Dosage and Administration

■ **Administration** Amoxapine is administered orally. Although amoxapine has been administered in 3 divided doses throughout the day, it is long-acting and, when dosage does not exceed 300 mg daily, the entire daily dose may be administered at one time, preferably at bedtime to avoid daytime sedation. When dosage exceeds 300 mg daily, the daily dose should be given in divided doses.

■ **Dosage** There is a wide range of amoxapine dosage requirements, and dosage of the drug must be carefully individualized.

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

The usual effective dosage of amoxapine is 200–300 mg daily. The usual initial dosage is 100–150 mg daily. Depending on tolerance and response, dosage may be increased to 200–300 mg daily by the end of the first week of therapy. An initial dosage of 300 mg daily may be given, but considerable sedation may occur in some patients during the first few days of therapy at this dosage level. If no response occurs after administration of 300 mg of amoxapine daily for at least 2 weeks, dosage may be increased to a maximum of 400 mg daily in outpatients. Hospitalized patients under close supervision may generally be given higher dosages than outpatients; dosage may be increased cautiously up to 600 mg daily in divided doses in hospitalized patients who have not responded adequately and do not have a history of seizures. Single doses should not exceed 300 mg.

Geriatric patients should usually be given lower than average dosages. Therapy usually should be initiated with 50–75 mg daily in these patients and may be increased to 100–150 mg daily by the end of the first week of therapy, if tolerated. Some geriatric patients may require further increases in dosage; however, dosage in geriatric patients should not exceed 300 mg daily.

Antidepressant effects usually occur within 2 weeks in most patients who respond to amoxapine therapy and may occur within 4–7 days.

After symptoms are controlled, dosage should be gradually reduced to the lowest level which will maintain relief of symptoms.

Cautions

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

Extrapyramidal reactions have occurred in less than 1% of patients receiving amoxapine. In addition, tardive dyskinesia has been reported rarely in patients receiving the drug. Like antipsychotic agents, amoxapine 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.

■ **Pediatric Precautions** Safety and efficacy of amoxapine for the treatment of depression in children younger than 16 years of age have not been established.

The US Food and Drug Administration (FDA) has determined that antidepressants increase the risk of suicidal thinking and behavior (suicidality) in children and adolescents with major depressive disorder and other psychiatric disorders. However, FDA also states that depression and certain other psychiatric disorders are themselves associated with an increased risk of suicide. Anyone considering the use of amoxapine in a child or adolescent for any clinical use must therefore balance the potential risk of therapy with the clinical need. (See Cautions: Precautions and Contraindications and Cautions: Pediatric Precautions, in the Tricyclic Antidepressants General Statement 28:16.04.28.)

Pharmacokinetics

■ **Absorption** Amoxapine is rapidly and almost completely absorbed from the GI tract. Peak plasma concentrations of amoxapine occur within 1–2 hours after a single oral dose.

■ **Distribution** In rats, amoxapine is widely distributed throughout body tissues, with highest concentrations distributed into lungs, spleen, kidneys, heart, and brain and lower concentrations distributed into testes and muscle.

Amoxapine is approximately 90% bound to plasma proteins.

Amoxapine and 8-hydroxyamoxapine have been detected in human milk in concentrations of approximately one-fifth and one-third those of maternal steady-state serum concentrations, respectively.

■ **Elimination** The plasma half-life of amoxapine is approximately 8 hours. Amoxapine is metabolized in the liver principally to 8-hydroxyamoxapine and, to a lesser extent, to 7-hydroxyamoxapine; both metabolites are pharmacologically active and have half-lives of 30 hours and 6.5 hours, respectively.

Approximately 60–69% of a dose of amoxapine is excreted in urine within 6 days principally as conjugated metabolites; approximately 7–18% of the drug is excreted in feces principally as unconjugated metabolites. Less than 5% of amoxapine is excreted in urine as unchanged drug.

