AHFS® DRUG INFORMATION

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Thioridazine

Thioridazine Hydrochloride

AHFS Class: Phenothiazines (28:16.08.24)

VA Class: CN701

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Introduction

Thioridazine is a phenothiazine antipsychotic agent. The drug is considered a conventional or first-generation antipsychotic agent.[100]

See Uses in the associated General Statement for more information.

Uses

■ Psychotic Disorders

Thioridazine is used for the symptomatic management of psychotic disorders. However, because thioridazine has the potential for substantial, and possibly life-threatening, proarrhythmic effects and can precipitate sudden death, use of the drug is reserved for patients with schizophrenia whose disease fails to respond adequately to appropriate courses with at least 2 different antipsychotic agents, either because of insufficient efficacy or the inability to achieve an effective dosage due to intolerable adverse effects. In addition, use of thioridazine in patients with refractory schizophrenia has not been evaluated in controlled clinical trials and efficacy of the drug in such patients is not known.

Drug therapy is integral to the management of acute psychotic episodes and accompanying violent behavior in patients with schizophrenia and generally is required for long-term stabilization to improve symptoms between episodes and to minimize the risk of recurrent acute episodes. Antipsychotic agents are the principal class of drugs used for the management of all phases of schizophrenia and generally are effective in all subtypes of the disorder and subgroups of patients. Patient response and tolerance to antipsychotic agents are variable, and patients who do not respond to or tolerate one drug may be successfully treated with an agent from a different class or with a different adverse effect profile. For additional information on the symptomatic management of schizophrenia, see Uses: Psychotic Disorders, in the Phenothiazines General Statement 28:16.08.24.

■ Other Uses

Thioridazine is used for the short-term treatment of adults with major depression who have varying degrees of associated anxiety, and for the symptomatic management of agitation, anxiety, depressed mood, tension, sleep disturbances, and fears in geriatric patients (see Cautions).

Thioridazine also has been used for the treatment of severe behavioral problems in children marked by combativeness and/or explosive hyperexcitable behavior (out of proportion to immediate provocations), and for the short-term treatment of hyperactive children who exhibit excessive motor activity with accompanying conduct disorders. However, the possible risks of developing tardive dyskinesia, withdrawal dyskinesia, and other extrapyramidal reactions associated with the drug should be considered. Some clinicians recommend routine administration of the Abnormal Involuntary Movement Scale (AIMS) to all children receiving antipsychotic agents for this indication.

See Dosage and Administration in the associated General Statement for more information.

Dosage and Administration

■ Administration

Thioridazine and thioridazine hydrochloride are administered orally. When thioridazine hydrochloride oral concentrate solution is used, the dose should be diluted (e.g., with water or fruit juice) just before administration.

■ Dosage

Dosage of thioridazine and thioridazine hydrochloride is expressed in terms of the hydrochloride salt. Dosage must be carefully adjusted according to individual requirements and response using the lowest possible effective dosage. Dosage should be increased more gradually in debilitated or geriatric patients.

Psychotic Disorders

For the symptomatic management of psychotic disorders, the usual initial adult dosage of thioridazine is 50–100 mg 3 times daily. Dosage may gradually be increased, depending on the patient's therapeutic response and tolerance. The manufacturer recommends that dosages greater than 300 mg daily be reserved for adults with severe neuropsychiatric conditions. Dosages up to 800 mg daily given in 2–4 divided doses may be required in hospitalized, institutionalized, or severely psychotic adults. Dosage during prolonged maintenance therapy with thioridazine should be kept at the lowest effective level; once an adequate response has been obtained, dosage should be gradually reduced and subsequently adjusted according to the patient's therapeutic response and tolerance. Because of the risk of adverse reactions associated with cumulative effects of phenothiazines, patients with a history of long-term therapy with thioridazine and/or other antipsychotic agents should be evaluated periodically to determine whether drug therapy could be discontinued.

For the management of hospitalized, severely disturbed, or psychotic children 2–12 years of age, the usual initial dosage of thioridazine is 0.5 mg/kg daily, administered in divided doses. Dosage may be gradually increased until optimum therapeutic effect is obtained. Dosage for children should not exceed 3 mg/kg daily.

Other Conditions

For the short-term treatment of adults with major depression who also have varying degrees of associated anxiety, or for the symptomatic management of agitation, anxiety, depressed mood, tension, sleep disturbances, and fears in geriatric patients (see Cautions), the usual initial dosage of thioridazine is 25 mg 3 times daily. Dosage ranges from 20–200 mg daily in these patients, depending on the severity of the condition.

See Cautions in the associated General Statement for more information.

Cautions

Thioridazine shares the toxic potentials of other phenothiazines, and the usual precautions of phenothiazine therapy should be observed. (See Cautions in the Phenothiazines General Statement 28:16.08.24.) At recommended dosages, adverse effects of thioridazine are generally mild and transient.

Geriatric patients with dementia-related psychosis treated with either conventional (first-generation) or atypical (second-generation) antipsychotic agents are at an increased risk of mortality.[101] [102] [103] [104] For additional information on the use of antipsychotic agents for dementia-associated psychosis and other behavioral disturbances, see Geriatric Considerations under Psychotic Disorders: Schizophrenia and Other Psychotic Disorders, in Uses and see Cautions: Geriatric Precautions, in the Phenothiazines General Statement 28:16.08.24.

Care should be taken to avoid skin contact with thioridazine oral suspension or thioridazine hydrochloride oral concentrate solution, since contact dermatitis has occurred rarely.

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 thioridazine oral liquid with carbamazepine oral suspension also results in a rubbery, orange precipitate, it has been recommended that thioridazine oral liquid not be administered simultaneously with carbamazepine oral suspension. It is not known whether the development of this precipitate results in decreased bioavailability of either thioridazine or carbamazepine.

■ Arrhythmias and Associated Precautions and Contraindications

Dose-related serious cardiac effects, including prolongation of the QT interval corrected for rate (QT_C), arrhythmias (e.g., atypical ventricular tachycardia [torsades de pointes]), and/or sudden death, have been reported in patients receiving thioridazine. A causal relationship to the drug has not been established; however, since thioridazine and its major metabolite mesoridazine have been shown to prolong the QT_C interval, such a relationship is possible. Although, thioridazine has been shown to prolong the QT_C interval in a dose-dependent manner, prolongation of the QT_C interval and sudden death have been reported occasionally at usual dosages. In a crossover study, healthy men receiving a single 50-mg dose of thioridazine hydrochloride had a greater increase in QT_C interval (mean maximum of about 23 msec) than those receiving either a 10-mg dose or placebo; however, the manufacturer states that even further prolongation of the QT_C interval may be observed in clinical practice.

The risk of atypical ventricular tachycardia (e.g., torsades de pointes) and/or sudden death may be increased in patients with bradycardia, hypokalemia, or congenital long QT syndrome and in those receiving thioridazine concomitantly with drugs that can prolong the QT_C interval. Use of antiarrhythmic agents (e.g., disopyramide, procainamide, quinidine) that can prolong the QT_C interval and potentially exacerbate the cardiotoxic effects of thioridazine should be avoided in treating arrhythmias associated with the antipsychotic agent. (See Acute Toxicity: Treatment.) In patients who experience symptoms of possible atypical ventricular tachycardia (torsades de pointes), such as dizziness, palpitations, or syncope, further cardiac evaluation (e.g., Holter monitoring) should be considered.

Cardiotoxic effects may be associated with increased plasma concentrations of thioridazine and its metabolites. Increased plasma concentrations of the drug are most likely to develop in patients with poor metabolizer phenotypes of the cytochrome P-450 (CYP) 2D6 isoenzyme; and in patients receiving drugs known to inhibit the CYP2D6 isoenzyme (e.g., fluoxetine, paroxetine) or reduce the clearance of thioridazine by other mechanisms (e.g., fluvoxamine, pindolol, propranolol).

Because thioridazine may be associated with serious adverse cardiac effects, ECG and serum potassium concentrations should be determined at baseline and periodically thereafter; such monitoring may be particularly useful during a period of dosage adjustment. Serum potassium concentrations should be within the normal range before thioridazine therapy is initiated; patients with a QT_C interval exceeding 450 msec should not receive thioridazine. Thioridazine should be discontinued if the QT_C interval exceeds 500 msec. Patients receiving thioridazine should be informed about the risk of developing adverse cardiac effects and the possibility of switching from thioridazine to another antipsychotic agent should be considered based on the possible risks and likely benefits associated with thioridazine.

Because thioridazine has been shown to be more cardiotoxic in overdosage than other antipsychotic agents, some clinicians caution against its use in actively suicidal patients.

Patients receiving of thioridazine concomitantly with drugs that prolong the QT_C interval, inhibit the CYP2D6 isoenzyme (e.g., fluoxetine, paroxetine), or reduce clearance of the phenothiazine by other mechanisms (e.g., fluvoxamine, pindolol, propranolol); those with poor metabolizer phenotypes of the CYP2D6 isoenzyme; and those with underlying conditions that might prolong the QT_C interval (e.g., congenital long QT syndrome, history of arrhythmias) may be at increased risk of developing cardiac arrhythmias (e.g., atypical ventricular tachycardia [torsades de pointes]) that may be fatal. Therefore, use of thioridazine in such patients is contraindicated.

Drug Interactions

■ Drugs Affecting Hepatic Microsomal Enzymes

Drugs that inhibit the cytochrome P-450 (CYP) 2D6 isoenzyme (e.g., fluoxetine, paroxetine) appear to inhibit the metabolism of the phenothiazine which has resulted in elevated plasma concentrations of the phenothiazine. Since thioridazine has been shown to prolong the QT interval corrected for rate (QT_C) in a dose-dependent manner, increased plasma concentrations of the drug may be expected to augment such prolongation and thus may increase the risk of serious, potentially fatal, cardiac arrhythmias (e.g., atypical ventricular tachycardia [torsades de pointes]). Therefore, concomitant use of thioridazine with drugs that inhibit the CYP2D6 isoenzyme is contraindicated.

■ Other Drugs that Reduce Clearance of Thioridazine

Fluvoxamine

In a limited number of male patients with schizophrenia, concomitant use of thioridazine and fluvoxamine (25 mg twice daily for 1 week) resulted in a threefold increase in steady-state plasma concentrations of thioridazine and its 2 active metabolites (mesoridazine and sulforidazine). Therefore, fluvoxamine and thioridazine should not be used concomitantly.

Propranolol

Concomitant use of propranolol (100–800 mg daily) and thioridazine reportedly resulted in increased plasma concentrations of thioridazine (approximately 50–400%) and its metabolites (approximately 80–300%). Therefore, propranolol and thioridazine should not be used concomitantly.

Pindolol

Concomitant use of pindolol and thioridazine has resulted in moderate, dose-related increases in serum concentrations of thioridazine and 2 of its metabolites in addition to higher than expected serum concentrations of pindolol. Therefore, pindolol and thioridazine should not be used concomitantly.

■ Drugs that Prolong QT_C Interval

Although specific drug interaction studies have not been performed to evaluate the concomitant use of thioridazine with drugs that prolong the QT_C interval, the manufacturers state that additive effects of such concomitant therapy on the QT_C interval can be expected. Therefore, concomitant use of thioridazine with these drugs is contraindicated.

See Lab Test Interferences in the associated General Statement for more information.

Acute Toxicity

■ Pathogenesis

Although the minimum toxic or lethal doses and blood concentrations of thioridazine remain to be definitely established, it has been suggested that blood thioridazine concentrations of 1 mg/dL or greater are toxic, and those of 2–8 mg/dL are potentially lethal.

■ Manifestations

Overdosage of phenothiazines (e.g., thioridazine) may be expected to produce effects that are extensions of common adverse effects. (See Acute Toxicity: Manifestations, in the Phenothiazines General Statement 28:16.08.24.) However, results of case reports and several studies suggest that overdosage of thioridazine may be associated with cardiotoxicity (e.g., prolongation of QT intervals and QRS complex) more frequently than other antipsychotic agents.

■ Treatment

Management of thioridazine overdosage generally involves symptomatic and supportive care with cardiovascular (e.g., ECG) monitoring. A patent airway must be established and maintained, and adequate oxygenation and ventilation must be ensured.

Following acute ingestion of thioridazine, gastric lavage and repeated doses of activated charcoal should be considered. Induction of emesis is less preferable to gastric lavage because of the risk of dystonia and the potential for aspiration of vomitus. In addition, emesis should not be induced in patients expected to deteriorate rapidly or in those with impaired consciousness.

To detect arrhythmias, continuous ECG monitoring may be necessary for at least 24 hours or for as long as the QT_C is prolonged. Management of thioridazine-induced arrhythmias may include ventricular pacing, defibrillation, administration of IV magnesium sulfate, lidocaine, phenytoin, or isoproterenol and correction of electrolyte abnormalities and/or acid-base balance. Lidocaine must be administered with caution in patients with overdosage of thioridazine since use of this antiarrhythmic in such patients may increase the risk of developing seizures. Antiarrhthmic agents that can prolong the QT interval (e.g., class IA [disopyramide, procainamide, quinidine] or III agents) should be *avoided* in treating overdosage-associated arrhthmias in which prolongation of the QT_C is a manifestation. For additional information on treatment of acute toxicity, see Acute Toxicity: Treatment, in the Phenothiazines General Statement 28:16.08.24.

See Pharmacology in the associated General Statement for more information.

Pharmacology

The principal pharmacologic effects of thioridazine are similar to those of chlorpromazine. On a weight basis, thioridazine is about as potent as chlorpromazine. Thioridazine has strong anticholinergic and sedative effects and weak extrapyramidal effects. Thioridazine has little antiemetic activity.

See Pharmacokinetics in the associated General Statement for more information.

See Chemistry and Stability in the associated General Statement for more information.

Chemistry and Stability

■ Chemistry

Thioridazine is a phenothiazine antipsychotic agent. The drug is an alkylpiperidine derivative of phenothiazine which differs structurally from other phenothiazine derivatives in the presence of a thiomethyl group at the 2 position of the phenothiazine nucleus. Thioridazine is commercially available as the base and as the hydrochloride salt. Each 110 mg of thioridazine hydrochloride is approximately equivalent to 100 mg of thioridazine.

Thioridazine occurs as a white or slightly yellow, crystalline or micronized powder, which is odorless or has a faint odor and is practically insoluble in water and freely soluble in dehydrated alcohol. Thioridazine hydrochloride occurs as a white to slightly yellow, granular powder with a faint odor and a very bitter taste, and is freely soluble in water.

■ Stability

Commercially available thioridazine hydrochloride oral concentrate solution should be stored in tight, light-resistant containers at a temperature less than 30°C, preferably between 15–30°C; freezing should be avoided. Thioridazine hydrochloride tablets should be protected from light and stored in well-closed containers at a temperature less than 40°C, preferably at 15–30°C.

Testing has shown that mixing thioridazine oral liquid with carbamazepine oral suspension results in a rubbery, orange precipitate. (See Cautions.) It is not known whether the development of this precipitate results in decreased bioavailability of either thioridazine or carbamazepine. Therefore, it is recommended that thioridazine oral liquid not be administered simultaneously with carbamazepine oral suspension.

