General Statement 28:20.04.) Fatal cardiorespiratory arrest has been reported following abuse or misuse of methamphetamine.

■ **Nervous System Effects** Adverse nervous system effects of methamphetamine may include nervousness, insomnia, irritability, talkativeness, dizziness, headache, blurred vision, mydriasis, dizziness, dysphoria, euphoria, tremor, restlessness and hyperexcitability. Rarely, psychotic episodes have occurred in patients receiving recommended dosages. The drug may also exacerbate motor and vocal ties and Tourette's disorder. Seizures, aggressive behavior, and hostility also have been reported with stimulants. (See Psychiatric Precautions under Cautions: Precautions and Contraindications, in the Amphetamines General Statement 28:20.04.)

■ **GI Effects** GI disturbances of methamphetamine may include nausea, vomiting, abdominal cramps, diarrhea or constipation, dryness of the mouth, anorexia, and unpleasant taste.

■ **Other Adverse Effects** Urticaria, impotence, and changes in libido may occur in patients receiving methamphetamine. Visual disturbances (difficulty with accommodation, blurred vision) have been reported with stimulants.

■ **Precautions and Contraindications** The manufacturer's patient information (medication guide) should be provided to the patient or caregiver each time methamphetamine is dispensed, and the clinician should discuss and answer questions about its contents (e.g., benefits and risks of stimulant therapy, appropriate use) as needed. The patient or caregiver also should be instructed to read and understand the contents of the medication guide before initiating therapy and each time the prescription is refilled.

Patients should be warned that methamphetamine may impair their ability to perform hazardous activities requiring mental alertness or physical coordination (e.g., operating machinery, driving a motor vehicle).

Methamphetamine should be administered with caution, if at all, to patients with hyperexcitability states or to those receiving drugs that may produce this