Chemistry and Stability

■ **Chemistry** Amoxapine, a tricyclic dibenzoxazepine derivative, is the desmethyl analog of loxapine. Amoxapine differs structurally from the dibenzazepine, dibenzocycloheptene, and dibenzoxepin tricyclic antidepressants in that it has both a nitrogen and an oxygen atom in its 7-membered ring and a piperazinyl ring rather than a propylamino chain attached to the center ring. Amoxapine occurs as a white to pale yellow, crystalline powder and is slightly soluble in water and in alcohol. The drug has an apparent pK_a of 7.6.

■ **Stability** Amoxapine tablets should be stored in tight containers at 15–30°C.

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

Preparations

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

Amoxapine

Oral		
Tablets, scored	25 mg*	Amoxapine Tablets
	50 mg*	Amoxapine Tablets
	100 mg*	Amoxapine Tablets
	150 mg*	Amoxapine Tablets

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

Clomipramine Hydrochloride

Chlorimipramine Hydrochloride, Chloroimipramine Hydrochloride, CMI

■ Clomipramine, a dibenzazepine-derivative tricyclic antidepressant, is the 3-chloro analog of imipramine.

Uses

■ **Obsessive-Compulsive Disorder** Clomipramine is used in the treatment of obsessive-compulsive disorder when obsessions or compulsions cause marked distress, are time-consuming (take longer than 1 hour daily), or interfere substantially with the patient's normal routine, occupational or academic functioning, or usual social activities or relationships. Obsessions are recurrent and persistent thoughts, impulses, or images that, at some time during the disturbance, are experienced as intrusive and inappropriate (i.e., "ego dystonic") and that cause marked anxiety or distress but that are not simply excessive worries about real-life problems. Compulsions are repetitive behaviors (e.g., hand washing, ordering, checking) or mental acts (e.g., praying, counting, repeating words silently) performed in response to an obsession or according to rules that must be applied rigidly (e.g., in a stereotyped fashion). Although the behaviors or acts are aimed at preventing or reducing distress or preventing some dreaded event or situation, they either are not connected in a realistic manner with what they are designed to neutralize or prevent or are clearly excessive. At some time during the course of the disturbance, the patient, if an adult, recognizes that the obsessions or compulsions are excessive or unreasonable; children may not make such recognition.

The efficacy of clomipramine for the management of obsessive-compulsive disorder has been established in several multicenter, placebo-controlled, parallel-group studies, including 2 studies of 10 weeks' duration in adults and one study of 8 weeks' duration in children and adolescents 10–17 years of age. In these clinical studies, clomipramine was more effective than placebo in reducing the severity of obsessive-compulsive manifestations in patients with moderate to severe obsessive-compulsive disorder. The drug produced substantial improvement in scores on both the Yale-Brown Obsessive-Compulsive Scale (YBOCS) and the National Institute of Mental Health (NIMH) Clinical Global Obsessive-Compulsive Scale (NIMH-OC), while the response with placebo was clinically insignificant. Scores on the YBOCS decreased by an average of approximately 10 from baseline values of 26–28, representing an average improvement of 35–42% in adults and 37% in children and adolescents treated with clomipramine. Scores on the NIMH-OC were reduced by an average of 3.5 units from a mean baseline of 10 in adults, children, and adolescents treated with clomipramine, which represents an improvement in obsessive-compulsive disorder from severe at baseline to subclinical after treatment with the drug. The maximum dosage of clomipramine hydrochloride was 250 mg daily for most adults and 3 mg/kg (up to 200 mg) daily for children and adolescents.

Although obsessive-compulsive manifestations often persist to some extent

in patients who respond to clomipramine, responders generally find it easier to resist the manifestations and spend less time engaged in the associated behavior. Data from a retrospective analysis suggest that clomipramine may be more effective in patients who developed obsessive-compulsive disorder during middle age (35–62 years of age) than in those in whom onset occurred during early adulthood (16–23 years old), independent of the length of illness.