For further information on chemistry and stability, pharmacology, pharmacokinetics, uses, cautions, acute toxicity, drug interactions, and dosage and administration of thioridazine, see the Phenothiazines General Statement 28:16.08.24.

Preparations

Excipients in commercially available drug preparations may have clinically important effects in some individuals; consult specific

product labeling for details.

Thioridazine Hydrochloride

Routes	Forms	Strengths	Brand Names	Manufacturer
Oral	Solution, concentrate	30 mg/mL*	Thioridazine Oral Solution	Roxane
		100 mg/mL*	Thioridazine Oral Solution	Actavis, Roxane
	Tablets	10 mg*	Thioridazine Tablets	Mutual, Mylan
		15 mg*	Thioridazine Tablets	Geneva
		25 mg*	Thioridazine Tablets	Mutual, Mylan
		50 mg*	Thioridazine Tablets	Mutual, Mylan
		100 mg*	Thioridazine Tablets	Mutual, Mylan
		150 mg*	Thioridazine Tablets	Geneva
		200 mg*	Thioridazine Tablets	Geneva

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

■ **Comparative Pricing**

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

Thioridazine HCl 10MG Tablets (MYLAN): 90/$21.99 or 270/$41.96

Thioridazine HCl 100MG Tablets (MYLAN): 90/$34.99 or 270/$87.97

Thioridazine HCl 25MG Tablets (MYLAN): 90/$25.97 or 270/$55.97

Thioridazine HCl 50MG Tablets (MYLAN): 90/$29.99 or 270/$79.97

References

Please see the general statement for a list of references.

Only references cited for selected revisions after 1984 are available electronically.

100. American Psychiatric Association. Practice guideline for the treatment of patients with schizophrenia, second edition. From the APA website.

101. Food and Drug Administration. FDA Alert: Information for healthcare professionals: antipsychotics. Rockville, MD; 2008 Jun 16. From the FDA website.

102. Food and Drug Administration. FDA News: FDA requests boxed warnings on older class of antipsychotic drugs. Rockville, MD; 2008 Jun 16. From the FDA website.

103. Schneeweiss S, Setoguchi S, Brookhart A et al. Risk of death associated with the use of conventional versus atypical antipsychotic drugs among elderly patients. *CMAJ*. 2007; 176:627-32. PubMed FREE full text article in PubMed Central

104. Gill SS, Bronskill SE, Normand SL et al. Antipsychotic drug use and mortality in older adults with dementia. *Ann Intern Med*. 2007; 146:775-86. PubMed

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

Because steady-state plasma concentrations of concomitantly administered anticonvulsants may be altered in patients receiving combination therapy including felbamate, monitoring of plasma concentrations of other anticonvulsant agents and appropriate adjustment of felbamate and/or other anticonvulsant dosage may be necessary during concomitant therapy; the value of monitoring plasma concentrations of felbamate has not been established. Specialized references and the manufacturer's labeling should be consulted for specific recommendations. Although clinical trials indicate that routine monitoring of laboratory parameters is not necessary for safe use of felbamate, clinicians should exercise clinical judgment regarding monitoring of laboratory parameters during therapy with the drug.

Patients receiving felbamate should be instructed to take the drug only as prescribed and to store the drug in its tightly closed container at room temperature away from excessive heat, direct sunlight, moisture, and children.

Because of the possibility of increasing seizure frequency, anticonvulsant drugs, including felbamate, should not be discontinued suddenly.

Felbamate is contraindicated in patients with known hypersensitivity to the drug or any ingredient in the formulation. The drug also is contraindicated in patients who have demonstrated hypersensitivity reactions to other carbamates. Felbamate should not be used in patients with a history of any blood dyscrasia or hepatic dysfunction.

■ **Pediatric Precautions** Felbamate is indicated as adjunctive therapy for the treatment of partial and generalized seizures associated with Lennox-Gastaut syndrome in children 2–14 years of age; safety and efficacy of the drug for this indication in children younger than 2 years of age have not been established. Safety and efficacy of felbamate for other indications in children have not been established.

■ **Geriatric Precautions** Safety and efficacy of felbamate in geriatric patients have not been evaluated systematically, and clinical trials did not include sufficient numbers of patients older than 65 years of age to determine whether they respond differently than younger patients. Other clinical experience has not identified any differences in responses between geriatric and younger patients. If felbamate is used in geriatric patients, the initial dosage usually should be at the low end of the dosage range and caution should be exercised since renal, hepatic, and cardiovascular dysfunction and concomitant disease or other drug therapy are more common in this age group than in younger patients.

■ **Mutagenicity and Carcinogenicity** No evidence of mutagenicity was demonstrated by felbamate in the Ames *Salmonella* microbial mutagen test, the CHO/HGPRT mammalian cell forward gene mutation assay, the sister chromatid exchange assay in CHO cells, or bone marrow cytogenetics assay.

Studies to determine the carcinogenic potential of felbamate were performed in mice and rats. Mice received felbamate orally in dosages of 300, 600, and 1200 mg/kg daily for 92 weeks, while male rats received the drug orally in dosages of 30, 100, and 300 mg/kg and female rats received 10, 30, and 100 mg/kg daily for 104 weeks. The maximum dosages used in these studies produced steady-state plasma felbamate concentrations that were equal to or less than the steady-state plasma concentrations in patients with epilepsy receiving 3600 mg of the drug daily. There was an increase in hepatic cell adenomas in male and female mice receiving the high dosages as well as in female rats receiving the high dosages. Hepatic hypertrophy also was increased in a dose-related manner in mice, principally in males, but also in females. Hepatic hypertrophy was not found in female rats. The relationship between the occurrence of benign hepatocellular adenomas and the finding of liver hypertrophy resulting from hepatic enzyme induction has not been evaluated. There also was an increase in benign interstitial cell tumors of the testes in male rats receiving high dosages of felbamate. The relevance of these findings to humans is not known.

As a result of the synthetic process involved in producing felbamate, the drug could contain small amounts of two known animal carcinogens, the genotoxic compound ethyl carbamate (urethane) and the nongenotoxic compound methyl carbamate. Theoretically, it is possible that a 50-kg patient receiving 3600 mg of felbamate could be exposed to up to 0.72 mcg of urethane and 1800 mcg of methyl carbamate. These daily doses of urethane and methyl carbamate are approximately 1/35,000 and 1/5500, respectively, on a mg/kg basis (1/10,000 and 1/1600, respectively, on a mg/m² basis) of the dose levels shown to be carcinogenic in rodents. Any presence of these two compounds in felbamate used in the lifetime carcinogenicity studies was inadequate to cause tumors.

■ **Pregnancy, Fertility, and Lactation** Reproduction studies in rats and rabbits receiving felbamate doses of up to 13.9 and 4.2 times, respectively, the human daily dose of the drug on mg/kg basis (3 and less than 2 times, respectively, the human daily dose on a mg/m² basis) did not reveal evidence of teratogenicity; however, in rats, there was a decrease in pup weight and an increase in pup deaths during lactation. The cause of these deaths is not known. The dose at which there was no effect on rat pup mortality was 6.9 times the human dose on a mg/kg basis (1.5 times the human dose on a mg/m² basis). Felbamate crosses the placenta in rats. There are, however, no adequate and controlled studies to date using the drug in pregnant women, and the effect of felbamate on labor and delivery in humans also is not known. Placental disorder, fetal death, microcephaly, genital malformation, and sudden infant death syndrome (SIDS) have been reported with felbamate, usually when used as adjunctive therapy; however, a causal relationship to the drug has not been established. Felbamate should be used during pregnancy only when clearly needed.

Reproduction studies in rats revealed no evidence of impaired fertility in males or females receiving oral felbamate dosages of up to 13.9 times the human total daily dosage of 3600 mg on a mg/kg basis (up to 3 times the human total daily dosage on a mg/m² basis).

Felbamate is distributed into milk. Since the potential effect in nursing infants is not known, felbamate should be used with caution in nursing women.

Description

Felbamate, a dicarbamate, is an anticonvulsant agent. Felbamate is structurally related to but pharmacologically distinct from meprobamate. Felbamate has a unique spectrum of activity compared with other currently available anticonvulsants.

The exact mechanism of action of felbamate is not known, but available data suggest that the drug increases seizure threshold and reduces seizure spread. A predominant effect on any particular cell process has not been demonstrated to date, but felbamate appears to exhibit a spectrum of anticonvulsant activity that is pharmacologically distinct from other currently available agents. In animals, felbamate protects against seizures induced by electrical stimulation, suggesting that it would be effective in the management of tonic-clonic (grand mal) seizures and partial seizures. In animals, felbamate also protects against seizures induced by pentylenetetrazol, indicating that it may be effective in the management of absence (petit mal) seizures. Felbamate also protects against seizures in animals induced by picrotoxin, glutamate, or *N*-methyl-D-aspartic acid; it does not protect against seizures induced by bicuculline or strychnine.

In vitro studies indicate that felbamate has weak inhibitory effects on binding at γ-aminobutyric acid (GABA) receptors and benzodiazepine receptors. The monocarbamate, *p*-hydroxy, and 2-hydroxy metabolites of felbamate appear to contribute little, if any, to the anticonvulsant action of the drug.

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

Preparations

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

Felbamate

Oral		
Suspension	600 mg/5 mL	Felbatol®, Meda
Tablets	400 mg	Felbatol® (scored), Meda
	600 mg	Felbatol® (scored), Meda

Gabapentin

■ Gabapentin is an anticonvulsant structurally related to the inhibitory CNS neurotransmitter γ-aminobutyric acid (GABA).

Uses

■ **Seizure Disorders** Gabapentin is used in combination with other anticonvulsant agents in the management of partial seizures with or without secondary generalization in adults and children 12 years of age and older and in the management of partial seizures in children 3–12 years of age. Although the comparative efficacy of therapeutically effective dosages of gabapentin versus other anticonvulsants remains to be established, the anticonvulsant potential of

gabapentin has been established in studies in which gabapentin or placebo was administered as adjunctive therapy in adults and children older than 3 years of age with refractory partial seizures.

In several placebo-controlled clinical studies, gabapentin was effective in reducing seizure frequency, including that of secondarily generalized tonic-clonic seizures, in 17–26% of patients with partial seizures refractory to therapy with conventional anticonvulsant drugs (e.g., phenytoin, carbamazepine, phenobarbital, valproic acid). Patients in these studies had a history of at least 4 partial seizures (with or without secondary tonic-clonic generalization) per month despite optimum therapy with one or more anticonvulsants and were eligible for study entry if they continued to have at least 2–4 seizures per month during a 12-week baseline period while receiving their established anticonvulsant regimen. Efficacy of gabapentin in these studies was evaluated principally in terms of the percentage of patients with a reduction in seizure frequency of 50% or greater compared with baseline values (i.e., responder rate) and the change in seizure frequency associated with the addition of gabapentin or placebo to existing anticonvulsant treatment (i.e., response ratio, calculated as treatment seizure frequency minus baseline seizure frequency divided by the sum of the treatment and baseline seizure frequencies). Combined analysis of these response parameters in patients receiving various dosages of gabapentin (600, 900, 1200, or 1800 mg in 3 divided doses daily) or placebo indicated a dose-related reduction in the frequency of partial seizures with gabapentin, although a dose-response relationship was not consistently found in the individual studies. The efficacy of adjunctive therapy with gabapentin for the management of partial seizures does not appear to be affected by patient gender or age, although the influence of these characteristics on efficacy has not been studied systematically.

Gabapentin also is used in combination with other anticonvulsant agents in the management of partial seizures in children 3–12 years of age. Efficacy of gabapentin as adjunctive therapy in children 3–12 years of age with partial seizures was established in a multicenter randomized controlled trial. Response ratios were substantially better in patients receiving gabapentin 25–35 mg/kg daily compared with patients receiving placebo; for the same population, the responder rate for the drug (21%) was not substantially different from placebo (18%). Another study in children 1 month to 3 years of age reported no substantial difference in either the response ratio or responder rate for those receiving gabapentin compared with those receiving placebo.

Because addition of gabapentin to an existing anticonvulsant regimen does not appreciably alter steady-state plasma concentrations of concomitantly administered anticonvulsants, additional monitoring of plasma concentrations of anticonvulsant agents for adjustment of gabapentin and/or other anticonvulsant dosage generally is not necessary during such concomitant therapy; the value of monitoring plasma concentrations of gabapentin has not been established. Although clinical trials indicate that routine monitoring of laboratory parameters is not necessary for the safe use of gabapentin, clinicians should exercise clinical judgment regarding such monitoring during therapy with the drug.

■ **Neuropathic Pain** ***Postherpetic Neuralgia*** Gabapentin is used in the management of postherpetic neuralgia (PHN) in adults. In 2 placebo-controlled clinical studies in patients with postherpetic neuralgia, gabapentin was effective in relieving pain (based on an 11-point numeric rating scale) in patients who continued to experience pain for longer than 3 months after healing of the herpes zoster rash. In these studies, gabapentin dosage was titrated over the first 3 days of therapy to a maximum dosage of 900 mg daily and then was increased further over a period of 3–4 weeks in increments of 600 mg to 1.2 g daily at intervals of 3–7 days to the designated target dosage. In 1 study, 29% of patients receiving a target dosage of 3.6 g daily reported a reduction in pain of at least 50% compared with baseline; in the other study, the same level of pain relief (50% reduction) was achieved in 32 or 34% of patients receiving a target gabapentin dosage of 1.8 or 2.4 g daily, respectively.

Other Neuropathic Uses Gabapentin is used for the treatment of pain associated with diabetic neuropathy†. In an 8-week controlled clinical study in patients with diabetic neuropathy, gabapentin was more effective than placebo in improving pain (based on an 11-point numeric rating scale), sleep, and mood during weeks 2–8 of the study. Most patients in this study (67%) received gabapentin in dosages of 3.6 g daily. In addition, 2 comparative studies reported that gabapentin was at least as effective as amitriptyline in relieving pain associated with diabetic neuropathy. Analysis of data from randomized studies in patients with pain associated with diabetic neuropathy indicates that 40% of patients who received gabapentin for neuropathic pain obtained good pain relief.

Gabapentin also has been used with some evidence of benefit for the relief of chronic neurogenic pain† in a variety of conditions including trigeminal neuralgia†, pain and control of paroxysmal symptoms of multiple sclerosis†, complex regional pain syndromes† (CRPS), HIV-related peripheral neuropathy†, and neuropathic pain associated with cancer†. Limited evidence indicates that gabapentin is not effective for the management of acute pain. Gabapentin also has been used in the treatment of restless legs syndrome† (RLS). Additional study and experience are needed to further elucidate the precise role of gabapentin in the management of these conditions.

■ **Vasomotor Symptoms** Gabapentin has been used for the management of vasomotor symptoms† in women with breast cancer and in postmenopausal women. Therapy with the drug has improved both the frequency and severity of vasomotor symptoms (hot flushes [flashes]) in these women.

