Thioridazine
Thioridazine Hydrochloride
AHFS Class: Phenothiazines (28:16.08.24)
VA Class: CN701

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

See Dosage and Administration in the associated General Statement for more information.
For the short-term treatment of adults with major depression who also have varying degrees of 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 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 (QTc), 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 QTc interval, such a relationship is possible. Although, thioridazine has been shown to prolong the QTc interval in a dose-dependent manner, prolongation of the QTc 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 QTc 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 QTc 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 QTc interval. Use of antiarrhythmic agents (e.g., disopyramide, procainamide, quinidine) that can prolong the QTc 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 QTc interval exceeding 500 msec should not receive thioridazine. Thioridazine should be discontinued if the QTc 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 QTc 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 QTc 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
#### 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.

Thioridazine has little antiemetic activity. It is as potent as chlorpromazine. Thioridazine has strong anticholinergic and sedative effects and weak extrapyramidal effects.

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

Thioridazine occurs as a white or slightly yellow, crystalline or micronized powder, which is odorless or has a faint odor and is freely soluble in water. It 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.

Temperature and Storage
Thioridazine hydrochloride is approximately equivalent to 100 mg of thioridazine. 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, crytalline 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 Preparations.

See Pharmacology in the associated General Statement for more information.

Chemistry and Stability

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, crytalline 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.
<table>
<thead>
<tr>
<th>Routes</th>
<th>Forms</th>
<th>Strengths</th>
<th>Brand Names</th>
<th>Manufacturer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral</td>
<td>Solution, concentrate</td>
<td>30 mg/mL*</td>
<td>Thioridazine Oral Solution</td>
<td>Roxane</td>
</tr>
<tr>
<td></td>
<td></td>
<td>100 mg/mL*</td>
<td>Thioridazine Oral Solution</td>
<td>Actavis, Roxane</td>
</tr>
<tr>
<td>Tablets</td>
<td></td>
<td>10 mg*</td>
<td>Thioridazine Tablets</td>
<td>Mutual, Mylan</td>
</tr>
<tr>
<td></td>
<td></td>
<td>15 mg*</td>
<td>Thioridazine Tablets</td>
<td>Geneva</td>
</tr>
<tr>
<td></td>
<td></td>
<td>25 mg*</td>
<td>Thioridazine Tablets</td>
<td>Mutual, Mylan</td>
</tr>
<tr>
<td></td>
<td></td>
<td>50 mg*</td>
<td>Thioridazine Tablets</td>
<td>Mutual, Mylan</td>
</tr>
<tr>
<td></td>
<td></td>
<td>100 mg*</td>
<td>Thioridazine Tablets</td>
<td>Mutual, Mylan</td>
</tr>
<tr>
<td></td>
<td></td>
<td>150 mg*</td>
<td>Thioridazine Tablets</td>
<td>Geneva</td>
</tr>
<tr>
<td></td>
<td></td>
<td>200 mg*</td>
<td>Thioridazine Tablets</td>
<td>Geneva</td>
</tr>
</tbody>
</table>

* 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.


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.


Exhibit D.19, page 1

cleric of any unusual behavioral changes. Patients, family members, and caregivers should be advised not to make any adjustments in the medication regimen without first consulting 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 on the lookout for any sudden changes. In addition, patients, family members, and caregivers should be aware of any 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 any of these new and worrisome behaviors occur, the responsible clinician should be contacted immediately.

Fetal and Lactation Toxicity 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 death 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).

Fetal toxicity was observed in mice. Females treated with felbamate in amounts resulting in plasma felbamate concentrations of 100, 300, and 1000 mg/kg daily for 104 weeks. Female maxiumum doses used in these studies were consistent with the therapeutic doses used in clinical practice.

Fetal toxicity was observed in mice. Females treated with felbamate in amounts resulting in plasma felbamate concentrations of 100, 300, and 1000 mg/kg daily for 104 weeks. Female maxiumum doses used in these studies were consistent with the therapeutic doses used in clinical practice.

Fetal toxicity was observed in mice. Females treated with felbamate in amounts resulting in plasma felbamate concentrations of 100, 300, and 1000 mg/kg daily for 104 weeks. Female maxiumum doses used in these studies were consistent with the therapeutic doses used in clinical practice.

Fetal toxicity was observed in mice. Females treated with felbamate in amounts resulting in plasma felbamate concentrations of 100, 300, and 1000 mg/kg daily for 104 weeks. Female maxiumum doses used in these studies were consistent with the therapeutic doses used in clinical practice.

Fetal toxicity was observed in mice. Females treated with felbamate in amounts resulting in plasma felbamate concentrations of 100, 300, and 1000 mg/kg daily for 104 weeks. Female maxiumum doses used in these studies were consistent with the therapeutic doses used in clinical practice.

Fetal toxicity was observed in mice. Females treated with felbamate in amounts resulting in plasma felbamate concentrations of 100, 300, and 1000 mg/kg daily for 104 weeks. Female maxiumum doses used in these studies were consistent with the therapeutic doses used in clinical practice.

Fetal toxicity was observed in mice. Females treated with felbamate in amounts resulting in plasma felbamate concentrations of 100, 300, and 1000 mg/kg daily for 104 weeks. Female maxiumum doses used in these studies were consistent with the therapeutic doses used in clinical practice.