Therapeutic response to clomipramine in patients with obsessive-compulsive disorder generally is evident within 2–6 weeks but may not be maximal until 3–4 months after beginning therapy with the drug. Thus, it is essential that patients receive an adequate trial of clomipramine at a therapeutic dosage in order to determine efficacy.

Many clinicians consider clomipramine or a serotonin-reuptake inhibitor (e.g., fluoxetine, fluvoxamine) to be the drugs of choice in obsessive-compulsive disorder. In addition, behavior therapy often is recommended in patients with obsessive-compulsive disorder even when pharmacologic therapy alone has been partially effective.

Results from comparative studies to date suggest that clomipramine is more effective than other tricyclic antidepressants (e.g., amitriptyline, desipramine, imipramine, nortriptyline) and as or more effective than selective serotonin-reuptake inhibitors (e.g., fluoxetine, fluvoxamine) in the management of obsessive-compulsive disorder. In a pooled analysis of separate short-term (10–13 weeks) studies comparing clomipramine, fluoxetine, fluvoxamine, or sertraline with placebo, clomipramine was calculated as being more effective (as determined by measures on the YBOC scale) than selective serotonin-reuptake inhibitors, although all drugs were superior to placebo. Like clomipramine, selective serotonin-reuptake inhibitors reduce but do not completely eliminate obsessions and compulsions. The decision whether to initiate therapy with clomipramine or a selective serotonin-reuptake inhibitor often is made based on the adverse effect profile of these drugs. For example, some clinicians prefer clomipramine in patients who may not tolerate the adverse effect profile of selective serotonin-reuptake inhibitors (nausea, headache, overstimulation, sleep disturbances) while selective serotonin-reuptake inhibitors may be useful alternatives in patients unable to tolerate the adverse effects (anticholinergic effects, cardiovascular effects, sedation) associated with clomipramine therapy. Consideration of individual patient characteristics (age, concurrent medical conditions), the pharmacokinetics of the drug, potential drug interactions, and cost of therapy may also influence clinicians when selecting between clomipramine and selective serotonin-reuptake inhibitors as first-line therapy in patients with obsessive-compulsive disorder. Although not clearly established, it has been suggested that the mechanism of action of clomipramine and other drugs (fluoxetine, fluvoxamine) used in the management of obsessive-compulsive disorder may be related to their serotonergic activity. Clomipramine also has been effective when used in combination with clonidine in several patients with obsessive-compulsive disorder; however, additional experience is needed to confirm the safety and efficacy of this combination.

The manufacturers state that the efficacy of clomipramine for long-term use (i.e., longer than 10 weeks) in the treatment of obsessive-compulsive disorder has not been established in placebo-controlled studies. After 36 weeks of treatment with clomipramine, improvement compared with placebo was observed on measures of rituals, mood, and social adjustment, although such effects were more substantial after 18 weeks of treatment. At follow-up 22 weeks after treatment ended, clomipramine differed from placebo on one measure of rituals. Clomipramine was not distinguishable from placebo in efficacy at follow-up 6 years after the conclusion of treatment. The combination of clomipramine or placebo with the same behavioral therapy resulted in greater improvement with clomipramine on measures of rituals, mood, and social adjustment at 8 weeks of treatment, but thereafter through the last 15 weeks of treatment and at follow-up through 52 weeks, clomipramine was indistinguishable from placebo. However, clomipramine has been used in some patients for prolonged periods (e.g., up to 1 year) without apparent loss of clinical effect. If clomipramine is used for extended periods, dosage should be adjusted so that patients are maintained on the lowest effective dosage, and the need for continued therapy with the drug should be reassessed periodically.

Discontinuance of clomipramine frequently results in a progressive recurrence of symptoms in patients with obsessive-compulsive disorder, and therefore long-term continued therapy with the drug may be advisable on an individual basis. In a study conducted under double-blind conditions, most patients with obsessive-compulsive disorder who had improved clinically following 5–27 months of clomipramine therapy experienced profound worsening of manifestations after discontinuance of the drug. This worsening started at 4 weeks and continued for the rest of the 7-week placebo period and appeared to be unrelated to the duration of clomipramine therapy or to the type of obsessive-compulsive manifestations originally present. However, readministration of clomipramine resulted in clinical improvement similar to that obtained prior to discontinuance of the drug.