Most women receiving systemic antineoplastic therapy for breast cancer experience vasomotor symptoms, particularly those receiving tamoxifen therapy. In a randomized, double-blind, placebo-controlled study in 420 women with breast cancer (68–75% were receiving tamoxifen) who were experiencing 2 or more episodes of hot flushes daily, the percentage reductions in hot flush severity score at 4 and 8 weeks of treatment were 21 and 15%, respectively, for placebo; 33 and 31%, respectively, for gabapentin 300 mg daily (100 mg 3 times daily), and 49 and 46%, respectively, for gabapentin 900 mg daily (300 mg 3 times daily). Comparisons among treatment groups showed that only the 900-mg daily dosage was associated with a statistically significant reduction in hot flush frequency and severity. Whether higher dosages will provide further reductions in vasomotor symptoms remains to be determined. The role of gabapentin in managing vasomotor symptoms in women with breast cancer relative to other nonhormonal therapies (e.g., selective serotonin-reuptake inhibitors [SSRIs], selective serotonin- and norepinephrine-reuptake inhibitors [SNRIs]) remains to be determined. Well-designed, comparative studies are needed to establish optimum nonhormonal therapy, both in terms of efficacy and patient tolerance of adverse effects, in these women.

Because of the risks associated with hormone replacement therapy (HRT) for vasomotor symptoms in perimenopausal and postmenopausal women, alternative nonhormonal therapies are being investigated. In a randomized, double-blind, placebo-controlled study in 59 postmenopausal women who were experiencing 7 or more hot flushes daily, intent-to-treat analysis revealed that 12 weeks of gabapentin 900 mg daily (300 mg 3 times daily) was associated with a 45% reduction in hot flush frequency and a 54% reduction in composite hot flush score (frequency and severity). In a continuation open-label phase in which patients were permitted upward titration of dosage as needed to a maximum of 2.7 g daily (25% received 900 mg or less daily, 61% received 900 mg–1.8 g daily, 14% received 1.8–2.7 g daily), the associated reductions in hot flush frequency and composite score were 54 and 67%, respectively. The role of gabapentin therapy relative to other nonhormonal therapies (e.g., SSRIs, SNRIs) for postmenopausal vasomotor symptoms, both in terms of efficacy and safety, as well as the optimum dosage remain to be established.

Current evidence indicates that gabapentin is effective and well tolerated in the short-term treatment of vasomotor symptoms associated with breast cancer treatment and with menopause. The principal adverse effects associated with gabapentin therapy in women with vasomotor symptoms have been somnolence, fatigue, dizziness, and rash (with or without peripheral edema). Additional study and experience are needed to further elucidate the role of gabapentin relative to other nonhormonal therapies, and to establish longer-term (i.e., beyond 17 weeks) efficacy and safety.

The possible role of gabapentin in the management of vasomotor symptoms† associated with antiandrogenic therapy in men with prostate cancer remains to be established. Current evidence of efficacy is limited; well-designed, controlled studies are under way in this population.

Dosage and Administration

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

If Neurontin® film-coated scored tablets containing 600 or 800 mg of gabapentin are to be used in patients requiring a 300- or 400-mg dose, the tablets can be halved to allow administration of the appropriate dose. Patients should be instructed to take one-half tablet; the remaining half-tablet should be used for the next dose. Half-tablets that are not used within several days should be discarded.

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

■ **Dosage** ***Seizure Disorders*** Because of the possibility of increasing seizure frequency, anticonvulsant drugs, including gabapentin, should *not* be discontinued abruptly. (See Cautions: Precautions and Contraindications.) Discontinuance of gabapentin therapy and/or addition of an alternative anticonvulsant drug to therapy should be done gradually over a minimum of 1 week.

For adjunctive therapy in the management of partial seizures with or without secondary generalization in adults and children older than 12 years of age, the effective dosage of gabapentin is 900 mg to 1.8 g daily administered in 3 divided doses. Gabapentin therapy is initiated at a dosage of 300 mg 3 times daily.

If necessary, the dosage of gabapentin may be increased up to 1.8 g daily in 3 divided doses. Dosages up to 2.4 g daily have been tolerated well as adjunctive therapy by patients in long-term clinical studies, and a small number of patients have tolerated dosages of 3.6 g daily for short periods. With thrice-daily dosing, the interval between doses should not exceed 12 hours. It is not necessary to monitor plasma gabapentin concentrations to optimize therapy.

For adjunctive therapy in the management of partial seizures, the effective dosage of gabapentin in patients 5 years of age and older is 25–35 mg/kg daily administered in 3 divided doses; for patients 3 and 4 years of age, the effective dosage is 40 mg/kg daily administered in 3 divided doses. Gabapentin therapy in patients 3–12 years of age should be initiated at a dosage of 10–15 mg/kg per day in 3 divided doses. Dosages up to 50 mg/kg daily have been well tolerated by patients 3–12 years of age in a long-term clinical study. When

administered 3 times daily, the interval between doses should not exceed 12 hours.

If gabapentin is discontinued and/or an alternative anticonvulsant is added to the regimen, such changes in therapy should be done gradually over a period of at least 1 week.

Postherpetic Neuralgia For the management of postherpetic neuralgia in adults, the initial dosage regimen of gabapentin is 300 mg once daily on the first day, 300 mg twice daily on the second day, and 300 mg 3 times daily on the third day. Subsequently, the dosage may be increased as needed for relief of pain up to a total daily dosage of 1.8 g administered in 3 divided doses. In clinical studies evaluating gabapentin for the treatment of postherpetic neuralgia, dosages of the drug ranging from 1.8–3.6 g daily were effective, but there was no evidence that dosages exceeding 1.8 g daily provided any additional benefit.

Diabetic Neuropathy For the symptomatic treatment of diabetic neuropathy† in adults, gabapentin dosages of 900 mg to 3.6 g daily have been used; however, pain relief generally has been observed in patients receiving dosages exceeding 1.8 g daily.

Vasomotor Symptoms Although the optimum dosage remains to be established, a gabapentin dosage of 300 mg 3 times daily has been effective in reducing both the severity and frequency of vasomotor symptoms† in women with breast cancer and in postmenopausal women. Some clinicians recommend that therapy be initiated with a dosage of 300 mg once daily at bedtime. If needed, the dosage can be increased to 300 mg twice daily, and then to 300 mg 3 times daily, at 3- to 4-day intervals. A dosage of 100 mg 3 times daily appears to be no more effective than placebo, whereas dosages exceeding 900 mg daily (e.g., up to 2.7 g daily administered as 900 mg 3 times daily) may provide additional benefit in some women.

■ **Dosage in Renal Impairment** In adults and children 12 years of age and older with impaired renal function and/or undergoing hemodialysis, dosage and/or frequency of administration of gabapentin should be modified in response to the degree of renal impairment. Such patients with a creatinine clearance of 60 mL/minute or greater may receive 300 mg to 1.2 g of gabapentin 3 times daily (i.e., up to a total dosage of 3.6 g daily), and those with a creatinine clearance of 30–59 mL/minute may receive 200–700 mg of gabapentin twice daily (i.e., up to a total dosage of 1.4 g daily). Patients with a creatinine clearance of 15–29 mL/minute may receive 200–700 mg of gabapentin once daily, and those with a creatinine clearance of 15 mL/minute may receive 100–300 mg of gabapentin daily. In patients with a creatinine clearance of less than 15 mL/minute, dosage of gabapentin should be reduced proportionally (e.g., patients with a creatinine clearance of 7.5 mL/minute should receive one-half the dosage that patients with a creatinine clearance of 15 mL/minute should receive). Anephric patients may receive maintenance doses of gabapentin based on estimates of creatinine clearance, with supplemental doses of 125–350 mg of gabapentin given after each 4-hour hemodialysis session.

The use of gabapentin in children less than 12 years of age with impaired renal function has not been evaluated.

Cautions

Gabapentin generally is well tolerated, and adverse effects of the drug usually are mild to moderate in severity and may be self-limiting. Nervous system effects are the most frequently reported adverse affects of gabapentin and those most frequently requiring discontinuance of the drug. The most frequent adverse effects of gabapentin as adjunctive therapy in the treatment of partial seizures in adults and children 12 years of age and older are somnolence, dizziness, ataxia, fatigue, and nystagmus. Discontinuance of gabapentin because of adverse effects was required in 7% of adults and children 12 years of age and older receiving the drug as adjunctive therapy in the treatment of partial seizures in premarketing uncontrolled and controlled clinical trials; the adverse effects most frequently associated with discontinuance of gabapentin were somnolence (1.2% of patients), ataxia (0.8% of patients), fatigue (0.6% of patients), nausea and/or vomiting (0.6% of patients), and dizziness (0.6% of patients). The most frequent adverse effects of gabapentin as adjunctive therapy in the treatment of partial seizures in patients 3–12 years of age were viral infection, fever, nausea and/or vomiting, somnolence, and hostility. Discontinuance of gabapentin because of adverse effects was required in approximately 7% of patients 3–12 years of age in clinical trials; the adverse effects most frequently associated with discontinuance of gabapentin were emotional lability (1.6%), hostility (1.3%), and hyperkinesia (1.1%).

Because clinical trials of gabapentin therapy in the treatment of partial seizures involved specific patient populations and use of the drug as adjunctive therapy, it is difficult to determine whether a causal relationship exists for many reported adverse effects, to compare adverse effect frequencies with other clinical reports, and/or to extrapolate the adverse effect experience from controlled clinical trials to usual clinical practice.

In placebo-controlled studies, the adverse effects most frequently reported in adults receiving gabapentin for the management of postherpetic neuralgia were dizziness, somnolence, and peripheral edema. Discontinuance of gabapentin because of adverse effects was required in 16% of patients receiving the drug in 2 clinical trials; the adverse effects most frequently associated with discontinuance of gabapentin for the management of postherpetic neuralgia were dizziness, somnolence, and nausea.

■ **Nervous System Effects** Nervous system effects were among the most frequent adverse effects reported in patients with epilepsy receiving gabapentin as adjunctive therapy in controlled clinical trials in adults and children 12 years of age and older. Somnolence was the most frequent adverse nervous system effect, occurring in about 19% of those receiving gabapentin; the incidence and severity of somnolence appear to be dose related. Dizziness or ataxia was reported in about 17 or 12.5%, respectively, of patients receiving gabapentin as adjunctive therapy in controlled trials; the incidence and severity of ataxia also appear to be dose related. Fatigue reportedly occurred in about 11% of adults receiving gabapentin as adjunctive therapy in controlled trials. Nystagmus was reported in about 8%, tremor in about 7%, nervousness in 2.4%, dysarthria in 2.4%, amnesia in 2.2%, depression in 1.8%, abnormal thinking in 1.7%, twitching in 1.3%, and abnormal coordination in 1.1% of patients receiving gabapentin as adjunctive therapy in controlled trials. Other nervous system effects occurring in more than 1% of patients receiving gabapentin as adjunctive therapy, but with equal or greater frequency in patients receiving placebo, were headache, seizures, confusion, insomnia, and emotional lability.

Vertigo, hyperkinesia, paresthesia, decreased or absent reflexes, increased reflexes, anxiety, hostility, asthenia, or malaise was reported in at least 1% of adults and children 12 years of age and older receiving gabapentin as adjunctive therapy in uncontrolled and controlled clinical trials. CNS tumors, syncope, abnormal dreaming, aphasia, hypoesthesia, intracranial hemorrhage, hypotonia, dysesthesia, paresis, dystonia, hemiplegia, facial paralysis, stupor, cerebellar dysfunction, positive Babinski sign, positive Romberg test, decreased position sense, subdural hematoma, apathy, hallucination, decrease or loss of libido, agitation, paranoia, depersonalization, euphoria, feeling high, doped-up sensation, psychosis, or migraine occurred in at least 0.1% but less than 1% of patients receiving gabapentin as adjunctive therapy in uncontrolled and controlled clinical trials. Choreoathetosis, orofacial dyskinesia, encephalopathy, nerve palsy, personality disorder, increased libido, subdued temperament, apraxia, fine motor control disorder, meningismus, local myoclonus, hyperesthesia, hypokinesia, mania, neurosis, hysteria, antisocial reaction, strange feelings, or lassitude occurred in less than 0.1% of patients receiving gabapentin as adjunctive therapy in uncontrolled and controlled clinical trials.

Somnolence, hostility (including aggressive behavior), emotional lability, fatigue, hyperkinesia, and dizziness were reported in 8.4, 7.6, 4.2, 3.4, 2.5, and 2.5% of children 3–12 years of age receiving gabapentin as adjunctive therapy in controlled clinical trials. Headache and convulsions were reported in more than 2% and equally or more frequently than among those receiving placebo in children 3–12 years of age receiving gabapentin as adjunctive therapy in controlled clinical trials. Somnambulism, aura disappeared, and occipital neuralgia were reported during controlled clinical trials in children 3–12 years of age, but were not reported in trials of adults receiving gabapentin. Thought disorders (e.g., concentration difficulty, change in school performance) have been reported in 1.7% of children 3–12 years of age receiving the drug.

Dizziness was reported in 28%, somnolence in 21.4%, asthenia in 5.7%, headache in 3.3%, ataxia in 3.3%, and abnormal thinking in 2.7% of adults receiving gabapentin for the management of postherpetic neuralgia (PHN) in controlled clinical trials. Abnormal gait, incoordination, amnesia, and hypesthesia occurred in 1.2–1.5% of patients receiving the drug. Pain, tremor, and neuralgia were reported in greater than 1% of patients receiving gabapentin in clinical studies for the management of PHN but occurred with equal or greater frequency in patients receiving placebo.

Suicidality The US Food and Drug Administration (FDA) has analyzed suicidality reports from placebo-controlled studies involving 11 anticonvulsants, including gabapentin, 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 (e.g., bipolar disorder, depression, anxiety), and other conditions (e.g., migraine, neuropathic pain). The 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.)

In uncontrolled and controlled clinical trials, suicidal attempt occurred in at least 0.1% but less than 1% of patients receiving gabapentin as adjunctive therapy, and suicide occurred in less than 0.1% of patients receiving the drug as adjunctive therapy.

■ **GI Effects** Dyspepsia was the most frequent adverse GI effect in adults and children 12 years of age and older receiving gabapentin as adjunctive therapy in controlled clinical trials, occurring in 2.2% of such patients. Dry mouth or throat occurred in 1.7%, constipation in 1.5%, dental abnormalities in 1.5%, and increased appetite in 1.1% of patients receiving the drug. Nausea and/or vomiting, abdominal pain, or diarrhea was reported in more than 1% of patients receiving gabapentin as adjunctive therapy in controlled clinical trials but occurred with equal or greater frequency in patients receiving placebo.

Anorexia, flatulence, or gingivitis was reported in at least 1% of adults and children 12 years of age and older receiving gabapentin as adjunctive therapy in uncontrolled and controlled clinical trials. Glossitis, gingival hemorrhage, thirst, stomatitis, increased salivation, taste loss, unusual taste, gastroenteritis, hemorrhoids, bloody stools, or fecal incontinence occurred in at least 0.1% but less than 1% of such patients receiving gabapentin as adjunctive therapy in uncontrolled and controlled clinical trials. Dysphagia, eructation, pancreatitis, peptic ulcer, colitis, blisters in mouth, tooth discolor, perléche, enlarged salivary gland, lip hemorrhage, esophagitis, hiatal hernia, hematemesis, proctitis, irritable bowel syndrome, rectal hemorrhage, or esophageal spasm was reported in less than 0.1% of adults and children 12 years of age or older receiving gabapentin as adjunctive therapy in uncontrolled and controlled clinical trials.