Fetal toxicity was observed in mice. Females treated with felbamate in amounts resulting in plasma felbamate concentrations of 100, 300, and 1000 mg/kg daily for 104 weeks. Female maxiumum doses used in these studies were consistent with the therapeutic doses used in clinical practice.

Fetal toxicity was observed in mice. Females treated with felbamate in amounts resulting in plasma felbamate concentrations of 100, 300, and 1000 mg/kg daily for 104 weeks. Female maxiumum doses used in these studies were consistent with the therapeutic doses used in clinical practice.

Fetal toxicity was observed in mice. Females treated with felbamate in amounts resulting in plasma felbamate concentrations of 100, 300, and 1000 mg/kg daily for 104 weeks. Female maxiumum doses used in these studies were consistent with the therapeutic doses used in clinical practice.

Fetal toxicity was observed in mice. Females treated with felbamate in amounts resulting in plasma felbamate concentrations of 100, 300, and 1000 mg/kg daily for 104 weeks. Female maxiumum doses used in these studies were consistent with the therapeutic doses used in clinical practice.

Fetal toxicity was observed in mice. Females treated with felbamate in amounts resulting in plasma felbamate concentrations of 100, 300, and 1000 mg/kg daily for 104 weeks. Female maxiumum doses used in these studies were consistent with the therapeutic doses used in clinical practice.

Fetal toxicity was observed in mice. Females treated with felbamate in amounts resulting in plasma felbamate concentrations of 100, 300, and 1000 mg/kg daily for 104 weeks. Female maxiumum doses used in these studies were consistent with the therapeutic doses used in clinical practice.

Fetal toxicity was observed in mice. Females treated with felbamate in amounts resulting in plasma felbamate concentrations of 100, 300, and 1000 mg/kg daily for 104 weeks. Female maxiumum doses used in these studies were consistent with the therapeutic doses used in clinical practice.
Gabapentin has been studied in a variety of clinical trials, demonstrating its efficacy in reducing seizure frequency, including in patients with drug-resistant epilepsy. Gabapentin has also been effective in the management of pain associated with diabetic neuropathy, postherpetic neuralgia, and trigeminal neuralgia. In patients with diabetic neuropathy, gabapentin has been shown to reduce pain intensity and symptoms, with improvements observed within 2-8 weeks of treatment. Gabapentin has also been used in the treatment of postherpetic neuralgia, reducing the pain associated with herpes zoster rashes. In patients with trigeminal neuralgia, gabapentin has been shown to reduce the frequency and intensity of pain episodes.

In patients with postherpetic neuralgia, gabapentin has been shown to reduce the number of pain episodes and the duration of pain. In diabetic neuropathy, gabapentin has been shown to reduce the number of painful nerve impulses, leading to a reduction in pain intensity. Gabapentin has also been effective in the treatment of complex regional pain syndrome (CRPS), reducing the pain intensity and symptoms associated with this condition.

Gabapentin has also been studied in the treatment of restless legs syndrome (RLS) and hot flashes associated with menopause. In a randomized, double-blind, placebo-controlled trial, gabapentin was shown to reduce the frequency and severity of RLS symptoms, with improvements observed within 2 weeks of treatment. In patients experiencing hot flashes, gabapentin has been shown to reduce the frequency and severity of these symptoms, with improvements observed within 4 weeks of treatment.

Gabapentin is administered orally, with the dose adjusted based on the patient's response and tolerability. The initial dose is typically 300 mg three times daily, with increases of 300 mg every week as needed, up to a maximum dose of 3,600 mg daily. The dose may be increased further if necessary, up to a maximum of 5,400 mg daily.

Dosage and Administration

Gabapentin is administered orally. The initial dose is typically 300 mg three times daily, with increases of 300 mg every week as needed, up to a maximum dose of 3,600 mg daily. The dose may be increased further if necessary, up to a maximum of 5,400 mg daily. The dosage should be adjusted based on the patient's response and tolerability. The drug may be administered without regard to meals.

Gabapentin is generally well tolerated, with side effects typically being mild to moderate. The most common side effects include dizziness, somnolence, and peripheral edema. Gabapentin may also cause sedation and dizziness, particularly at higher doses, and may interact with other medications, such as sedatives and antipsychotics. Gabapentin is contraindicated in patients with a history of hypersensitivity to the drug or its components.

Gabapentin is associated with a low risk of abuse and dependence, with the potential for abuse and dependence being lower than that of other anticonvulsant drugs. Gabapentin is not a controlled substance, and its long-term use should be monitored carefully. Gabapentin is not recommended for use in children under the age of 3 years due to the potential for adverse effects, including sedation and somnolence. Gabapentin is not recommended for use in pregnancy due to the potential for adverse effects on the fetus.

Gabapentin is associated with a low risk of withdrawal symptoms, and abrupt discontinuation should be avoided. Gabapentin is not recommended for use in patients with a history of substance use disorder or alcohol dependence. Gabapentin is not recommended for use in patients with a history of hepatic impairment or renal impairment.

Gabapentin is not recommended for use in patients with a history of severe renal impairment or end-stage renal disease. Gabapentin is not recommended for use in patients with a history of severe hepatic impairment or end-stage liver disease. Gabapentin is not recommended for use in patients with a history of severe cardiac impairment or end-stage cardiac disease.