Disorders with an Obsessive-Compulsive Component Depressive episodes may be associated with obsessive-compulsive disorder. Clomipramine and selective serotonin-reuptake inhibitors are effective antidepressants when obsessive manifestations accompany an episode of major depression. However, the antiobsessional effectiveness of clomipramine does not appear to depend on the presence of depression.

Clomipramine also may reduce obsessive-compulsive manifestations in some patients with schizophrenia and such accompanying manifestations. However, exacerbation of psychosis has been reported in some patients treated with clomipramine. Therefore, the possibility of exacerbating psychosis should be considered in patients with obsessive-compulsive manifestations and schizophrenia, and such patients receiving clomipramine should be observed closely for early signs of worsening psychosis.

There is a high incidence of obsessive-compulsive disorder in patients with Tourette's disorder (Gilles de la Tourette's syndrome), and clomipramine can reduce obsessive-compulsive manifestations associated with Tourette's and suppress associated motor and vocal tics. However, in at least one controlled study, clomipramine did not differ from placebo in the number of tics observed during 4 weeks of treatment.

Obsessive thoughts were decreased with the combination of clomipramine and lithium carbonate in a limited number of patients who had obsessive manifestations that previously failed to respond to clomipramine therapy alone. However, in a study of patients with obsessive-compulsive disorder treated with clomipramine for at least 6 months and who were partial responders to the drug, the addition of lithium carbonate for 4 weeks did not result in improvement in scores on the YBOCS.

■ **Panic Disorder** Clomipramine has been used effectively for the treatment of panic disorder† with or without agoraphobia†. In an uncontrolled study, clomipramine reduced both the weekly frequency and severity of panic attacks when given in an average dosage of 45 mg daily (range: 6.25–75 mg daily). In many patients, complete or nearly complete relief from panic attacks was reported during therapy. The number of days that panic attacks occurred was less with clomipramine (mean dosage of 83 mg daily) than with placebo after 8 weeks of treatment in one study. Therapeutic response generally is seen within about 1–3 weeks but may take up to 6 weeks. Although clomipramine therapy generally is well tolerated, a transient increase in the number and intensity of panic attacks may occur during initial therapy with the drug. (See Dosage and Administration: Dosage.) Clomipramine (mean dosage of 109 mg daily; range: 25–200 mg daily) was at least as effective as imipramine (mean dosage of 109 mg daily; range: 25–200 mg daily) in patients with panic disorder and had a faster onset of action in reducing panic attacks and improving phobic avoidance and associated anxiety.

Clomipramine generally is equally effective in patients with panic disorder with or without agoraphobia. In a limited number of patients whose panic disorder with agoraphobia did not respond to exposure-based behavioral treatment, measures of fear (i.e., fear of bodily incapacitation, fear of losing control), state and trait anxiety, depression, severity of condition, and avoidance of separation situations indicated improvement compared with placebo after receiving clomipramine for about 5 weeks (3 weeks at the maximum dosage of 150 mg daily). Despite such improvement, the efficacy of clomipramine in the treatment of such patients was uncertain. A clinical response, as indicated by improvement by at least 50% on assessment of avoidance of separation situations with the Phobic Avoidance Rating Scale, was produced by clomipramine in 29% of the patients, while such response was observed with behavioral treatment in 47% of the patients.

Preliminary results from an uncontrolled study suggest that clomipramine is effective in patients with panic disorder or agoraphobia with panic attacks who have concurrent mitral valve prolapse.

Although it has been suggested that the mechanism of action of clomipramine in patients with panic disorder may be related to the drug's serotonergic activity, the absence of clear superiority compared with less selective antidepressants (e.g., desipramine) suggests that this may not be the case.