Nausea and/or vomiting was reported in 8.4% of children 3–12 years of age receiving gabapentin as adjunctive therapy in controlled clinical trials. Diarrhea and anorexia were reported in more than 2% of children 3–12 years of age receiving gabapentin as adjunctive therapy in controlled clinical trials.

Diarrhea was reported in 5.7%, dry mouth in 4.8%, constipation in 3.9%, nausea in 3.9%, and vomiting in 3.3% of adults receiving gabapentin for the management of postherpetic neuralgia (PHN) in controlled clinical trials. Abdominal pain and flatulence occurred in 2.7 and 2.1%, respectively, of patients receiving the drug. Dyspepsia and dyspnea were reported in greater than 1% of patients receiving gabapentin in clinical studies of the management of PHN, but occurred with equal or greater frequency in patients receiving placebo.

■ **Cardiovascular Effects** Peripheral edema was reported in 1.7%, and vasodilation in 1.1% of adults and children 12 years of age and older receiving gabapentin as adjunctive therapy in controlled clinical trials. Hypertension occurred in more than 1% of patients receiving the drug as adjunctive therapy in uncontrolled and controlled clinical trials, and hypotension, angina pectoris, peripheral vascular disorder, palpitation, tachycardia, heart murmur, or generalized edema was reported in at least 0.1% but less than 1% of such patients. Atrial fibrillation, heart failure, thrombophlebitis, deep-vein thrombophlebitis, myocardial infarction, cerebrovascular accident, pulmonary thrombosis, ventricular extrasystole, bradycardia, atrial premature contraction, pericardial rub, heart block, pulmonary embolus, hyperlipidemia, hypercholesterolemia, pericardial effusion, or pericarditis occurred in less than 0.1% of patients receiving gabapentin as adjunctive therapy in uncontrolled and controlled clinical trials.

Peripheral edema was reported in 8.3% of adults receiving gabapentin for the management of postherpetic neuralgia (PHN) in controlled clinical trials.

■ **Respiratory Effects** Rhinitis occurred in 4.1%, pharyngitis in 2.8%, and coughing in 1.8% of adults and children 12 years of age and older receiving gabapentin as adjunctive therapy in controlled clinical trials. Pneumonia occurred in more than 1%; epistaxis, dyspnea, or apnea in at least 0.1% but less than 1%; and mucositis, aspiration pneumonia, hyperventilation, hiccup, laryngitis, nasal obstruction, snoring, bronchospasm, hypoventilation, or lung edema in less than 0.1% of patients receiving gabapentin as adjunctive therapy in uncontrolled and controlled clinical trials.

Bronchitis and respiratory infection were reported in 3.4 and 2.5%, respectively, of children 3–12 years of age receiving gabapentin as adjunctive therapy in controlled clinical trials. Pharyngitis, upper respiratory infection, rhinitis, and coughing were reported in more than 2% of children 3–12 years of age receiving gabapentin as adjunctive therapy in controlled clinical trials. Pseudocroup and hoarseness were reported during controlled clinical trials in children 3–12 years of age, but were not reported in trials in adults receiving gabapentin as adjunctive therapy.

Pharyngitis was reported in 1.2% of adults receiving gabapentin for the management of postherpetic neuralgia (PHN) in controlled clinical trials.

■ **Ocular and Otic Effects** Diplopia was reported in 5.9%, and amblyopia in 4.2%, of adults and children 12 years of age and older receiving gabapentin as adjunctive therapy in controlled clinical trials. Abnormal vision was reported in more than 1% of patients receiving gabapentin as adjunctive therapy in uncontrolled and controlled clinical trials.

Cataract, conjunctivitis, dry eyes, ocular pain, visual field defect, photophobia, bilateral or unilateral ptosis, ocular hemorrhage, ocular twitching, or hordeolum (stye) occurred in at least 0.1% but less than 1% of adults and children 12 years of age and older receiving gabapentin as adjunctive therapy in uncontrolled and controlled clinical trials. Ocular itching, abnormal accommodation, ocular focusing difficulty, watery eyes, retinopathy, glaucoma, iritis, corneal disorders, lacrimal dysfunction, degenerative ocular changes, blindness, retinal degeneration, miosis, chorioretinitis, or strabismus was reported in less than 0.1% of patients receiving the drug as adjunctive therapy in uncontrolled and controlled clinical trials.

Hearing loss, earache, tinnitus, inner ear infection, otitis, or otic fullness occurred in at least 0.1% but less than 1% of adults and children 12 years of age and older receiving gabapentin as adjunctive therapy in uncontrolled and controlled clinical trials. Eustachian tube dysfunction, labyrinthitis, otitis externa, perforated eardrum, or sensitivity to noise was reported in less than 0.1% of patients receiving gabapentin as adjunctive therapy in uncontrolled and controlled clinical trials.

Otitis media was reported in more than 2% of children 3–12 years of age receiving gabapentin as adjunctive therapy in clinical studies.

Amblyopia occurred in 2.7%, and conjunctivitis, diplopia, and otitis media each occurred in 1.2% of adults receiving gabapentin for the management of postherpetic neuralgia (PHN) in controlled clinical trials.

■ **Musculoskeletal Effects** Myalgia was reported in 2%, back pain in 1.8%, and fracture in 1.1% of adults and children 12 years of age and older receiving gabapentin as adjunctive therapy in controlled clinical trials. Arthralgia was reported in more than 1% of adults and children 12 years of age and older receiving the drug as adjunctive therapy in uncontrolled and controlled clinical trials, and tendinitis, arthritis, joint stiffness, or joint swelling occurred in at least 0.1% but less than 1% of such patients. Costochondritis, osteoporosis, bursitis, and contracture were reported in less than 0.1% of patients receiving gabapentin as adjunctive therapy in uncontrolled and controlled clinical trials.

Back pain was reported in greater than 1% of adults receiving gabapentin in clinical studies for the management of postherpetic neuralgia (PHN) but occurred with equal or greater frequency in patients receiving placebo.

■ **Endocrine Effects** Hyperthyroidism, hypothyroidism, goiter, hypoestrogenism, and cushingoid manifestations were reported in less than 0.1% of adults and children 12 years of age and older receiving gabapentin as adjunctive therapy in uncontrolled and controlled trials.

■ **Genitourinary Effects** Impotence was reported in 1.5% of patients receiving gabapentin as adjunctive therapy in controlled clinical trials. Hematuria, dysuria, cystitis, urinary frequency, urinary retention, urinary incontinence, vaginal hemorrhage, amenorrhea, dysmenorrhea, menorrhagia, breast cancer, inability to climax, and abnormal ejaculation occurred in at least 0.1% but less than 1% of patients receiving the drug as adjunctive therapy in uncontrolled and controlled clinical trials, and renal pain, renal lithiasis, acute renal failure, anuria, nephrosis, nocturia, pyuria, urinary urgency, leukorrhea, genital pruritus, vaginal pain, ovarian failure, testicular pain, epididymitis, and swollen testicle were reported in less than 0.1% of such patients.

■ **Dermatologic and Sensitivity Reactions** Pruritus or abrasion occurred in 1.3% of adults and children 12 years of age and older receiving gabapentin as adjunctive therapy in controlled clinical trials. Rash or acne were reported in more than 1% of patients receiving the drug in controlled studies but occurred with equal or greater frequency with placebo.

Facial edema was reported in at least 1% of patients receiving gabapentin as adjunctive therapy in uncontrolled or controlled clinical trials. Allergy, alopecia, eczema, dry skin, increased sweating, urticaria, hirsutism, seborrhea, cysts, and herpes simplex occurred in at least 0.1% but less than 1% of patients receiving the drug as adjunctive therapy in uncontrolled and controlled trials. Herpes zoster, skin discoloration, skin papules, photosensitivity reaction, leg ulcer, scalp seborrhea, psoriasis, desquamation, maceration, skin nodule, subcutaneous nodule, melanosis, skin necrosis, or local swelling was reported in less than 0.1% of such patients.

Angioedema, erythema multiforme, and Stevens-Johnson syndrome have been reported during postmarketing experience with gabapentin; however, the manufacturers state that data are insufficient to provide an estimate of the incidence of such effects or to establish a causal relationship to gabapentin.

Rash also was reported in 1.2% of adults receiving gabapentin for the management of postherpetic neuralgia (PHN) in controlled clinical trials.

■ **Hepatic Effects** Hepatomegaly occurred in at least 0.1% but less than 1% of adults and children 12 years of age and older receiving gabapentin as adjunctive therapy in uncontrolled and controlled clinical trials.

Elevated liver function test results and jaundice have been reported during postmarketing experience with gabapentin; however, the manufacturers state that data are insufficient to provide an estimate of the incidence of such effects or to establish a causal relationship to gabapentin.

Hepatitis was reported during controlled clinical trials in children 3–12 years of age, but was not reported in trials in adults receiving gabapentin.

■ **Electrolyte and Metabolic Effects** A decrease in body weight occurred in at least 0.1% but less than 1% of adults and children 12 years of age and older receiving gabapentin as adjunctive therapy in uncontrolled and controlled clinical trials; weight gain also has been reported. Glycosuria was reported in less than 0.1% of patients receiving the drug as adjunctive therapy in uncontrolled and controlled clinical trials.

Weight gain and hyperglycemia were reported in 1.8 and 1.2%, respectively, of adults receiving gabapentin for the management of postherpetic neuralgia (PHN) in controlled clinical trials.

Fluctuation in blood glucose concentrations and hyponatremia have been reported during postmarketing experience with gabapentin; however, the manufacturers state that data are insufficient to provide an estimate of the incidence of such effects or to establish a causal relationship to gabapentin.

Weight increase was reported in 3.4% of children 3–12 years of age receiving gabapentin in controlled clinical trials.

■ **Hematologic Effects** Leukopenia was reported in 1.1% of adults and children 12 years of age and older receiving gabapentin as adjunctive therapy in controlled clinical trials. Purpura (generally described as bruises resulting from physical trauma) was reported in at least 1% of patients receiving gabapentin as adjunctive therapy in uncontrolled and controlled clinical trials.

Anemia, thrombocytopenia, or lymphadenopathy occurred in at least 0.1% but less than 1% of adults and children 12 years of age and older receiving gabapentin as adjunctive therapy in uncontrolled and controlled clinical trials. Increased leukocyte count, lymphocytosis, non-Hodgkin's lymphoma, or increased bleeding time was reported in less than 0.1% of such patients.

Coagulation defect was reported during controlled clinical trials in children 3–12 years of age, but was not reported in trials in adults receiving gabapentin.

■ **Other Adverse Effects** Viral infection or fever occurred in more than 1% of adults and children 12 years of age and older receiving gabapentin as adjunctive therapy in controlled trials but was equally or more frequent with placebo. Odd smell occurred in less than 0.1% of patients receiving the drug in uncontrolled and controlled trials. Alcohol intolerance, hangover effect, or breast pain occurred in less than 0.1% of adults receiving gabapentin as adjunctive therapy in uncontrolled and controlled clinical trials.

Fever has been reported during postmarketing experience with gabapentin; however, the manufacturers state that data are insufficient to provide an estimate of the incidence of such effects or to establish a causal relationship to gabapentin.

Viral infection and fever were reported in 10.9 and 10.1%, respectively, of children 3–12 years of age receiving gabapentin as adjunctive therapy in controlled clinical trials. Dehydration and infectious mononucleosis were reported during controlled clinical trials in children 3–12 years of age, but were not reported in trials in adults receiving gabapentin as adjunctive therapy.

Infection and accidental injury were reported in 5.1 and 3.3%, respectively, of adults receiving gabapentin for the management of postherpetic neuralgia (PHN) in controlled clinical trials. Flu syndrome was reported in greater than 1% of patients receiving gabapentin for the management of PHN but occurred with equal or greater frequency in patients receiving placebo in clinical studies.

■ **Precautions and Contraindications** The US Food and Drug Administration (FDA) has informed healthcare professionals about an increased risk of suicidality (suicidal behavior or ideation) observed in an analysis of studies using various anticonvulsants, including gabapentin, compared with placebo. (See Suicidality under Cautions: Nervous System Effects.) Based on the current analysis of the available data, FDA recommends that all patients who are currently receiving or beginning therapy with any anticonvulsant for any indication be closely monitored for the emergence or worsening of depression, suicidal thoughts or behavior (suicidality), and/or any 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 drug 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 recommends that clinicians who prescribe gabapentin or any other anticonvulsant balance the risk for suicidality with the risk of untreated illness. Epilepsy and many other illnesses for which anticonvulsants are prescribed are themselves associated with an increased risk of morbidity and mortality and an increased risk of suicidal thoughts and behavior. If suicidal thoughts and behavior emerge during anticonvulsant therapy, the clinician must consider whether the emergence of these symptoms in any given patient may be related to the illness being treated.

Because of the possibility of increased seizure frequency, anticonvulsant drugs, including gabapentin, should not be discontinued suddenly. In controlled studies, the incidence of status epilepticus was 0.6% in adults and children 12 years of age and older receiving gabapentin and 0.5% in those receiving placebo. In all (uncontrolled and controlled) clinical studies of gabapentin as adjunctive therapy in adults and children 12 years of age and older, the incidence of status epilepticus was 1.5%. Because adequate historical data are unavailable for comparison, it has not been established whether the incidence of status epilepticus in patients with epilepsy treated with gabapentin is higher or lower than would be expected in a similar population of patients not treated with the drug. Discontinuance of gabapentin and/or addition of an alternative anticonvulsant drug to existing therapy should be done gradually over a minimum of 1 week.

Adverse CNS events (emotional lability, hostility [including aggressive behaviors], thought disorders [including concentration problems and change in school performance], and hyperkinesia) have been reported in epileptic children 3–12 years of age. (See Cautions: Nervous System Effects.)

During the premarketing development of gabapentin, 8 sudden and unexplained deaths were reported among a cohort of 2203 patients with epilepsy (2103 patient-years of exposure). Although the rate of these deaths exceeds that expected to occur in a healthy (nonepileptic) population matched for age and gender, this rate was similar to that occurring in a similar population of epileptic patients not receiving gabapentin. This evidence suggests, but does not prove that the incidence of sudden, unexplained death observed with adjunctive gabapentin therapy may be reflective of the population itself rather than the effects of gabapentin.

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

Concomitant use of morphine in patients receiving gabapentin may result in increased plasma concentrations of gabapentin. Patients experiencing symptoms of CNS depression such as somnolence may require a decrease in dosage of morphine or gabapentin.

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

■ **Pediatric Precautions** Safety and efficacy of gabapentin as adjunctive therapy in the management of partial seizures in children younger than 3 years of age have not been established. Safety and efficacy of gabapentin in the management of postherpetic neuralgia also have not been established in children.