Gabapentin is not recommended for use in patients with a history of severe pulmonary impairment or end-stage pulmonary disease. Gabapentin is not recommended for use in patients with a history of severe gastrointestinal impairment or end-stage gastrointestinal disease.

Gabapentin is not recommended for use in patients with a history of severe neurological impairment or end-stage neurological disease. Gabapentin is not recommended for use in patients with a history of severe psychiatric impairment or end-stage psychiatric disease.
Gabapentin

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, the initial dosage of gabapentin is 300 mg three times daily, starting 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 300 mg to 3.6 g daily have been used; however, pain relief generally has been observed in patients receiving dosages of 1.8 g daily, 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 seems to be no more effective than placebo, whereas dosages exceeding 300 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 less than 15 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 twice daily and those with a creatinine clearance of 12.5-15 mL/minute may receive a total daily dosage of 1000-300 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 half the dosage that patients with a creatinine clearance of greater than 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 were among the most frequently reported adverse effects of gabapentin and those most frequently requiring discontinuation 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 approximately 7% of patients 12 years of age and older receiving the drug as adjunctive therapy in the treatment of partial seizures in uncontrolled trials and controlled clinical trials; CNS signs, symptoms, abnormal dreams, apathy, hypotonia, intracranial hemorrhage, hypoglycemia, dysaesthesia, paresis, dystonia, hemiplegia, facial palsy, headache, and rash occurred in less than 0.1% of patients receiving gabapentin as adjunctive therapy in the treatment of partial seizures in adults and children 12 years of age and older with impaired renal function and/or undergoing hemodialysis, gabapentin dosage of 300 mg to 1.2 g daily may provide additional benefit in some women.

**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 (0.3%).

Gabapentin is not indicated for the treatment of patients to whom the increased risk could be attributed. However, the relative risk has the potential to decrease over time as patients are treated and other conditions are all found to be at increased risk for suicidality when compared with placebo; thus, patients are encouraged to take the drugs with patients who are 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 in controlled clinical trials, but occurred with equal or greater frequency in patients receiving placebo.

**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 1.7%, and increased appetite in 1.5%, and increased appetite was the most frequent adverse GI effect in patients receiving gabapentin as adjunctive therapy in controlled clinical trials.
Gabapentin

\[ \text{AHFS DRUG INFORMATION} \ 2010 \]

- Hypersensitivity: Rash, pruritus, angioedema, anaphylaxis
- Cardiovascular Effects: Peripheral edema, atrial fibrillation, heart failure, peripheral vascular disorder, palpitation, tachycardia, heart murmur, or generalized edema
- Respiratory Effects: Rhinitis, coughing
- Gastrointestinal Effects: Diarrhea, constipation, nausea, vomiting, abdominal pain, flatulence, indigestion, diverticulitis
- Urinary System Effects: Nephrolithiasis, pyelonephritis, acute renal failure, anuria, nephrosis, cystitis, bladder tumors, renal pain, renal lithiasis, nephrosis, nocturia, pyuria, renal failure, anuria, nephrosis, acute renal failure
- Dermatologic and Sensitivity Reactions: Pruritus, rash, angioedema, urticaria, erythema multiforme
- Gastrointestinal Effects: Diarrhea, constipation, nausea, vomiting, abdominal pain, flatulence, indigestion, diverticulitis
- Genitourinary Effects: Hematuria, pyelonephritis, cystitis, bladder tumors, renal pain, renal lithiasis, nephrosis, nocturia, pyuria, renal failure, anuria, nephrosis, acute renal failure
- Hematologic Effects: Leukopenia, anemia, lymphopenia, thrombocytopenia, neutropenia, anemia, lymphopenia, thrombocytopenia, neutropenia
- Laboratory Test Changes: Elevated liver function tests and jaundice have been reported during treatment with gabapentin. Weight gain has also been reported.}

In controlled and uncontrolled clinical trials, elevations in liver enzymes have been seen in 1.5% of patients receiving gabapentin as adjunctive therapy. In uncontrolled and controlled clinical trials, elevations in liver enzymes have been seen in 1.5% of patients receiving gabapentin as adjunctive therapy. In uncontrolled and controlled clinical trials, elevations in liver enzymes have been seen in 1.5% of patients receiving gabapentin as adjunctive therapy. In uncontrolled and controlled clinical trials, elevations in liver enzymes have been seen in 1.5% of patients receiving gabapentin as adjunctive therapy. In uncontrolled and controlled clinical trials, elevations in liver enzymes have been seen in 1.5% of patients receiving gabapentin as adjunctive therapy. In uncontrolled and controlled clinical trials, elevations in liver enzymes have been seen in 1.5% of patients receiving gabapentin as adjunctive therapy. In uncontrolled and controlled clinical trials, elevations in liver enzymes have been seen in 1.5% of patients receiving gabapentin as adjunctive therapy. In uncontrolled and controlled clinical trials, elevations in liver enzymes have been seen in 1.5% of patients receiving gabapentin as adjunctive therapy. In uncontrolled and controlled clinical trials, elevations in liver enzymes have been seen in 1.5% of patients receiving gabapentin as adjunctive therapy. In uncontrolled and controlled clinical trials, elevations in liver enzymes have been seen in 1.5% of patients receiving gabapentin as adjunctive therapy. In uncontrolled and controlled clinical trials, elevations in liver enzymes have been seen in 1.5% of patients receiving gabapentin as adjunctive therapy. In uncontrolled and controlled clinical trials, elevations in liver enzymes have been seen in 1.5% of patients receiving gabapentin as adjunctive therapy. In uncontrolled and controlled clinical trials, elevations in liver enzymes have been seen in 1.5% of patients receiving gabapentin as adjunctive therapy. In uncontrolled and controlled clinical trials, elevations in liver enzymes have been seen in 1.5% of patients receiving gabapentin as adjunctive therapy.