For further information on treatment of panic disorder, see Uses: Panic Disorder, in the Tricyclic Antidepressants General Statement 28:16.04.28.

■ **Major Depressive Disorder** Clomipramine has been used effectively in the treatment of major depressive disorder†. Clinical studies have shown that the antidepressant effect of clomipramine exceeds that of placebo and is comparable to that of usual dosages of other tricyclic antidepressants (e.g., amitriptyline, doxepin, imipramine) or selective serotonin-reuptake inhibitors (e.g., fluoxetine, paroxetine). Several (e.g., 4–6) weeks may be required for optimal antidepressant effect at a given clomipramine dosage. Despite comparable efficacy, the adverse effect profile (e.g., anticholinergic effects) of clomipramine may limit its usefulness relative to other antidepressants, and antidepressant therapy should be individualized based on patient response and tolerance. Clomipramine appears to offer no substantial advantage over other tricyclic antidepressants for the management of typical depression in the absence of obsessive-compulsive manifestations and may be more poorly tolerated, particularly compared with tricyclics exhibiting only mild to moderate anticholinergic effects. Although some clinicians have preferred clomipramine to other tricyclic antidepressants for atypical depression (e.g., because of clomipramine's dopaminergic activity), other agents (e.g., selective serotonin-reuptake inhibitors such as fluoxetine) generally have replaced this preference for clomipramine in such depression.

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

■ **Chronic Pain** Like other tricyclic antidepressants, clomipramine has been used for the treatment of chronic pain†, including central pain, idiopathic pain disorder, tension headache, diabetic peripheral neuropathy, and pain of other neuropathic origin (e.g., cancer pain). Antidepressants have been used alone or as adjuncts to conventional analgesics in the management of such

pain. In patients with central pain (e.g., phantom or stump pain; post-herpetic neuralgia, deafferentation pain secondary to posttraumatic nerve lesions), reduction in pain intensity, as indicated by scores on a visual analog scale for pain, was greater during treatment with clomipramine for 3 weeks than with placebo. Treatment of idiopathic pain disorder with clomipramine (mean dosage of 97 mg daily) for 6 weeks resulted in improvement, as indicated by the physicians' global assessment, in 63% of patients. The patients' scores on visual analog scales that included assessment of pain also were improved. In patients with tension headache, a greater decrease in headache pain, as indicated by scores on a visual analog scale, occurred with clomipramine administered for 6 weeks than with placebo. Treatment of diabetic peripheral neuropathy with clomipramine for 2 weeks resulted in a greater decrease compared with placebo in the severity of symptoms overall, as evaluated by a physician through use of a scale that quantified pain, paresthesia, dysesthesia, numbness, nightly deterioration, and sleep disturbances.

■ **Cataplexy and Associated Narcolepsy** Clomipramine has been used for the symptomatic management of cataplexy† in a limited number of patients with cataplexy and associated narcolepsy. Cataplexy attacks and sleep paralysis resolved or were reduced in frequency during clomipramine therapy (25–200 mg daily); however, the drug did not consistently improve sleep attacks. Although the precise mechanism of clomipramine's anticataplectic action is not known, it has been suggested that its serotonergic and REM-suppressing activity may be involved.

■ **Autistic Disorder** Clomipramine has been effective in a limited number of patients with autistic disorder†. In a double-blind study, clomipramine therapy (mean dosage: 152 mg daily) was superior to both desipramine and placebo in improving standardized ratings of autistic manifestations, including repetitive and obsessive-compulsive behaviors and hyperactivity in a limited number of pediatric outpatients aged 6–18 years with autistic disorder. However, in an open study involving younger inpatients aged 3–9 years with autistic disorder but with relatively low intellectual functioning and without prominent obsessive-compulsive manifestations, clomipramine was not found to be effective and was commonly associated with adverse effects, including acute urinary retention.