■ **Geriatric Precautions** Safety and efficacy of gabapentin in the management of partial seizures in geriatric patients have not been evaluated systematically, and clinical trials did not include sufficient numbers of patients 65 years of age and older to determine whether they respond differently than do younger patients. However, in clinical studies of the drug in patients ranging from 20–80 years of age, gabapentin plasma clearance, renal clearance, and renal clearance adjusted for body surface area declined with age. Although safety and efficacy of gabapentin in geriatric patients with postherpetic neuralgia have not been established specifically, 30% of the patients receiving the drug in clinical studies were 65–74 years of age and 50% were 75 years of age and older. In these studies, gabapentin appeared to be more effective for the management of postherpetic neuralgia in patients older than 75 years of age than in younger patients. The manufacturers state that the apparent greater efficacy in geriatric patients may be related to decreased renal function in this age group. Although adverse effects reported in older patients generally were similar to those reported in younger adults, the incidence of peripheral edema and ataxia appears to increase with age. If gabapentin is used in geriatric patients, the initial dosage may need to be reduced and caution should be exercised since renal, hepatic, and cardiovascular dysfunction and concomitant disease or other drug therapy are more common in this age group than in younger patients.

■ **Pregnancy, Fertility, and Lactation** ***Pregnancy*** Although there are no adequate and controlled studies to date in humans, gabapentin has been shown to be teratogenic in mice and rats. Delayed ossification of several bones in the skull, vertebrae, forelimbs, and hindlimbs occurred in mice, and hydroureter and hydronephrosis occurred in rat pups when gabapentin was administered prior to and during mating or during organogenesis in dosages 1–4 times or up to 1–5 times (on a mg/m^2 basis), respectively, the maximum human daily dosage of 3.6 g. The dosage at which these effects did not occur in mice was approximately half the human daily dosage on a mg/m^2 basis. The dosages (on a mg/m^2 basis) at which these effects did not occur in rat pups were those equal to the maximum human daily dosage (in a teratogenicity study) or approximately 3 times the maximum human daily dosage (in a fertility and general reproductive performance study). There also was an increased incidence of postimplantation fetal loss in rabbits receiving gabapentin dosages one-fourth to 8 times the maximum human daily dosage (on a mg/m^2 basis). Other than hydroureter and hydronephrosis, the etiologies of which are unclear, the incidence of malformations was not increased compared with controls in offspring of mice, rats, or rabbits given dosages up to 50 times (mice), 30 times (rats), or 25 times (rabbits) the human daily dosage on a mg/kg basis, or 4 times (mice), 5 times (rats), or 8 times (rabbits) the human daily dosage on a mg/m^2 basis. Gabapentin should be used during pregnancy only when the potential benefits justify the possible risks to the fetus.

Reproduction studies revealed no adverse effects on fertility or reproduction in rats receiving gabapentin dosages up to 5 times the maximum recommended human daily dosage on a mg/m^2 basis.

Lactation Gabapentin is distributed into milk following oral administration. Because of the potential for serious adverse reactions to gabapentin in nursing infants, the drug should be administered to nursing women only if the potential benefits justify the risk to the infant.

Description

Gabapentin is an anticonvulsant agent structurally related to the inhibitory CNS neurotransmitter γ-aminobutyric acid (GABA). Although gabapentin was developed as a structural analog of GABA that would penetrate the blood-brain barrier (unlike GABA) and mimic the action of GABA at inhibitory neuronal synapses, the drug has no direct GABA-mimetic action and its precise mechanism of action has not been elucidated.

Results of some studies in animals indicate that gabapentin protects against seizure and/or tonic extensions induced by the GABA antagonists picrotoxin and bicuculline or by GABA synthesis inhibitors (e.g., 3-mercaptopropionic acid, isonicotinic acid, semicarbazide). However, gabapentin does not appear to bind to GABA receptors nor affect GABA reuptake or metabolism and does not act as a precursor of GABA or of other substances active at GABA receptors. Gabapentin also has no affinity for binding sites on common neuroreceptors (e.g., benzodiazepine; glutamate; quisqualate; kainate; strychnine-insensitive or -sensitive glycine; α_1-, α_2-, or β-adrenergic; adenosine A_1 or A_2; cholinergic [muscarinic or nicotinic]; dopamine D_1 or D_2; histamine H_1; type 1 or 2 serotonergic [5-HT_1 or 5-HT_2]; opiate μ, δ, or κ) or ion channels (e.g., voltage-sensitive calcium channel sites labeled with nitrendipine or diltiazem, voltage-sensitive sodium channel sites labeled with batrachotoxinin A 20α-benzoate). Conflicting results have been reported in studies of gabapentin affinity for and activity at *N*-methyl-d-aspartic acid (NMDA) receptors. Although

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

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

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

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

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

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

Preparations

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

Gabapentin

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

*available from one or more manufacturer, distributor, and/or repackager by generic (nonproprietary) name
‡Use is not currently included in the labeling approved by the US Food and Drug Administration

Lamotrigine

■ Lamotrigine is a phenyltriazine anticonvulsant.

Uses

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

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

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

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

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

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

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

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

Preparations

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

Molindone Hydrochloride

Oral		
Tablets	5 mg	Moban*, Endo
	10 mg	Moban*, Endo
	25 mg	Moban*, Endo
	50 mg	Moban*, Endo

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

Pimozide

■ Pimozide is a diphenylbutylpiperidine-derivative antipsychotic agent. The drug is considered a conventional or first-generation antipsychotic agent.

Uses

■ **Tourette's Syndrome** Pimozide is used for suppression of motor and vocal tics of Tourette's syndrome (Gilles de la Tourette's syndrome).

Pimozide has been used concomitantly with a stimulant in children with tic disorders (e.g., Tourette's syndrome) and comorbid attention deficit hyperactivity disorder (ADHD)† in whom stimulants alone cannot control tics.

Overview Tourette's syndrome is a neurologic genetic disorder with a spectrum of neurobehavioral manifestations that may vary with time and fluctuate in severity and frequency of symptoms during the natural course of the disease. The diagnosis of Tourette's syndrome usually is based on a history and observation of tics often accompanied by behavioral disorders (e.g., ADHD, obsessive-compulsive disorder). Tics may be sudden, brief, intermittent, involuntary, or semivoluntary movements (motor tics) or sounds (phonic or vocal tics). For a diagnosis of Tourette's syndrome, the criteria established by the Tourette Syndrome Classification Study Group may be used. According to this classification, both multiple motor tics and one or more phonic tics must be present at some time during the disease (although not necessarily concurrently), and such tics must occur many times a day and nearly every day, or intermittently, throughout a period of more than 1 year. Motor and phonic tics must be witnessed directly by a reliable examiner some time during the disease or be recorded by video or cinematography. In addition, anatomical location, number, frequency, type, complexity, or severity of tics must undergo a change over time. Involuntary movements and sounds must not be explained by a medical condition other than Tourette's syndrome. Although the onset of the syndrome must occur in patients younger than 21 years of age, in most patients the disease is manifested by 11 years of age, usually beginning in children 2–15 years old. Generally, tics become more severe when patients reach the age of 10 years, and 50% of patients are free from tics by the time they reach the age of 18 years. Severity of tics usually decreases when reaching adulthood. These and other diagnostic criteria are designed to assist clinicians in reaching an accurate diagnosis (e.g., differentiating Tourette's syndrome from other tic disorders) and those investigating the genetic factors associated with the syndrome.

Therapeutic Considerations Initially, management of Tourette's syndrome should include proper education of patients, family members, and teachers in order to provide a proper environment (at home and in school) for children with the disease. Drug therapy usually is considered when symptoms of the disorder begin to interfere with the patient's activities of daily living (e.g., work, school, social activities). Because Tourette's syndrome is associated with a wide variety of neurologic and behavioral manifestations, drug therapy should be individualized and the most severe symptoms should be treated first. The goal in the management of ties is to relieve tic-related discomfort and embarrassment and to achieve a degree of control of tics that allows the patient to function as normally as possible. Dopamine receptor blocking agents are considered the most effective drugs for the management of tics, although only haloperidol and pimozide are approved by the US Food and Drug Administration (FDA) for the treatment of Tourette's syndrome. Haloperidol generally has been considered the drug of choice for the management of Tourette's syndrome and pimozide has been an effective alternative in some patients who have had an inadequate response to or did not tolerate haloperidol. Limited data suggest that pimozide may be more effective than haloperidol in reducing tics. Some clinicians, however, prefer other antipsychotic drugs including molindone, phenothiazines (e.g., fluphenazine, thioridazine, trifluoperazine), risperidone, thiothixene, or tiapride (not commercially available in the US). It is not known whether some other atypical antipsychotics (e.g., clozapine, olanzapine, quetiapine) are effective in the management of tics or other symptoms of Tourette's syndrome; however, limited data indicate that ziprasidone may decrease the severity of tics. Tetrabenazine (not commercially available in the US), a drug that interferes with monoamine neurotransmitters and blocks dopamine receptors, has been effective for the management of tics and, unlike conventional antipsychotic agents, tetrabenazine does not appear to cause tardive dyskinesia. Although several other drugs (e.g., cannabinoids, clonazepam, pergolide, nicotine gum, nicotine transdermal system) have been shown to be effective in the management of tics, these agents have not been evaluated in well-designed, controlled studies. Focal motor and vocal ties have responded to injections of botulinum toxin in the affected muscles.

Pimozide is considered an orphan drug and is used for suppression of motor and vocal tics of Tourette's syndrome (Gilles de la Tourette's syndrome) in children and adults. The drug usually should be reserved for the treatment of those patients with Tourette's syndrome who have an inadequate response to, or who do not tolerate, conventional therapy (e.g., haloperidol) and whose development and/or daily life function is severely compromised by the presence of motor and vocal tics. Pimozide usually is *not* intended as a treatment of first choice for this syndrome, *nor* is it intended for suppression of tics that are only annoying or cosmetically troublesome.

Controlled studies in patients with Tourette's syndrome have shown that pimozide is effective in reducing the number of stimulated and unstimulated motor and vocal tics and the severity of associated symptomatology. Results of several studies suggest that pimozide is at least as effective as haloperidol in the management of Tourette's syndrome and may be associated with fewer and possibly less severe adverse effects, particularly sedation, in some patients. The long-term safety of pimozide in the management of this syndrome, however, remains to be determined, and additional well-controlled studies comparing pimozide and haloperidol are needed to assess their relative efficacy and safety. Haloperidol generally has been considered the drug of choice for the management of Tourette's syndrome, and pimozide has been an effective alternative in some patients who have an inadequate response to or do not tolerate haloperidol. Because limited data suggest that pimozide may be more effective than haloperidol in reducing tics and pimozide appears to be better tolerated than haloperidol, some clinicians and experts prefer the use of pimozide in patients with Tourette's syndrome. Limited data suggest that pimozide may be more effective than clonidine and that pimozide and penfluridol (not commercially available in the US) may have comparable efficacy in the management of Tourette's syndrome. Well-controlled clinical studies comparing the efficacy and safety of pimozide and other agents used in the management of Tourette's syndrome are needed.

Comorbid Conditions Patients with Tourette's syndrome often exhibit comorbid conditions (e.g., ADHD, obsessive-compulsive disorder). Although CNS stimulants, including amphetamines, have been reported to exacerbate motor and vocal tics in patients with Tourette's syndrome, results of several studies indicate that stimulants are effective in the management of ADHD in patients with Tourette's syndrome and the rate of tics is not increased in the majority of patients. In patients in whom the rate of tics increases, some experts recommend addition of an α-adrenergic agonist (e.g., clonidine, guanfacine), risperidone, pimozide, or haloperidol. Clonidine or guanfacine have been used in the management of ADHD. Although less effective than stimulants, clonidine and guanfacine do not increase the frequency or severity of tics. Tricyclic antidepressants (e.g., imipramine, nortriptyline) also may be used for the treatment of mild cases of ADHD and concomitant tics or Tourette's syndrome in patients who do not respond to or otherwise do not tolerate stimulants, in whom tics are exacerbated by stimulants, or those who develop clinically important depression.

In addition, there is a high incidence of obsessive-compulsive disorder in patients with Tourette's syndrome. Many clinicians recommend that patients with Tourette's syndrome and coexisting obsessive-compulsive disorder receive therapy with a selective serotonin-reuptake inhibitor or a selective serotonin- and norepinephrine-reuptake inhibitor (e.g., citalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, venlafaxine) alone or, if needed, in combination with buspirone, clonazepam, lithium, or a dopamine receptor antagonist. In a limited number of patients, other drugs (e.g., clomipramine, risperidone) also have been effective in the management of this comorbid condition.

■ **Schizophrenia** Pimozide has been used for the symptomatic management of a variety of psychiatric illnesses†, principally schizophrenia†, but other agents generally are preferred.

Pimozide appears to be as effective as phenothiazines or haloperidol for the symptomatic management of schizophrenia†. The drug is effective in reducing hallucinations, thought disorders, change in affect, and autism. Pimozide also appears to be effective for the management of social adjustment problems, emotional withdrawal, motor retardation, apathy, and conceptual disorganization. Delusions, bizarre mannerisms, chronic paranoia, anxiety, guilt feelings, disorientation, and hostility also may be reduced during therapy with the drug. Pimozide should *not* be used for the management of schizophrenia in patients whose main manifestations include excitement, agitation, or hyperactivity, because the efficacy of the drug in these patients has not been established.

Pimozide also has been used for the symptomatic management of acute schizophrenic episodes†. Results of initial clinical studies were not encouraging, but subsequent uncontrolled clinical studies suggest that pimozide may be effective in the management of acute schizophrenic episodes when used at dosages substantially higher than those used for the management of schizophrenia. Limited data suggest that high-dose pimozide therapy may be as effective as haloperidol or phenothiazines; however, the frequency and severity of pimozide-induced extrapyramidal reactions are increased at high dosages. Pimozide currently is *not* recommended for the management of acute schizo-

phrenic episodes. For further information on the symptomatic management of schizophrenia, see Uses: Psychotic Disorders, in the Phenothiazines General Statement 28:16.08.24.

■ **Mania** Pimozide has been used for the management of manic episodes† (mania) in patients with major affective disorders. Although limited data suggest that pimozide may be as effective as phenothiazines, the efficacy of the drug has not been clearly established, and pimozide currently is *not* recommended for the management of manic episodes.

■ **Behavioral Disorders** The efficacy of pimozide for the management of behavioral disorders in patients with mental retardation has not been established, but limited data suggest that the drug may reduce irritability, anxiety, and hyperactivity and improve social behavior in mentally retarded adolescents, without substantially affecting cognition or learning performance. Further controlled studies are needed.

■ **Dyskinesias** Pimozide has been used for the management of various dyskinesias†, including chronic progressive hereditary chorea (Huntington's chorea), acute chorea (Sydenham's chorea), tardive dyskinesia, and tardive dystonia; however, the usefulness of the drug for the management of dyskinesias is questionable because it has both dyskinesia-ulleviating and dyskinesia-producing properties. Because pimozide tends to worsen parkinsonian symptoms, the drug should not be used for the management of levodopa-induced dyskinesias in patients with parkinsonian syndrome.

■ **Other Uses** Results of uncontrolled clinical studies suggest that pimozide may be useful for the management of phencyclidine-induced psychosis† or various personality disorders† (e.g., paranoid, schizoid, compulsive). Pimozide also has reportedly been beneficial in some patients for the management of pathologic jealousy†, erotomania†, and monosymptomatic hypochondriacal psychosis†, including delusions of parasitosis.

Although pimozide has been used in the treatment of anorexia nervosa†, use of the drug for this purpose does not appear to provide substantial benefit.