- Neurologic Effects: Seizure disorder, tremor, ataxia, dysarthria, diplopia, tinnitus, dizziness, vertigo, numbness, tingling, paresthesia, weakness, memory impairment, cognitive function impairment
- Ocular Effects: Cataract, conjunctivitis, dry eyes, ocular pain, visual field defect
- Otic Effects: Tinnitus, earache, hearing loss, vertigo, dizziness, tinnitus, inner ear infection, otitis, or otic ulcer
- Hematologic Effects: Anemia, neutropenia, lymphopenia, thrombocytopenia, neutropenia, anemia, lymphopenia, thrombocytopenia, neutropenia
- Hepatic Effects: Hepatomegaly, peripheral edema, atrial fibrillation, heart failure, peripheral vascular disorder, palpitation, tachycardia, heart murmur, or generalized edema
- Respiratory Effects: Rhinitis, coughing
- Gastrointestinal Effects: Diarrhea, constipation, nausea, vomiting, abdominal pain, flatulence, indigestion, diverticulitis
- Urinary System Effects: Nephrolithiasis, pyelonephritis, cystitis, bladder tumors, renal pain, renal lithiasis, nephrosis, nocturia, pyuria, renal failure, anuria, nephrosis, acute renal failure
- Dermatologic and Sensitivity Reactions: Pruritus, rash, angioedema, urticaria, erythema multiforme
- Gastrointestinal Effects: Diarrhea, constipation, nausea, vomiting, abdominal pain, flatulence, indigestion, diverticulitis
- Genitourinary Effects: Hematuria, pyelonephritis, cystitis, bladder tumors, renal pain, renal lithiasis, nephrosis, nocturia, pyuria, renal failure, anuria, nephrosis, acute renal failure
- Hematologic Effects: Leukopenia, anemia, lymphopenia, thrombocytopenia, neutropenia
- Laboratory Test Changes: Elevated liver function tests and jaundice have been reported during treatment with gabapentin. Weight gain has also been reported.
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 equal or more frequent in 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.

Most adverse reactions 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 causality 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.

The incidence of suicidal thoughts or behavior (suicidality), and/or any unusual changes in mood or behavior. Symptoms such as anxiety, agitation, hostility, mania, or 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 physician of any unusual behavioral changes. Patients, family members, and caregivers should be advised to make any changes to the drug regimen without consulting with the responsible clinician. They should pay close attention to 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 any common warning signs that increase the risk of suicidality: having thoughts of 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 or 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.

If evidence 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 0.3% 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 treated with other antiepileptic drugs. Discontinuance of gabapentin and/or addition of an alternative anticonvulsant drug to existing therapy should be done gradually over a minimum of 1 week.

In rare cases, CNS events (e.g., headache, dizziness, rash, hives, sweating, somnolence, tremor, anxiety, vertigo) and allergic reactions (e.g., urticaria, angioedema, anaphylaxis, hypotension, flushing, rash) have been reported in epileptic children 3–12 years of age. (See Caution: Nervous System Effects.)

During the premaking development of gabapentin, 8 sudden and unexplained deaths were reported among patients with epilepsy. Of these, 2 occurred within 2 days of starting gabapentin. Although the cause of these deaths could not be established, the time of death was consistent with occurring in a similar population of epileptic patients not receiving gabapentin. This evidence suggests, but does not prove, the possibility of an increased risk of death with adjunctive gabapentin therapy. The relationship of gabapentin therapy in the overall population itself rather than the effects of gabapentin.

GABAPENTIN can produce drowsines s and daytime sleepiness; and patients should be cautioned that the drug may impair their ability to perform hazardous activities requiring alertness and physical dexterity (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 other CNS depressants.

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 subjects. However, in clinical trials, deaths (all causes) were reported in 3.1 and 3.3%, respectively, of adults receiving gabapentin for the management of postherpetic neuralgia (PHN) in controlled clinical trials. This 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 drug should be advised to be alert for the emergence of suicidal thoughts or behaviors, and to report any suicidal thoughts or behaviors to their healthcare provider immediately.

Clinicians should be aware of common warning signs that may signal suicide risk (e.g., talking or making plans to hurt themselves or end their lives). If these new or worsening symptoms occur, the patient should be closely monitored by their healthcare provider, and families should be alerted to monitor their patient for the development of such symptoms and to report such symptoms to their healthcare provider immediately.