■ **Trichotillomania** Clomipramine has been used in a limited number of patients with trichotillomania† (an urge to pull out one's hair). In one double-blind, crossover study, clomipramine (mean dosage of 181 mg daily; range: 100–250 mg daily) was shown to be more effective than desipramine (mean dosage of 173 mg daily; range: 150–200 mg daily) in the short-term management of trichotillomania. However, relapse has been reported in some patients receiving long-term treatment with clomipramine.

■ **Onychophagia** Clomipramine has been used in a limited number of patients with severe onychophagia† (nail biting) and no history of obsessive-compulsive disorder. In one study, the severity of nail biting decreased in patients treated with clomipramine hydrochloride 25–200 mg daily for 5 weeks. However, the relatively high dropout rate secondary to adverse effects and drug intolerance suggests that clomipramine should not be considered as first-line therapy in most patients with onychophagia.

■ **Stuttering** Clomipramine has been used in a limited number of patients with stuttering†. Following 5 weeks of therapy (mean dosage: 147 mg daily), clomipramine improved the severity of stuttering, preoccupation with thoughts about stuttering, amount of energy spent resisting stuttering, and expectancy of stuttering. Additional study of the efficacy of clomipramine in the management of stuttering is necessary.

■ **Eating Disorders** Clomipramine has been used in a limited number of patients with anorexia nervosa†. In a placebo-controlled study, clomipramine therapy was associated with increased appetite, hunger, and calorie consumption during initial therapy; however, the drug was not associated with improved eating behavior after 8 weeks of therapy or greater weight gain. In addition, body weight did not differ between the clomipramine and placebo groups at 1-year follow-up and a measure of outcome based on nutritional status, sexual adjustment, socioeconomic adjustment, and mental state did not differ between the 2 groups at 4-year follow-up. Few controlled studies on the pharmacotherapy for anorexia nervosa have been published, and results with most drugs have been unimpressive. Because malnourished depressed patients may be particularly susceptible to the adverse cardiovascular effects or other severe toxicities (including death) of tricyclic antidepressants, the American Psychiatric Association (APA) states that tricyclic antidepressants should be avoided in underweight individuals and in those exhibiting suicidal ideation. For further information on use of antidepressants in the treatment of eating disorders see Uses: Eating Disorders, in Fluoxetine Hydrochloride 28:16.04.20.

■ **Premature Ejaculation** Clomipramine has been used with some success in the treatment of premature ejaculation†. In a controlled study, mean ejaculatory latency was prolonged in patients receiving 25 or 50 mg of the drug daily. Sexual and relationship satisfaction also was improved. A trial with drug therapy may be particularly useful in patients who fail or refuse behavioral or psychotherapeutic treatment or when partners are unwilling to cooperate with such therapy.

■ **Premenstrual Syndrome** Clomipramine has been used in the management of premenstrual syndrome†. In a limited number of women with severe premenstrual irritability and/or depressed mood, clomipramine given either continuously or intermittently (i.e., premenstrual administration) during 3 menstrual cycles at a dosage of 25–75 mg daily was more effective than placebo in reducing premenstrual irritability and depressed mood. However, preliminary data suggest that patients with premenstrual syndrome may be particularly sensitive to the adverse effects associated with the drug.

Dosage and Administration

■ **Administration** Clomipramine hydrochloride is administered orally. The drug also has been administered IM† or IV†, but a parenteral dosage form is not commercially available in the US.

During initial therapy when the dosage is being titrated, the manufacturers recommend that clomipramine be given in divided doses with meals to lessen adverse GI effects. After dosage titration, the total daily dose may be given once daily at bedtime to minimize adverse effects such as sedation during waking hours and enhance patient compliance.

■ **Dosage** Dosage of clomipramine hydrochloride is expressed in terms of the hydrochloride.

Because there is wide interindividual variation in dosage and dosage may differ in various disease states, the dosage of clomipramine hydrochloride must be individualized carefully.