Dosage and Administration

■ **Administration** Pimozide is administered orally. The drug may usually be administered once daily but also may be given in divided doses, particularly if once-daily dosing is not well tolerated. Some clinicians recommend administration of the drug as a single dose at bedtime to minimize adverse effects.

■ **Dosage** When pimozide is used for suppression of motor and vocal tics in patients with Tourette's syndrome, the initial dosage of the drug should be low and dosage adjustments should be made gradually. Dosage of pimozide must be carefully adjusted to balance symptomatic relief and the suppression of tics against the adverse effects of the drug. Patients receiving pimozide should have an ECG performed before therapy with the drug is initiated and periodically thereafter, particularly during the period of dosage adjustment. (See Cautions: Precautions and Contraindications.)

Adult Dosage For the suppression of motor and vocal tics in adults with Tourette's syndrome, the usual initial dosage of pimozide is 1–2 mg daily. The manufacturer and some clinicians state that dosage may be increased every other day according to the patient's tolerance and therapeutic response. Because of pimozide's prolonged elimination half-life, other clinicians suggest that dosage be increased at longer intervals (e.g., every 5–7 days) until signs and symptoms of the disorder decrease by at least 70%, adverse effects occur without symptomatic benefit, or symptomatic benefit and adverse effects occur at the same time. If adverse effects are minimal and do not interfere with functioning (e.g., dry mouth, slight sedation) but adequate response has not been achieved, dosage should not be increased further until these adverse effects resolve. If adverse effects interfere with functioning but are not severe, dosage can be reduced by 1-mg increments at weekly intervals until such effects resolve. Dosage should be reduced by 50% immediately or the drug withheld if severe adverse effects occur. (See Cautions: Precautions and Contraindications.) Once serious adverse effects resolve, therapy can be reinstituted with more gradual titration, increasing dosage at intervals ranging from 7–30 days. Most patients are adequately treated with dosages less than 0.2 mg/kg daily or 10 mg daily, whichever is less, and the manufacturer recommends that these dosages not be exceeded.

Pediatric Dosage For the suppression of motor and vocal tics in children with Tourette's syndrome, the usual initial dosage of pimozide is 0.05 mg/kg daily, preferably at bedtime. The dose may be increased every third day to a maximum of 0.2 mg/kg or 10 mg per day. Reliable dose-response data for the effects of the drug on tic manifestations in children younger than 12 years of age are not available.

Dosage of pimozide during prolonged maintenance therapy should be kept at the lowest possible effective level. Once an adequate response has been achieved, periodic attempts (e.g., every 6–12 months) should be made to reduce dosage of the drug to determine whether the initial intensity and frequency of tics persist. When attempting to reduce the dosage of pimozide, consideration should be given to the possibility that observed increases of tic intensity and frequency may represent a transient, withdrawal-related phenomenon rather than a return of the syndrome's symptoms. Before concluding that an increase in tic manifestations is a function of the underlying disorder rather than a response to drug withdrawal, at least 1–2 weeks should be allowed to elapse. If pimozide therapy is to be discontinued, dosage of the drug should be gradually reduced.

Cautions

■ **Nervous System Effects** The most frequent and potentially severe adverse effects of pimozide involve the CNS.

Extrapyramidal Reactions Extrapyramidal reactions occur frequently with pimozide, especially during the first few days of therapy. In most patients, these reactions consist of parkinsonian symptoms (e.g., tremor, rigidity, akinesia) that are mild to moderate in severity and usually reversible following discontinuance of the drug. Dystonic reactions and feelings of motor restlessness (i.e., akathisia) occur less frequently. Generally, the occurrence and severity of most extrapyramidal reactions are dose related because they occur at relatively high dosages and disappear or become less severe following a reduction in dosage; however, severe extrapyramidal reactions have reportedly occurred at relatively low dosages. Extrapyramidal reactions appear to occur in about 10–15% of patients receiving usual dosages of pimozide. Administration of anticholinergic antiparkinsonian agents (e.g., benztropine, trihexyphenidyl) or diphenhydramine may be necessary to control parkinsonian extrapyramidal reactions. If persistent extrapyramidal reactions occur, pimozide therapy may have to be discontinued.

The most common dystonic reaction is torticollis, which generally is accompanied by orofacial symptoms and, in some instances, oculogyric crisis, as well as spasms of the face, tongue, and jaw. Dyskinesias of the mouth and throat areas, trismus, dysarthria, muscle cramps, and athetoid movements have occurred occasionally.

Akathisia occurs relatively frequently in patients receiving pimozide, but usually can be managed by reducing the dosage of pimozide or by concomitant administration of an anticholinergic antiparkinsonian agent, diphenhydramine, a benzodiazepine, or propranolol.

Like other antipsychotic agents, pimozide has been associated with neuroleptic malignant syndrome (NMS), a potentially fatal syndrome requiring immediate discontinuance of the drug and intensive symptomatic treatment. For additional information on NMS, see Extrapyramidal Reactions in Cautions: Nervous System Effects, in the Phenothiazines General Statement 28:16.08.24.

Tardive Dyskinesia Like other antipsychotic agents, pimozide has been associated with persistent dyskinesias. Tardive dyskinesia may occur in some patients during long-term administration of pimozide or possibly following discontinuance of the drug. The risk of developing tardive dyskinesia appears to be greater in geriatric patients receiving high dosages of the drug, especially females. The symptoms are persistent and in some patients appear to be irreversible. Tardive dyskinesia is characterized by rhythmic involuntary movements of the tongue, face, mouth, or jaw (e.g., protrusion of the tongue, puffing of cheeks, chewing movements, puckering of the mouth), which sometimes may be accompanied by involuntary movements of the extremities and trunk. Although not clearly established, the risk of developing the syndrome and the likelihood that it will become irreversible may increase with the duration of therapy and total cumulative dose of antipsychotic agent(s) administered; however, the syndrome may occur, although much less frequently, after relatively short periods of treatment with low dosages. There is no proven or uniformly effective treatment for tardive dyskinesia; anticholinergic antiparkinsonian agents do not alleviate and often exacerbate the symptoms of this syndrome. If possible, antipsychotic agents should be discontinued if signs or symptoms of tardive dyskinesia occur. The syndrome may partially or completely remit if antipsychotic agents are discontinued, although some patients may require many months for improvement. Tardive dyskinesia may be masked if therapy is reinstituted, dosage is increased, or therapy with another antipsychotic agent is initiated. The effect that masking of the symptoms may have on the long-term course of the syndrome is not known. Fine vermicular movement of the tongue may be an early sign of tardive dyskinesia; prompt discontinuance of pimozide after this sign occurs may prevent development of the syndrome.

In general, abrupt withdrawal of antipsychotic agents following short-term administration is not associated with adverse effects; however, transient dyskinetic signs have occurred following abrupt withdrawal in some patients receiving maintenance therapy. In some of these patients, the dyskinetic movements are indistinguishable, except on the basis of duration, from persistent tardive dyskinesia. It is not known whether gradual withdrawal of antipsychotic agents reduces the incidence of withdrawal-emergent neurologic signs; however, if pimozide therapy must be discontinued, gradual withdrawal of the drug is recommended, if possible, pending further accumulation of data.

Other Nervous System Effects Pimozide is generally considered to be relatively nonsedating compared with other antipsychotic agents, but sedation, lethargy, and/or drowsiness appear to be the most common adverse effects of the drug in patients with Tourette's syndrome. Other adverse nervous system effects of pimozide include insomnia, dizziness, excitement, agitation, nervousness, fainting, aggressiveness, irritability, anxiety, tension, headache, depression, decreased attentiveness, confusion, nightmares, hallucinations, phobia, impaired motivation, speech disorder, handwriting change, fatigue, weakness, transient affective disturbance, and aggravation of psychotic symptomatology. Rarely, pimozide has been associated with seizures, including tonic-clonic (grand mal) seizures, in patients without a previous history of seizure disorder.

Adverse anticholinergic effects of pimozide include dry mouth, blurred vision, difficulty with accommodation, urinary retention, constipation, and urinary and fecal incontinence.

■ **Cardiovascular Effects** Various ECG changes, such as prolongation of the QT (including QT_c) interval; flattening, notching, and inversion of the T wave; and appearance of U waves, have occurred in some patients receiving pimozide. The clinical importance of pimozide-induced ECG changes has not been clearly established, but some clinicians believe that the changes are comparable to those induced by phenothiazines. Sudden, unexpected deaths have occurred in some patients receiving high doses of the drug (i.e., exceeding 10 mg; in the range of 1 mg/kg) for conditions other than Tourette's syndrome or in patients receiving concomitant pimozide and clarithromycin. (See Drug Interactions: Drugs and Foods Affecting Hepatic Microsomal Enzymes.) A possible mechanism for these deaths is prolongation of the QT interval, predisposing the patients to ventricular arrhythmia. Patients receiving pimozide should have ECG evaluations before and periodically during therapy with the drug. (See Cautions: Precautions and Contraindications.)

Pimozide rarely may produce hypotension, orthostatic hypotension, hypertension, tachycardia, or palpitations. In some patients, particularly geriatric or debilitated patients, transient hypotension for several hours after administration of the drug has occurred.

■ **Endocrine and Metabolic Effects** Amenorrhea, dysmenorrhea, and mild galactorrhea have occurred in some patients receiving pimozide. Like other antipsychotic agents, pimozide increases serum prolactin concentrations. (See Cautions: Mutagenicity and Carcinogenicity.) Loss of libido, impotence, and weight gain or, more frequently, weight loss, has occurred in patients receiving pimozide.

■ **GI Effects** Adverse GI effects of pimozide include increased salivation, nausea, vomiting, anorexia, GI distress, diarrhea, constipation, and abdominal cramps or pain. Thirst, altered taste, gingival hyperplasia, and increased appetite also have been reported.

■ **Other Adverse Effects** Rash, urticaria, skin irritation, facial edema (may be severe), periorbital edema, sweating, cataracts, visual disturbances or sensitivity to light, chest pain, nocturia, and urinary frequency have been reported in patients receiving pimozide. Hemolytic anemia also has occurred in pimozide-treated patients, although a causal relationship to the drug has not been established. Hyponatremia has occurred in patients receiving the drug following marketing approval.

The possibility that pimozide may cause other adverse effects reported with other antipsychotic agents should be considered. In addition, because clinical experience with pimozide for the management of Tourette's syndrome is limited, uncommon adverse effects may not have been detected to date.

■ **Precautions and Contraindications** Pimozide shares the toxic potentials of other antipsychotic agents (e.g., phenothiazines, butyrophenones), and the usual precautions associated with therapy with these agents should be observed. (See Cautions in the Phenothiazines General Statement 28:16.08.24.) Because treatment with pimozide exposes the patient to potentially serious risks, the decision to use the drug for the long-term management of Tourette's syndrome should be carefully considered by the patient (and/or the patient's family or guardians) and the physician. The use of pimozide for the management of Tourette's syndrome involves different considerations of risks and benefits than the use of other antipsychotic agents for other conditions. Because the goal of treatment is symptomatic improvement, the patient's view of the need for treatment and assessment of response are critical in evaluating the relative benefits and risks of pimozide therapy. Patients should be informed that pimozide has an adverse effect profile similar to that of other antipsychotic agents and that adverse effects associated with these agents may occur with pimozide.

Geriatric patients with dementia-related psychosis treated with either conventional (first-generation) or atypical (second-generation) antipsychotic agents are at an increased risk of mortality. For additional information on the use of antipsychotic agents for dementia-associated psychosis and other behavioral disturbances, see Geriatric Considerations under Psychotic Disorders: Schizophrenia and Other Psychotic Disorders, in Uses and see also Cautions: Geriatric Precautions, in the Phenothiazines General Statement 28:16.08.24.

Because of the likelihood that a proportion of patients receiving long-term therapy with an antipsychotic agent will develop tardive dyskinesia, patients in whom long-term pimozide therapy is considered should be fully informed, if possible, about the risk of developing this syndrome. The decision to inform the patient (and/or the patient's family or guardians) should take into account the clinical circumstances and the competency of the patient to understand the information. Because of the risk of tardive dyskinesia, long-term pimozide therapy should generally be reserved for patients whose syndrome is responsive to the drug and for whom alternative, equally effective, but potentially less toxic therapy is not available or appropriate. In patients requiring long-term treatment, the smallest effective dosage and shortest duration of therapy producing an adequate clinical response should be employed. Patients receiving pimozide should be evaluated periodically to determine whether maintenance dosage could be decreased or the drug discontinued.

Because sudden, unexpected deaths, which may be related to an effect of pimozide on the heart, have occurred in some patients receiving high doses of the drug (i.e., exceeding 10 mg; in the range of 1 mg/kg) for conditions other than Tourette's syndrome, an ECG should be performed before pimozide therapy is initiated and periodically thereafter, particularly during the period of dosage adjustment. Some clinicians recommend that a cardiologist be consulted before initiating therapy with the drug in patients with a baseline QT_c interval exceeding 440 ms. Patients should be instructed *not* to exceed the prescribed dosage and should be aware of the need for the initial ECG and follow-up ECGs during pimozide therapy. Prolongation of the QT_c interval (QT interval corrected for rate) to greater than 470 ms in children or 520 ms in adults, or more than 25% beyond the patient's pretreatment value, or the development of other T-wave abnormalities should be considered a basis for stopping further dosage increases and considering a dosage reduction. Dosage reduction also should be considered if bradycardia (less than 50 bpm) occurs. Some clinicians recommend that pimozide be withheld if T-wave inversion, U waves, or cardiac arrhythmia occurs and reinstituted only after ECG findings are normal. Because pimozide may cause ECG changes, the drug should be used with caution in patients with cardiovascular disorders. Because hypokalemia has been associated with ventricular arrhythmias, potassium insufficiency secondary to diuretics, diarrhea, or other causes should be corrected before pimozide therapy is initiated, and normal serum potassium concentrations should be maintained during pimozide therapy.

The clinical importance is not known, but pimozide has produced a dose-related increase in benign pituitary tumors in female mice. (See Cautions: Mutagenicity and Carcinogenicity.) The tumorigenic potential of pimozide should be given careful consideration by the patient and physician in the decision to use the drug, especially if the patient is young and long-term therapy is anticipated.

Patients should be warned that pimozide may impair their ability to perform activities requiring mental alertness or physical coordination (e.g., operating machinery, driving a motor vehicle), especially during the first few days of therapy.

Because pimozide produces adverse anticholinergic effects, the drug should be used with caution in individuals whose conditions may be aggravated by anticholinergic activity.

Like other antipsychotic agents, pimozide should be used with caution in patients receiving anticonvulsant agents and in those with EEG abnormalities or a history of seizures because the drug may lower the seizure threshold. If necessary, adequate anticonvulsant therapy should be maintained during pimozide therapy.

Pimozide should be used with caution in patients with hepatic or renal impairment.

Because pimozide has an antiemetic effect, the drug should be used with caution when suppression of nausea and vomiting might obscure diagnosis of an underlying physical disorder.