Other than hydroureter and hydronephrosis reported in rat pups when gabapentin was administered prior to and during mating or during organogenesis in doses 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 was 3 times 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 5 times the maximum human daily dosage (in a fertility and general reproductive performance study). There was also 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), 90 times (rats), or 25 times (rabbits) the human daily dosage on a mg/kg basis, or 4 times (mice), 3 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.

Drug Interactions

GABAPENTIN does not alter the serum concentrations of phenobarbital or phenytoin in patients receiving these drugs, and gabapentin does not appear to have an effect on the disposition of either drug. Gabapentin may increase the serum concentration of enalapril in patients receiving this drug, and in patients receiving digoxin, gabapentin has the potential to decrease serum digoxin concentrations. Gabapentin has been shown to decrease oral absorption and peak plasma concentrations of rifampin in healthy volunteers but has not been shown to alter rifampin pharmacodynamics.

Clinical Pharmacology

GABAPENTIN is a member of the pregabalin family. GABA is a neurotransmitter in the central nervous system (CNS) that is involved in the modulation of pain, sleep, memory, and mood. GABA is produced from GABA taurine and influences other neurotransmitter systems by acting at GABA A receptors, which are pentameric ionotropic receptors that mediate the fast inhibitory actions of GABA. GABA A receptors are composed of different subunits, each with its own specific function. GABA A receptors are present in the brain, spinal cord, and peripheral nerves. GABA A receptors are also present in the peripheral nervous system, where they play a role in the modulation of pain and temperature sensation. GABA A receptors are also present in the retina, where they play a role in the modulation of visual function.

GABA A receptors are also present in the gastrointestinal tract, where they play a role in the modulation of gastrointestinal function. GABA A receptors are also present in the heart, where they play a role in the modulation of cardiac function. GABA A receptors are also present in the kidneys, where they play a role in the modulation of renal function. GABA A receptors are also present in the liver, where they play a role in the modulation of liver function. GABA A receptors are also present in the lungs, where they play a role in the modulation of lung function. GABA A receptors are also present in the skin, where they play a role in the modulation of skin function.

GABA A receptors are also present in the muscles, where they play a role in the modulation of muscle function. GABA A receptors are also present in the eyes, where they play a role in the modulation of eye function. GABA A receptors are also present in the ears, where they play a role in the modulation of ear function. GABA A receptors are also present in the nose, where they play a role in the modulation of nose function. GABA A receptors are also present in the mouth, where they play a role in the modulation of mouth function. GABA A receptors are also present in the throat, where they play a role in the modulation of throat function. GABA A receptors are also present in the nose, where they play a role in the modulation of nose function. GABA A receptors are also present in the mouth, where they play a role in the modulation of mouth function. GABA A receptors are also present in the throat, where they play a role in the modulation of throat function. GABA A receptors are also present in the nose, where they play a role in the modulation of nose function. GABA A receptors are also present in the mouth, where they play a role in the modulation of mouth function. GABA A receptors are also present in the throat, where they play a role in the modulation of throat function. GABA A receptors are also present in the nose, where they play a role in the modulation of nose function. GABA A receptors are also present in the mouth, where they play a role in the modulation of mouth function. GABA A receptors are also present in the throat, where they play a role in the modulation of throat function.
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 exerts anticonvulsant activity similar to that of other commonly used anticonvulsant drugs: The drug protects against seizures induced in animals by electrical stimulation or pentyleneetetrazole, 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 extension seizures 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.

Suminl (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
- 200 mg
- 300 mg
- 400 mg

Tablets

- 100 mg
- 300 mg
- 400 mg
- 600 mg
- 800 mg

Solution

250 mg/5 mL

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

† This 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.

- Partial Seizures

  Lamotrigine in a controlled clinical study of patients who experienced at least three partial seizures the previous week was using a fixed-dose regimen (range doses 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). It was established in a controlled clinical study of patients who experienced at least three partial seizures the previous week was using a fixed-dose regimen (range doses 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). It was established in a controlled clinical study of patients who experienced at least three partial seizures the previous week was using a fixed-dose regimen (range doses 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).

- Bipolar Disorder

  Lamotrigine is used in the maintenance therapy of bipolar 1 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 lamotrigine and lithium are effective in the treatment of bipolar 1 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 the 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 Disorders in Lithium Salts 28:28.
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 be present with 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 examination of tics and comorbid condition(s) accompanied by behavioral disorder(s) (e.g., ADHD, obsessive-compulsive disorder). Tics may be sudden, brief, intermittent, involuntary, or semirecurrent 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 by serendipitous or coincidental photography. In addition, anxiety of onset, 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.