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

Obsessive-Compulsive Disorder For the management of obsessive-compulsive disorder in adults, children, or adolescents, the recommended initial dosage of clomipramine hydrochloride is 25 mg daily. During the first 2 weeks of therapy, dosage should be increased gradually as tolerated to approximately 100 mg daily in adults. In children and adolescents, dosage should be increased gradually, as tolerated, during the first 2 weeks of therapy up to a maximum of 3 mg/kg or 100 mg daily, whichever is lower. This initial period of titration is intended to minimize adverse effects by permitting tolerance to develop or allowing the patient time to adapt if tolerance does not develop.

During the next several weeks, the dosage of clomipramine hydrochloride may be increased gradually up to a maximum of 250 mg daily in adults and 3 mg/kg or 200 mg daily (whichever is lower) in children and adolescents. Daily clomipramine hydrochloride dosages exceeding 250 mg in adults or 3 mg/kg (up to 200 mg) in children and adolescents should be avoided because of the increased risk of seizures (see Cautions: Nervous System Effects).

Because of the long elimination half-lives of both clomipramine and its active metabolite, desmethylclomipramine, clinicians should take into consideration that steady-state plasma concentrations may not be achieved for 2–3 weeks or even longer. Therefore, the manufacturers state that it may be appropriate to wait 2–3 weeks between any further dosage adjustments after the initial dosage titration period.

Although the optimum duration of clomipramine therapy has not been established, obsessive-compulsive disorder is a chronic condition and it seems reasonable to consider continuation of therapy in responding patients. Although the manufacturers state that the efficacy of clomipramine when given for periods exceeding 10 weeks has not been established systematically in controlled studies, the drug has been given under double-blind conditions for up to 1 year without loss of clinical efficacy. Pending further accumulation of data, some clinicians recommend that clomipramine therapy be continued for at least 18 months in patients with obsessive-compulsive disorder before attempting to discontinue therapy. However, the dosage should be adjusted during maintenance therapy so that patients are maintained on the minimum effective dosage and patients should be reassessed periodically to determine the need for continued therapy.

Clomipramine should not be used concomitantly with MAO inhibitors and it is recommended that at least 2 weeks elapse between discontinuance of therapy with a MAO inhibitor and initiation of clomipramine therapy and vice versa. A similar interval is recommended between discontinuance of therapy with a selective serotonin-reuptake inhibitor (e.g., citalopram, escitalopram, fluvoxamine, paroxetine, sertraline) and initiation of therapy with a tricyclic antidepressant agent such as clomipramine and vice versa. However, because fluoxetine and its active metabolite have a long half-life, at least 5 weeks should elapse between discontinuance of fluoxetine therapy and initiation of clomipramine therapy.

Abrupt discontinuance of clomipramine therapy should be avoided since a variety of withdrawal symptoms have been reported. (See Cautions: Nervous System Effects and also see Chronic Toxicity.) In addition, patients may experience a worsening of psychiatric status when the drug is discontinued abruptly. Therefore, it is recommended that dosage be tapered gradually (e.g., over a period of approximately 2 weeks) and the patient monitored carefully when clomipramine therapy is discontinued.

Panic Disorder For the management of panic disorder† with or without agoraphobia†, clomipramine hydrochloride usually has been effective in dosages ranging from 12.5–150 mg (maximum: 200 mg) daily. Most patients with panic attacks respond to a clomipramine hydrochloride dosage of less than 50 mg daily; however, patients with agoraphobia may require a higher dosage. Because clomipramine may worsen anxiety symptoms during initial therapy, some clinicians recommend that patients be started on a low dosage initially, and then the dosage can be increased gradually until therapeutic response or bothersome adverse effects occur.

Other Uses For the management of major depressive disorder† or chronic pain†, clomipramine hydrochloride is generally given in dosages ranging from 100–250 mg daily.

For the management of cataplexy and associated narcolepsy†, clomipramine hydrochloride has been given in dosages ranging from 25–200 mg daily.