Because increased plasma concentrations of pimozide have occurred following concomitant use of pimozide and sertraline, the manufacturers of pimozide and sertraline state that concomitant use of the drugs is contraindicated. In addition, increased plasma pimozide concentrations were observed during concurrent use with paroxetine. The manufacturers of paroxetine state that concomitant use of these drugs is contraindicated because of the narrow therapeutic index of pimozide and its known ability to prolong the QT interval. Because of the risk of QT-interval prolongation, the manufacturer of citalopram hydrobromide and escitalopram oxalate states that concurrent use of either of these drugs with pimozide is contraindicated. Concurrent use of pimozide and fluoxetine also is contraindicated because of the potential for adverse drug interactions or QT_c prolongation. In addition, fluvoxamine should not be used concurrently with pimozide. (See Drug Interactions: Selective Serotonin-reuptake Inhibitors.)

Because pimozide prolongs the QT interval, the drug also is contraindicated in patients with congenital long QT syndrome or a history of cardiac arrhythmias, and in patients receiving other drugs that prolong the QT interval or that inhibit the metabolism of pimozide by inhibiting the cytochrome P-450 (CYP) 3A4 isoenzyme such as macrolide antibiotics (e.g., clarithromycin, erythromycin, azithromycin, dirithromycin, troleandomycin), azole antifungal agents (e.g., itraconazole, ketoconazole), protease inhibitors (e.g., ritonavir, saquinavir, indinavir, nelfinavir), nefazodone, or zileuton. (See Drug Interactions: Drugs That Prolong the QT Interval, and Drugs and Foods Affecting Hepatic Microsomal Enzymes.)

Pimozide is contraindicated in the treatment of simple tics or tics other than those associated with Tourette's syndrome. Pimozide should not be used in patients receiving drugs that may cause motor and vocal tics (e.g., pemoline [no longer commercially available in the US], methylphenidate, amphetamines) until such drugs have been withdrawn to determine whether the drugs or Tourette's syndrome is responsible for the tics.

Pimozide is contraindicated in patients with known hypokalemia or hypomagnesemia.

Pimozide is contraindicated in patients with severe toxic CNS depression or in those who are comatose from any cause; patients with blood dyscrasias, depressive disorders, or parkinsonian syndrome; and in patients who are hypersensitive to the drug. It is not known whether cross-sensitivity exists among antipsychotic agents; however, pimozide should be used with particular caution in patients with known hypersensitivity to other antipsychotic agents.

■ **Pediatric Precautions** The onset of Tourette's syndrome usually occurs between the ages of 2 and 15 years, but data on the use and efficacy of pimozide in children younger than 12 years of age are limited. Further study is needed to fully evaluate the use and efficacy of the drug for Tourette's syndrome in this age group. Limited clinical evidence suggests that the safety profile of pimozide in children aged 2–12 years generally is comparable to that observed in older patients. Safety and efficacy of pimozide for the management

of other conditions in children have not been evaluated, and use of the drug in children for any condition other than Tourette's syndrome is *not* recommended.

■ **Mutagenicity and Carcinogenicity** No evidence of pimozide-induced mutagenesis was seen in the Ames microbial mutagen test, the micronucleus test in rats, or the dominant lethal assay in mice.

No evidence of carcinogenesis was seen in rats receiving oral pimozide dosages up to 50 times the maximum recommended human dosage for 2 years; however, because of the limited number of rats surviving the study, the meaning of the results is unclear. Reversible gingival hyperplasia has occurred in dogs receiving oral pimozide dosages greater than 1.5 mg/kg daily (about 5 times the maximum recommended human dosage) for 12 months, and has occurred in at least one patient receiving the drug following marketing approval. Following oral administration of pimozide 0.62, 5, or 40 mg/kg daily for 18 months in mice, dose-related increases in the incidence of pituitary adenomas and mammary gland adenocarcinomas were observed in females. Pituitary changes at a dosage of 0.62 mg/kg daily were characterized as hyperplasia, while benign adenomas occurred at the higher dosages. The mechanism of pimozide-induced pituitary tumors in mice and the clinical importance of this finding are not known; however, the tumorigenic potential of pimozide should be given careful consideration by the patient and physician in the decision to use the drug, especially if the patient is young and long-term therapy is anticipated.

Although an increase in mammary neoplasms has been found in rodents following long-term administration of prolactin-stimulating antipsychotic agents, no clinical or epidemiologic studies conducted to date have shown an association between long-term administration of these drugs and mammary tumorigenesis in humans. Current evidence is considered too limited to be conclusive, and further study is needed to determine the clinical importance in most patients of elevated serum prolactin concentrations associated with antipsychotic agents. Because in vitro tests indicate that approximately one-third of human breast cancers are prolactin dependent, pimozide should be used with caution in patients with previously detected breast cancer.

■ **Pregnancy, Fertility, and Lactation** Reproduction studies in rats and rabbits using oral pimozide dosages up to 2.5 mg/kg daily (up to about 8 times the maximum recommended human dosage) have not revealed evidence of fetal malformation; however, in rats receiving oral pimozide dosages of 2.5 mg/kg daily or higher, a decreased pregnancy rate, increased fetal resorption, and retarded development of fetuses occurred. The observed effects may have resulted from delay or inhibition of implantation. In rabbits, dose-related maternotoxicity, mortality, decreased weight gain, and embryotoxicity, including increased fetal resorption, occurred. There are no adequate and controlled studies to date using pimozide in pregnant women, and the drug should be used during pregnancy only when the potential benefits justify the possible risks to the fetus.

Reproduction studies in animals using oral pimozide were not adequate to fully assess potential effects of the drug on fertility. Female rats receiving oral pimozide dosages up to 2.5 mg/kg daily had prolonged estrus cycles.

It is not known whether pimozide is distributed into milk. Because of the potential for serious adverse reactions (e.g., tumorigenicity, unknown cardiovascular effects) to pimozide in nursing infants, a decision should be made whether to discontinue nursing or the drug, taking into account the importance of the drug to the woman.

Drug Interactions

■ **Selective Serotonin-reuptake Inhibitors** ***Citalopram*** In a controlled study, administration of a single 2-mg dose of pimozide in individuals receiving citalopram (40 mg once daily for 11 days) was associated with mean increases in the QT_c interval of approximately 10 msec compared with pimozide given alone. Citalopram did not substantially affect the mean AUC or peak plasma concentrations of pimozide. The mechanism for this potential pharmacodynamic interaction is not known. The manufacturer of citalopram hydrobromide states that concurrent use of citalopram and pimozide is contraindicated.

Escitalopram In a controlled study, administration of a single 2-mg dose of pimozide in individuals receiving racemic citalopram (40 mg once daily for 11 days) was associated with mean increases in the QT_c interval of approximately 10 msec compared with pimozide given alone. Racemic citalopram did not substantially affect the mean AUC or peak plasma concentrations of pimozide. Concurrent pimozide and escitalopram administration has not been specifically evaluated to date. Pending further accumulation of data, the manufacturer of escitalopram states that concurrent use of escitalopram and pimozide is contraindicated.

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

Fluvoxamine Concomitant use of fluvoxamine is contraindicated in patients receiving pimozide, since fluvoxamine may inhibit the metabolism of pimozide and increase the potential for serious adverse cardiac effects.

Paroxetine In a controlled study, concurrent administration of single 2-mg doses of pimozide in healthy individuals receiving paroxetine (dosage titrated up to 60 mg daily) was associated with mean increases of 151 and 62% in the area under the plasma concentration-time curve (AUC) and peak plasma concentrations of pimozide, respectively, compared with pimozide given alone. The manufacturers of paroxetine state that concomitant use of paroxetine and pimozide is contraindicated because of the narrow therapeutic index of pimozide and its known ability to prolong the QT interval.

Sertraline Administration of a single 2-mg dose of pimozide in individuals receiving sertraline 200 mg daily has resulted in a mean increase of about 40% in pimozide AUC and peak plasma concentrations, but was not associated with changes in ECG parameters. The effect on QT interval and pharmacokinetic parameters of pimozide administered in higher doses (i.e., doses exceeding 2 mg) in combination with sertraline is as yet unknown. Concomitant use of sertraline and pimozide is contraindicated because of the low therapeutic index of pimozide and because the reported interaction between the 2 drugs occurred at a low dose of pimozide. The mechanism of this interaction is as yet unknown.

■ **Other CNS Agents** Pimozide may be additive with, or may potentiate the action of, other CNS depressants such as opiates or other analgesics, barbiturates or other sedatives, anxiolytics, or alcohol. When pimozide is used concomitantly with other CNS depressants, caution should be used to avoid excessive CNS depression.

■ **Drugs That Prolong the QT Interval** Because pimozide prolongs the QT interval, an additive effect on the QT interval might occur if the drug is administered with other agents that may prolong the QT interval such as phenothiazines, tricyclic antidepressants, or antiarrhythmic agents. Therefore, the manufacturer states that pimozide is contraindicated in patients receiving dofetilide, quinidine, sotalol, and other class IA and III antiarrhythmics; chlorpromazine, droperidol, mesoridazine (no longer commercially available in the US), and thioridazine; gatifloxacin, moxifloxacin, and sparfloxacin; halofantrine (licensed in the US but not commercially available); mefloquine; pentamidine; arsenic trioxide; levomethadyl acetate (no longer commercially available in the US); dolasetron mesylate; probucol (no longer commercially available in the US); tacrolimus; ziprasidone; and any other drugs that have demonstrated QT prolongation as one of their pharmacodynamic effects. (See Cautions: Cardiovascular Effects and see also Cautions: Precautions and Contraindications.)

■ **Drugs and Foods Affecting Hepatic Microsomal Enzymes** Prolongation of QT interval and, rarely, serious cardiovascular effects, including ventricular arrhythmias and death, have been reported in patients receiving drugs that inhibit the cytochrome P-450 (CYP) 3A4 isoenzyme such as macrolide antibiotics (e.g., clarithromycin, erythromycin, azithromycin, dirithromycin, troleandomycin), azole antifungal agents (e.g., itraconazole, ketoconazole), protease inhibitors (e.g., ritonavir, saquinavir, indinavir, nelfinavir), nefazodone, or zileuton concomitantly with pimozide. Macrolide antibiotics inhibit metabolism of pimozide, which may result in increased plasma concentrations of unchanged drug. Such alterations in pharmacokinetics of pimozide may be associated with prolongation of the QT and QT_c intervals, and, rarely, associated with ventricular arrhythmias. The manufacturer of pimozide states that concomitant administration of pimozide and macrolide antibiotics, azole antifungal agents, protease inhibitors, nefazodone, or zileuton is contraindicated.

Patients receiving pimozide should avoid grapefruit juice because it may inhibit drug metabolism by the CYP3A4 isoenzyme.

Because pimozide also may be metabolized by the CYP1A2 isoenzyme, the manufacturer states the theoretical potential for drug interactions with drugs that inhibit this enzyme system should be considered.

Acute Toxicity

■ **Pathogenesis** The acute lethal dose of pimozide in humans is not known. The oral LD_{50} of pimozide is 228, 5120, 188, and 40 mg/kg in mice, rats, guinea pigs, and dogs, respectively. The IV and subcutaneous LD_{50}s of pimozide are 11.1 and 40 mg/kg, respectively, for mice, and 5 and 40 mg/kg, respectively, for rats.

■ **Manifestations** In general, overdosage of pimozide may be expected to produce effects that are extensions of pharmacologic effects and adverse reactions, predominantly ECG abnormalities (including prolongation of the QT interval and torsades de pointes), severe extrapyramidal reactions, hypotension, seizures, and comatose state with respiratory depression.

A 17-year-old female who reportedly intentionally ingested 100 mg of pimozide and underwent gastric lavage (apparently no drug was recovered) had a complete and uneventful recovery except for slight tremor of the extremities that subsided within a few hours after ingestion. A 2½-year-old male who accidentally reportedly ingested 60 mg of pimozide exhibited mild extrapyramidal symptoms that subsequently subsided, and the patient recovered completely. Delayed-onset dystonia, hypotension, tachycardia, and drowsiness were reported in an 18-month-old female who ingested up to 6 mg (0.5 mg/kg) of pimozide; manifestations developed more than 12 hours after the accidental ingestion. The dystonia subsided over the following 12 hours while the drowsiness and tachycardia persisted for 40 hours. The child recovered fully without sequelae.

■ **Treatment** Treatment of pimozide overdosage generally involves symptomatic and supportive care, with ECG, blood pressure, and respiratory monitoring. There is no specific antidote for pimozide intoxication.

Following acute ingestion of the drug, the stomach should be emptied immediately, preferably by gastric lavage. If the patient is comatose, having seizures, or lacks the gag reflex, gastric lavage may be performed if an endotracheal tube with cuff inflated is in place to prevent aspiration of gastric contents. As in the case of phenothiazine overdosage, induction of emesis should generally *not* be attempted because a pimozide-induced dystonic reaction of the head or neck may result in aspiration of gastric contents during emesis; however, if the ingestion has only recently occurred (i.e., within an hour or so), induction of emesis may be considered. Following gastric lavage and/or emesis, activated charcoal should be administered. A patent airway should be established, using controlled or mechanically assisted respiration as necessary. ECG monitoring should be initiated immediately and continued until ECG parameters are within normal ranges. For hypotension or circulatory collapse, IV fluids, plasma, albumin, and/or vasopressor agents (e.g., norepinephrine) may be used. Epinephrine should *not* be used. For severe extrapyramidal reactions, anticholinergic antiparkinsonian agents or diphenhydramine should be administered. Because of the long elimination half-life of pimozide, patients should be observed for at least 4 days following acute ingestion of the drug. Clinicians should consider contacting a poison control center for additional information on the management of pimozide overdosage.

Pharmacology

The principal pharmacologic effects of pimozide are similar to those of haloperidol and, to a lesser extent, those of phenothiazines. In animal studies that are correlated with antipsychotic activity, pimozide is, on a weight basis, almost as potent as haloperidol and more potent than chlorpromazine following oral or subcutaneous administration.

■ **Nervous System Effects** In the CNS, pimozide has pharmacologic actions similar to those of haloperidol. The precise mechanism(s) of pimozide in suppressing motor and vocal tics in patients with Tourette's syndrome and its antipsychotic action have not been determined, but it may be related principally to the antidopaminergic effects of the drug. Although it has not been clearly established, most evidence suggests that pimozide is a selective dopamine-2 (D_2) receptor antagonist. Like butyrophenones (e.g., haloperidol), pimozide appears to predominantly block postsynaptic dopamine receptor sites, although the drug also may block presynaptic dopamine receptor sites. Blockade of dopamine receptors by pimozide may be accompanied by a series of secondary alterations in central dopamine metabolism and function that may contribute to the drug's therapeutic and adverse effects. Pimozide inhibits electrically induced dopamine release in brain tissue in vitro and increases synthesis and turnover of brain dopamine. Unlike most other currently available antipsychotic agents, pimozide appears to have little effect on catecholamines other than dopamine, although turnover of brain norepinephrine may be increased at high doses. Like other antipsychotic agents, however, pimozide has various effects on CNS receptor systems (e.g., γ-aminobutyric acid [GABA]) that are not fully characterized. Pimozide may decrease brain acetylcholine indirectly via its antidopaminergic effects, but such activity is considered relatively weak. Unlike haloperidol and chlorpromazine, the drug does not provide protection against a lethal dose of norepinephrine in rats.