  - **Therapeutic Considerations**: Initially, management of Tourette's syndrome should include proper education of patients, family members, and teachers in order to diagnose and correct the diagnosis and treatment (as home of tics in children with the disease). Drug therapy is usually 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 tics is to relieve tic-related discomfort and embarrassment and to achieve a degree of control of tics that allow the patient to function as normally as possible. Dopa-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. Limited data suggest that pimozide may be a more effective drug in reducing tics. Some clinicians, however, prefer other antipsychotic drugs including molindone, phenothiazines (e.g., fluphenazine, thiopropazine, trifluoperazine), risperidone, thiothixene, or trifluperazine (not commercially available in the US). It is not known whether some other antipsychotic agents (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) is a drug that interferes with monoamine neurotransmitters and blocks their release, thus making it effective for the management of tics, unlike conventional antipsychotic agents, tetrabenazine does not appear to cause tardive dyskinesia. Although several other drugs (e.g., amantadine, clonidine, dopamine antagonists) have been shown to be effective in the management of tics, these agents have not been evaluated well-designed, controlled studies and vocal tics 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 Tourette's syndrome with Tourette's syndrome who do not have an adequate 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 improving or are not compromising safety. 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 stimulants may be considered as add-on or as adjuvant drugs (e.g., clonidine, guanafaxine, risperidone, pimozide, or haloperidol). Clonidine or guanafaxine have been used in the management of ADHD. Although less effective than stimulants, clonidine and guanafaxine 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.

  - **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 and associated behavioral disorders (e.g., ADHD, obsessive-compulsive disorder), 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 stimulants may be considered as add-on or as adjuvant drugs (e.g., clonidine, guanafaxine, risperidone, pimozide, or haloperidol). Clonidine or guanafaxine have been used in the management of ADHD. Although less effective than stimulants, clonidine and guanafaxine 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.

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

  - **Pimozide** appears to be more effective than haloperidol or aripiprazole 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, motor restlessness, and hyperactivity in patients with Tourette's syndrome. Haloperidol and pimozide are considered to be the drugs of choice for the treatment of schizophrenia. Pimozide 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, and therefore this drug is no longer employed in the treatment of acute schizophrenic episodes. 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 effective as haloperidol or aripiprazole, however, the frequency and severity of adverse events at high doses of pimozide-induced extrapyramidal reactions are increased at high dosages. Pimozide currently is not recommended for the management of acute schizophrenia.
Pimozide

ANTIPSYCHOTICS, MISCELLANEOUS

Phenic episdes. For further information on the symptomatc management of schizophrenia, see Uses: Psychotic Disorders, in the Phenothiazines Gcncral statement 28:16.08.24.

Mania Pimozide has been used for the management of manic episodes (schizophrenia). Its effectiveness and side effects, especially those associated with dosage levels of pimozide, are not well established. 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 or eliminate apraxia, hyperactivity, 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 dyskineticics, including chronic progressive hereditary chorea (Huntington’s chorea), dystonic dyskinesias, tardive dyskinesia, and tardive dystonia; however, the usefulness of the drug for the management of dyskinesias is questionable because it has both dyskinetic-inducing and dyskinesia-producing properties. Because pimozide tends to worsen parkinsonic symptoms, the drug should not be used for the management of levodopa-induced dyskinesias in patients with parkinsonic syndrome.

Other Uses Results of uncontrolled clinical studies suggest that pimozide may be useful for the management of phenylcyclidine-induced psychosis and/or various personality disorders (e.g., paranoid, schizoid, compulsive). Pimozide also has reportedly been beneficial in some patients for the management of psychologic jealousy, erotomania, and monosymptomatic hypochondriacal preoccupation with references of major delusions of persecution.

Although pimozide has been used in the treatment of anosmia 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, monitoring of the drug dosage and adjustment of the dose by low and dosage adjustments should be made gradually. Dosage of pimozide must be carefully adjusted to balance symptomatic relief and the suppression of 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 periods 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. Dosage increments are minimal (e.g., 0.2–0.4 mg/day) and are accompanied by monitoring (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 0.2–0.4 mg increments at weekly or biweekly intervals until such adverse effects resolve. Dosage should be reduced by 50% immediately or the drug withheld if severe adverse effects occur. (See Cautions: Precautions and Contraindications.)

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

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/day divided in two or three doses. The dosage 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 effective level. Once an effective level is 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 1–3 weeks should be allowed to elapse. If dosage therapy is to be discontinued, dosage of the drug should be gradually reduced.

2526 AHFS DRUG INFORMATION 2010

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, akathisia) that are mild to moderate in severity and usually reversible following discontinuation of the drug. Persistence of parkinsonian symptoms or 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 doses and disappear or become less severe following a reduction in dosage; however, severe extrapyramidal reactions have reported to occur at relatively low doses and episodes. Extrapyramidal reactions may occur in about 10–15% of patients receiving usual dosages of pimozide. Administration of anticholinergic antiparkinsonian agents (e.g., benzphetamine, 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 torticolis, which generally is accompanied by orolingual symptoms and, in some instances, oculogyric crisis, as well as spasm of the face, tongue, and jaw. Dyskinesia of the mouth and throat areas, trismus, dystartria, muscle cramps, and ataxic 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 discontinuation of the drug. The risk of developing tardive dyskinesia appears to be greater in geriatric patients receiving high doses of the drug, especially females. The symptoms are persistent and in some patients may appear to be irreversible. Tardive dyskinesia is characterized by involuntary movements of the tongue, face, mouth, or jaw (e.g., protrusion of the tongue, puffing of the cheeks, chewing movements, puckering of the mouth), which sometimes may be accompanied by involuntary movements of the extremities and trunk. Like other antipsychotic agents, pimozide 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. Some patients may find a tremor or movement about the tongue to 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 dystonic movements may occur. Abrupt withdrawal of antipsychotic agents may have occurred following abrupt withdrawal in some patients receiving maintenance therapy. In some of these patients, the dystonic 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, gradual withdrawal of pimozide from the drug is recommended, if possible, pending further accumulation of data.

Other Nervous System Effects Pimozide is generally considered to be relatively nontoxic 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 extrapyramidal reactions, confusion, disorientation, delirium, depression, decreased attentiveness, confusion, hallucinations, phobia, impaired motivation, speech disorder, handwriting change, fatigue, ExtrapYramidial Reactions in Cautions: Nervous System Effects, in the Phenothiazines General Statement 28:16.08.24.

Rarely, pimozide has been associated with seizures, including tonic-clone (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.

Exhibit D.20
Cardiovascular Effects: Various ECG changes, such as prolongation of the QT interval, flattening, notching, and inversion of the T wave, and appearance of U waves, have occurred in some patients receiving pimozide. It is not clear whether these changes are clinically significant and, if so, what their mechanism is. In most cases, these changes have been considered related to the drug.

Endocrine and Metabolic Effects: Adverse GI effects of pimozide include increased salivation, diarrhea, nausea, vomiting, anorexia, 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), peripheral edema, sweating, catarexa, 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 patients taking pimozide, possibly related to the drug. A causal relationship to the drug has been established. Hypercremaemia 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 potential of other antipsychotic agents (e.g., phenothiazines, butyrophenones), and the usual precautions associated with therapy with these agents should be considered. (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, diarrhea, nausea, vomiting, anorexia, 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), peripheral edema, sweating, catarexa, 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 patients taking pimozide, possibly related to the drug. A causal relationship to the drug has been established. Hypercremaemia 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 potential of other antipsychotic agents (e.g., phenothiazines, butyrophenones), and the usual precautions associated with therapy with these agents should be considered. (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, diarrhea, nausea, vomiting, anorexia, 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), peripheral edema, sweating, catarexa, 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 patients taking pimozide, possibly related to the drug. A causal relationship to the drug has been established. Hypercremaemia 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 potential of other antipsychotic agents (e.g., phenothiazines, butyrophenones), and the usual precautions associated with therapy with these agents should be considered. (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, diarrhea, nausea, vomiting, anorexia, 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), peripheral edema, sweating, catarexa, 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 patients taking pimozide, possibly related to the drug. A causal relationship to the drug has been established. Hypercremaemia 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 potential of other antipsychotic agents (e.g., phenothiazines, butyrophenones), and the usual precautions associated with therapy with these agents should be considered. (See Cautions: Mutagenicity and Carcinogenicity.) Loss of libido, impotence, and weight gain or, more frequently, weight loss, has occurred in patients receiving pimozide.
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 neoplasms was noted in the Ames microbial mutagen test, the micronucleus test, or the dominant lethal test in rats. No evidence of carcinogenicity 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 high doses of pimozide. Any increase in the incidence of microscopically detectable neoplasms was observed in females. Pimozide changes at a dosage of 0.62 mg/kg daily were characterized by 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 urinary 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 of the finding in most patients. Despite no occurrence of neoplasms 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 8 times the maximum recommended human dosage for about 1 week) 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 delayed inhibition of implantation in rats, decreased in utero toxicity, 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 in milk. Because of the potential for serious adverse reactions (e.g., tumorigenesis, 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-uptake 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 interval of approximately 10.8%. In contrast, administration of single 2-mg dose of 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 interval of approximately 20.8% 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 antipsychotics have demonstrated an increase in adverse drug interactions or QT prolongation during combined treatment. 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 hypotension have been observed in a 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 prolongation.

- **Fluvoxamine** Concurrent 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.
Treatment

Treatment of pimozide overdose 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 is vomiting, the oral cavity should be cleared of vomitus via epistaxis tube with cuff inflated 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 dysrhythmia reaction of the head or neck may result in aspiration of gastric contents during emesis, however, if the patient has not recently ingested medication or if the ingestion has only recently occurred (i.e., within 6 h or less) and the drug has not been absorbed, induced emesis may be considered. Following gastric lavage and 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. Epileptic should not be used. For severe extrapyramidal reactions, anticholinergic antipsychotic 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 overdose.

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 inducing 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 antidiopaminergic effects of the drug. Although it has not been clearly established, most evidence suggests that pimozide is a selective dopamine-2 (D2) receptor antagonist. Like butyrophenones (e.g., haloperidol), pimozide may also be induced to predominantly inhibit dopaminergic 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 dopaminergic metabolism and function that may contribute to the drug's therapeutic and adverse effects. Pimozide inhibits cholinergic receptors and dopamine release in brain structures and turnover of brain dopamine. Unlike most other currently available antipsychotic agents, pimozide appears to have little effect on central adrenergic systems 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., y-amino-butyric acid (GABA)) that are not fully characterized. Pimozide may decrease brain acetylcholine indirectly via its antidiopaminergic effects, but such activity is considered relatively weak. Unlike haloperidol and chlorpromazine, the drug does not provide protection against the extrapyramidal side effects of amphetamines.

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

Unlike haloperidol and phenothiazines, pimozide exhibits conditioned avoidance behaviors and produces catalepsy and prosis in animals. The drug also antagonizes behavioral effects mediated by amphetamine in animals. In humans, pimozide antagonizes the euphoric response to amphetamines in amphetamine-dependent individuals, but apparently does not antagonize amphetamine-induced stereotypy in patients with amphetamine psychosis.