Pimozide does not affect total sleep time or rapid eye movement (REM) sleep. The drug may cause EEG changes, including an increase in α-wave activity. Although not clearly established, pimozide may also lower the seizure threshold. The drug does not exhibit anticonvulsant activity in rats.

Although the exact mechanism(s) of action has not been elucidated, pimozide has an antiemetic effect. The antiemetic activity may be mediated via a direct effect of the drug on the medullary chemoreceptor trigger zone (CTZ), apparently by blocking dopamine receptors in the CTZ. Pimozide inhibits the central and peripheral effects of apomorphine.

Like haloperidol and phenothiazines, pimozide inhibits conditioned avoidance behaviors and produces catalepsy and ptosis in animals. The drug also antagonizes behavioral effects mediated by amphetamines in animals. In humans, pimozide antagonizes the euphoric response to amphetamines in amphetamine-dependent individuals, but apparently does not antagonize amphetamine-mediated behavioral effects in patients with schizophrenic disorder. Unlike many other centrally acting agents, pimozide does not appear to exhibit analgesic activity. The drug appears to exhibit anxiolytic activity in patients with chronic schizophrenic disorder who exhibit anxiety and in patients with various anxiety states.

In animals, pimozide does not substantially affect body temperature; however, the drug does inhibit apomorphine- and amphetamine-induced fever.

Pimozide exhibits some anticholinergic activity, although it is generally considered to be relatively weak compared with most other antipsychotic agents; however, anticholinergic effects (e.g., dry mouth, urinary retention, constipation) may occur during therapy with the drug.

■ **Cardiovascular Effects** Pimozide exhibits weak α-adrenergic blocking activity. The drug rarely may produce hypotension, orthostatic hypotension, hypertension, or tachycardia. Pimozide may also produce ECG changes, including prolongation of the QT interval; flattening, notching, and inversion of the T wave; and appearance of U waves. (See Cautions: Cardiovascular Effects.)

■ **Endocrine Effects** Pimozide induces secretion of prolactin from the anterior pituitary. The exact mechanism of increased prolactin secretion has not been determined, but it may be related principally to inhibition of dopamine receptors in the pituitary and hypothalamus.

■ **Other Effects** In vitro, pimozide exhibits weak antispasmodic effects, resulting from antagonism of various mediator substances (e.g., histamine, bradykinin, angiotensin). Pimozide also may inhibit transmembrane influx of extracellular calcium ions via slow calcium channels.

Pharmacokinetics

Limited information is available on the pharmacokinetics of pimozide.

■ **Absorption** Pimozide is slowly and variably absorbed from the GI tract following oral administration. Based on limited data, the drug appears to be at least 40–50% absorbed. Pimozide also appears to undergo extensive first-pass metabolism. It is not known whether food, disease, or concomitant administration of other drugs affects the absorption of pimozide.

Following oral administration of an individual dose of pimozide, peak plasma concentrations of the drug and its metabolites generally occur within 6–8 hours (range: 4–12 hours). Following oral administration of a single 6- or 24-mg dose in patients with chronic schizophrenic disorder, peak plasma pimozide concentrations of approximately 4 or 18–19 ng/mL, respectively, were attained. There are considerable interindividual variations in peak plasma concentrations and areas under the plasma concentration-time curves (AUCs) following single or multiple oral doses of pimozide. In a group of patients with chronic schizophrenic disorder receiving 2–10 mg of pimozide daily, steady-state serum concentrations of the drug varied considerably with specific dosages and ranged from undetectable (less than 1 ng/mL) to about 50 ng/mL. Because there is little correlation between plasma pimozide concentrations and clinical response, the clinical importance of interindividual variations is unclear. In a group of adults with acute schizophrenic disorder, a correlation between plasma pimozide concentration and dopamine receptor blocking activity, but not between clinical response and dopamine receptor blocking activity, was reported.

■ **Distribution** Distribution of pimozide into human body tissues and fluids has not been well characterized. Following subcutaneous administration in animals, pimozide is widely distributed, with highest concentrations attained in the liver, lungs, kidneys, and heart; the drug also is distributed into the brain, thymus, adrenals, thyroid, uterus, and ovaries, and apparently into bile. In animals, there is a direct relationship between the administered dose of pimozide and concentrations of the drug attained in the liver and brain. Following subcutaneous administration in animals, pimozide is widely distributed throughout the brain, principally as unchanged drug, with highest concentrations attained in the pituitary and caudate nucleus. The drug appeared to be selectively retained in the pituitary, caudate nucleus, chemoreceptor trigger zone (CTZ), floor of the third ventricle, lateral hypothalamus, and medulla. There was no correlation between concentrations of pimozide in the caudate nucleus and antagonism of effects mediated by amphetamine or apomorphine, but distribution of pimozide into nerve endings in the caudate nucleus was correlated with antagonism of these effects.

The extent of pimozide binding to plasma proteins is not known.

It is not known whether pimozide crosses the placenta or is distributed into milk.

■ **Elimination** Following multiple oral doses in patients with chronic schizophrenic disorder, the elimination half-life of pimozide averaged 55 hours. In one patient who developed a severe dystonic reaction, the elimination half-life of the drug was reportedly 154 hours.

The exact metabolic fate of pimozide is not clearly established, but the drug appears to undergo extensive first-pass metabolism. Pimozide is metabolized principally by oxidative *N*-dealkylation in the liver; this metabolism is catalyzed mainly by the cytochrome P-450 (CYP) 3A4 isoenzyme and, to a lesser extent, by cytochrome P-450 (CYP) isoenzyme 1A2. The major metabolites are 4,4-*bis*(4-fluorophenyl) butyric acid and 1-(4-piperidyl)-2-benzimidazolinone. The pharmacologic activity of these metabolites has not been determined; however, results of animal studies suggest that the metabolites of pimozide are inactive.

Pimozide and its metabolites are excreted principally in urine and, to a lesser extent, in feces. About 40% (range: 25–60%) of a single oral dose of the drug is excreted in urine and about 15% (range: 5–20%) in feces within 7 days; most urinary excretion occurs within 3–4 days, and most fecal excretion occurs within 3–6 days. Pimozide appears to be excreted in urine almost completely, as metabolites, with probably less than 1% excreted as unchanged drug. Fecal excretion has not been well characterized, but pimozide appears to be excreted in feces mainly as unchanged drug and to a small extent as metabolites. It is not known whether fecal excretion of the drug and metabolites represents unabsorbed drug or drug excreted via biliary elimination. In animals, pimozide and its metabolites are excreted in feces following parenteral administration, apparently via biliary elimination.

It is not known if pimozide and/or its metabolites are removed by hemodialysis or peritoneal dialysis.

Chemistry and Stability

■ **Chemistry** Pimozide is a diphenylbutylpiperidine-derivative antipsychotic agent. The drug is structurally similar to butyrophenones (e.g., haloper-

idol). Pimozide occurs as a white microcrystalline powder and has solubilities of less than 0.01 mg/mL in water and approximately 7 mg/mL in alcohol at room temperature. The drug has a pK_a of 7.32.

■ **Stability** Pimozide tablets should be stored in tight, light-resistant containers at 25°C but may be exposed to temperatures ranging from 15–30°C.

Preparations

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

Pimozide

Oral		
Tablets	1 mg	Orap® (scored), Gate
	2 mg	Orap® (scored), Gate

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

ANOREXIGENIC AGENTS AND RESPIRATORY AND CEREBRAL STIMULANTS 28:20

AMPHETAMINES 28:20.04

Amphetamines General Statement

■ Amphetamines exhibit pharmacologic actions that include CNS and respiratory stimulation and sympathomimetic effects.

Uses

Amphetamines are used as stimulants to decrease daytime sleepiness in the management of narcolepsy. Amphetamines also are used as adjuncts to psychological, educational, social, and other remedial measures in the treatment of attention deficit hyperactivity disorder (ADHD). Certain amphetamines also have been used as adjuncts to caloric restriction and behavioral modification in the short-term treatment of exogenous obesity. However, short-term or intermittent therapy with anorexigenic drugs is unlikely to maintain a long-term benefit, and prolonged administration of amphetamines for the treatment of obesity is not recommended. Amphetamines, particularly methamphetamine, have been misused and abused for their CNS stimulatory effects.

■ **Narcolepsy** Amphetamines are used as stimulants to decrease daytime sleepiness in the management of narcolepsy. Amphetamines should not be used to combat fatigue or exhaustion or to replace sleep in normal individuals.

Amphetamines remain the mainstay of treatment for narcolepsy based on a long record of clinical experience. However, because most clinical trials have involved small numbers of patients, the risk-to-benefit remains to be further established.

In determining the most appropriate stimulant therapy for a given patient, clinicians should consider benefit-to-risk (including adverse effect profile); drug cost, convenience of administration, and cost of ongoing care (including the possible need for laboratory monitoring).

Patients who fail to respond to an adequate trial of stimulant drug therapy should be assessed carefully for other possible causes of excessive sleepiness such as insufficient sleep, inadequate sleep hygiene, circadian rhythm disorders, obstructive sleep apnea syndrome, or periodic limb movement disorder.

Tolerance to the clinical effects may develop with long-term therapy, particularly at high dosages.

Narcolepsy rarely occurs in children, and the relative safety and efficacy of various stimulant drugs in this age group remains to be elucidated. Although amphetamines can be used, methylphenidate appears to be used most commonly based principally on extensive experience with the drug in pediatric patients with ADHD.

■ **Attention Deficit Hyperactivity Disorder** Amphetamines also are used as adjuncts to psychological, educational, social, and other remedial measures in the treatment of ADHD (hyperkinetic disorder, hyperkinetic syndrome of childhood, minimal brain dysfunction) in children, adolescents, and adults. Almost all studies comparing behavioral therapy versus stimulants alone have shown a much stronger therapeutic effect from stimulants than from behavioral therapy, and stimulants (e.g., methylphenidate, amphetamines) remain the drugs of choice for the management of ADHD. For a more detailed discussion on the management of ADHD, including the use of stimulants such as amphetamines, see Uses: Attention Deficit Hyperactivity Disorder, in Methylphenidate 28:20.92.

Few, if any, differences have been found between amphetamines (e.g., dextroamphetamine), methylphenidate, or pemoline (no longer commercially available in the US) or various dosage forms (short-, intermediate-, or long-acting formulations) of the drugs in short-term clinical studies in children with ADHD, and the choice of stimulant therapy should be individualized. Because hepatic toxicities have been associated with pemoline, some experts recommended its use *only* in patients who failed to respond to adequate trials of methylphenidate *and* an amphetamine, as well as adequate trials of second-line therapies (e.g., tricyclic antidepressants, bupropion). However, in 2005, the US Food and Drug Administration (FDA) determined that the risk of hepatic toxicity associated with the drug outweighs its benefits and the drug no longer is commercially available in the US.

Short-term and longer-term (up to 14 months' duration) studies have shown unequivocal beneficial effects of the stimulants on the defining core symptoms of ADHD (attention and concentration, activity, distractibility, impulsivity) and associated aggressiveness during continued therapy with the drugs. Children who fail to show positive therapeutic effects or who experience intolerable adverse effects with one stimulant should be tried on an alternative stimulant since most such children will exhibit a positive response to alternative stimulants and current evidence from crossover studies supports the efficacy of different stimulants in the same child; likewise, children who fail an adequate trial of 2 stimulants should be tried on a third type or formulation of stimulant. However, stimulants usually do not normalize the entire spectrum of behavioral problems, and many children effectively treated with these drugs still manifest a higher level of some behavioral problems than children without ADHD or other behavioral disturbances. Although stimulants have been shown to remain effective over many years, long-term benefits remain to be established.

■ **Exogenous Obesity** Amphetamines also have been used as adjuncts to caloric restriction and behavioral modification in the short-term treatment of exogenous obesity. The anorexigenic effect of sympathomimetic compounds used in the treatment of obesity appears to be temporary, seldom lasting more than a few weeks, and tolerance may occur. To help bring about and maintain loss of weight, the patient must be taught to curtail overeating and to consume a suitable diet. Prolonged administration of amphetamines is not recommended; however, obesity usually is a chronic disease, and short-term or intermittent therapy with anorexigenic drugs is unlikely to maintain a long-term benefit and is not recommended. Other anorexigenic agents (e.g., amphetamine congeners such as phentermine) with better safety profiles, including reduced potentials for misuse and abuse, generally are preferred to prototype amphetamines for the management of obesity. In the past, it was suggested that combined† therapy with fenfluramine (an amphetamine congener that stimulates release of serotonin [5-HT] at synapses and selectively inhibits the reuptake of serotonin at the presynaptic serotonergic nerve endings resulting in increased postsynaptic concentrations of serotonin in the CNS) and phentermine (an amphetamine congener that inhibits uptake of norepinephrine and dopamine) may provide complementary anorexigenic effects; therefore, such combined† therapy had been used widely in the 1990s in the management of obesity. However, because accumulated data on adverse effects associated with the drugs, fenfluramine hydrochloride (Pondimin®) and its dextrorotatory isomer dexfenfluramine hydrochloride (Redux®) were withdrawn from the US market in 1997. (See Cautions.)

Currently, the only legend (prescription) anorexigenic agent labeled by the US Food and Drug Administration (FDA) for use as an adjunct to behavioral modification, caloric restriction, and exercise in the long-term management of exogenous obesity is sibutramine, a β-phenethylamine that is structurally similar to amphetamine. Sibutramine therapy is indicated for patients with no underlying risk factor, but a pretreatment body mass index (BMI) of 30 kg/m² or greater, and for those with an underlying risk factor (e.g., hypertension, diabetes mellitus, hyperlipidemia) and a pretreatment BMI of 27 kg/m² or greater. Safety and efficacy of sibutramine for use exceeding 1 year have not been adequately studied to date. It appears that the anorexigenic effect of sibutramine, similar to dexfenfluramine, is secondary to inhibition of reuptake of norepinephrine and serotonin; however, unlike dexfenfluramine, sibutramine does not cause an increase in release of serotonin from nerve cells. Orlistat (a chemically synthesized derivative of lipostatin) is used as an adjunct to behavioral modification, caloric restriction, and exercise in the management of exogenous obesity. Some clinicians state that orlistat may be used in the long-term management of obesity; however, safety and efficacy of the drug beyond 2 years of therapy have not been established. Orlistat is not an anorexigenic agent, but is a reversible inhibitor of gastric, pancreatic, and pancreatic carboxylester lipases and thus appears to block fat absorption. (See Orlistat 56:92.)

■ **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 or pseudoephedrine. (See Chronic Toxicity.) Recent restrictions (including enactment of the Comprehensive Methamphetamine Control Act of 1996, the Methamphetamine Anti-Proliferation Act [MAPA] of 2000, and the Combat Methamphetamine Epidemic Act of 2005) on the availability of these compounds are hoped to reverse this resurgence in misuse and abuse. For a more detailed discussion on methamphetamine abuse, see Uses: Misuse and Abuse, in Pseudoephedrine 12:12.12.

Dosage and Administration

■ **Administration** Amphetamines are administered orally. When used in the treatment of narcolepsy or attention deficit hyperactivity disorder, the initial dose is given on awakening. Because of the potential for insomnia, when amphetamines are administered in divided doses, late evening doses should be avoided. When used as an anorexigenic, the dose is usually given 30–60 minutes before meals.