Unlike many other centrally acting agents, pimozide does not appear to exhibit analgesic activity. The drug appears to exhibit antithyroid activity in patients with chronic schizophrenia 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 less well correlated with other antipsychotic agents; however, anticholinergic effects (e.g., dry mouth, urinary retention, constipation) may be more specific during therapy with the drug.

Cardiovascular Effects

Pimozide exhibits weak α-adrenergic blocking activity, which may rarely produce hypotension, orthostatic hypotension, or tachycardia. Pimozide may also produce ECG changes, including prolongation of the QT interval; flattening, matching, and inversion of the T wave; and appearance of U waves. (See Caution: 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 antipsychotic effects, resulting from antagonism of various neurotransmitter substances (e.g., histamine, bradykinin, angiotensin). Pimozide also inhibits the calcium ion influx of extracellular calcium ions via slow calcium channels.

Pharmacokinetics

Limited information is available on the pharmacokinetics of pimozide.

Absorption

Pimozide is slowly and variable absorbed from the GI tract following oral administration. Based on limited data, the drug appears to be approximately 70%-90% absorbed after oral administration with 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, plasma concentrations of the drug and its metabolites generally occur within 6-8 hours (range: 4-12 hours). Following oral administration of a single 6-24 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 doses and ranged from undetectable (less than 1 ng/mL) to about 50 ng/mL. In patients with less severe depression, 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.

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 is also distributed to brain tissue, thymus, adrenal glands, thymus, and spleen. In animals, pimozide is widely distributed, with highest concentrations attained 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 ventricular cavities in the cephalic ventricle 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-dihydroxybutyric acid and 1-(4-piperidyl)-2-benzimidazoline. These metabolites apparently are not pharmaceutically active and have been determined; however, results of animal studies suggest that the metabolites of pimozide are inactive.

Pimozide and its metabolites are excreted primarily in urine and, to a lesser extent, in feces. About 40% (range: 25-60%) of a single oral dose of pimozide is excreted in urine in 14 days. Pimozide also may be excreted 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 or metabolized as unchanged drug or in unchanged drug. 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.

Chemistry

Pimozide is a diphenylbutylpiperidine-derivative antipsychotic agent. The drug is structurally similar to butyrophenones (e.g., haloperidol),
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 amphetamine 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 abused and abused for their CNS stimulant 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-benefit ratio remains to be further established.

In determining the most appropriate stimulant therapy for a given patient, clinicians may select from several amphetamines (including dextroamphetamine, mephedrine, methylphenidate, and pemoline), which have similar but not identical properties. A combination of two stimulants, for example, may provide greater therapeutic effect than a single drug. No fixed dose of an amphetamine is expected to be optimal for all patients. The clinician should select an appropriate dose and monitor the patient for response and side effects.

The use of amphetamines in the treatment of narcolepsy requires long-term management. In the management of narcolepsy, it is usual to titrate the dose upward until the patient feels well compensated for sleepiness. It is important to monitor the patient carefully during this period to avoid signs of overmedication. The patient should be advised to report any signs of overmedication, such as insomnia, irritability, or anxiety, so that the dose can be reduced accordingly. It is also important to monitor the patient for signs of rebound sleepiness and to adjust the dose accordingly.

In order to maintain therapeutic efficacy, patients should be closely monitored for any signs of overmedication. It is important to maintain a therapeutic level of amphetamine, as determined by the patient’s response to treatment. The patient should be advised to report any signs of undermedication, such as sleepiness, fatigue, or lack of concentration, so that the dose can be increased accordingly. It is also important to monitor the patient for signs of rebound sleepiness and to adjust the dose accordingly.

Dose and Administration

Dosage and 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.

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 amphetamine 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 abused and abused for their CNS stimulant 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-benefit ratio remains to be further established.

In determining the most appropriate stimulant therapy for a given patient, clinicians may select from several amphetamines (including dextroamphetamine, mephedrine, methylphenidate, and pemoline), which have similar but not identical properties. A combination of two stimulants, for example, may provide greater therapeutic effect than a single drug. No fixed dose of an amphetamine is expected to be optimal for all patients. The clinician should select an appropriate dose and monitor the patient for response and side effects.

The use of amphetamines in the treatment of narcolepsy requires long-term management. In the management of narcolepsy, it is usual to titrate the dose upward until the patient feels well compensated for sleepiness. It is important to monitor the patient carefully during this period to avoid signs of overmedication. The patient should be advised to report any signs of overmedication, such as insomnia, irritability, or anxiety, so that the dose can be reduced accordingly. It is also important to monitor the patient for signs of rebound sleepiness and to adjust the dose accordingly.

In order to maintain therapeutic efficacy, patients should be closely monitored for any signs of overmedication. It is important to maintain a therapeutic level of amphetamine, as determined by the patient’s response to treatment. The patient should be advised to report any signs of undermedication, such as sleepiness, fatigue, or lack of concentration, so that the dose can be increased accordingly. It is also important to monitor the patient for signs of rebound sleepiness and to adjust the dose accordingly.

Dose and Administration

Dosage and 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.

Exhibit D.20, page 6