■ **Dosage in Geriatric Patients** The manufacturers and some clinicians recommend selecting an initial clomipramine dosage at the lower end of the recommended range since decreased hepatic, renal, or cardiac function and concomitant illness and medications are more frequent in geriatric patients.

Cautions

Clomipramine shares the toxic potentials of the tricyclic antidepressants, and the usual precautions of tricyclic antidepressant administration should be observed. (See Cautions in the Tricyclic Antidepressants General Statement 28:16.04.28.)

Common adverse effects of clomipramine are extensions of its pharmacologic activity, principally anticholinergic effects; adverse effects secondary to antihistaminic and α-adrenergic activity also may occur. Like other tricyclics, adverse effects of clomipramine could affect compliance and result in dosage reduction; however, the possibility that such reductions could affect response should be considered.

In controlled studies, the most common adverse effects occurring more frequently in patients receiving clomipramine than in those receiving placebo included GI effects such as dry mouth, constipation, nausea, dyspepsia, anorexia, and increased appetite; nervous system effects such as somnolence, tremor, dizziness, nervousness, fatigue, and myoclonus; genitourinary effects such as changed libido, ejaculatory failure, impotence, and micturition disorder; sweating; weight gain; and visual changes. Approximately 20% of the 3616 patients who participated in US premarketing clinical trials for obsessive-compulsive or other disorders discontinued clomipramine therapy because of an adverse effect. About one-half of those who discontinued therapy (9% of the total) experienced multiple adverse effects, none of which could be classified as the principal reason. However, in the cases in which a principal reason for discontinuing therapy could be identified, most of the patients did so because of nervous system effects (5.4%), mainly somnolence, and GI effects (1.3%), mainly nausea and vomiting.

The incidences of adverse effects reported by the manufacturers to have occurred in at least 1% of clomipramine-treated patients were obtained from pooled data from placebo-controlled clinical trials involving 322 adults and 46 children or adolescents who received clomipramine for the treatment of obsessive-compulsive disorder. However, clinicians prescribing clomipramine should be aware that these figures cannot be used to predict the incidence of adverse effects during usual medical practice, in which patient characteristics and other factors differ from those that prevailed during these trials. Similarly, the cited incidences cannot be compared with the incidences obtained from other trials involving different treatments, uses, and investigators. However, the incidences from these trials provide the clinician with a basis for estimating the relative contribution of both drug and nondrug factors to the incidence of adverse effects in the populations studied. Various other adverse effects have been reported in 3525 out of approximately 3600 individuals who received multiple doses of clomipramine for obsessive-compulsive or other disorders during premarketing trials in the US; however, these adverse effects have not been definitely attributed to the drug.

Some evidence suggests that patients with depression may tolerate clomipramine relative to placebo more poorly than those with obsessive-compulsive disorder.

■ **Nervous System Effects** *Seizures* Seizure is the most clinically important risk associated with clomipramine therapy. However, seizure remains a relatively uncommon adverse effect of clomipramine therapy. The cumulative incidence of seizures in patients treated with clomipramine hydrochloride dosages of up to 300 mg daily was 0.64, 1.12, and 1.45% at 90, 180, and 365 days, respectively. The cumulative rates correct the crude incidence of 0.7% (25 of 3519 patients) for the variable duration of exposure to clomipramine in clinical trials. Seizures also have been associated with abrupt withdrawal of the drug.

Dose appears to be a predictor of the development of seizures. However, the influence of dose is confounded by the duration of exposure to the drug, making independent assessment of the effect of either factor alone difficult. Seizures occurred in about 0.5, or 2% of patients who received a maximum daily dose of 250 mg or higher than 250 mg, respectively, of the drug. The ability to predict seizures with daily doses exceeding 250 mg is limited because plasma concentrations achieved during clomipramine therapy may be dose dependent and vary considerably among individuals administered the same dosage.

Rare reports of fatalities in association with clomipramine-associated seizures have been reported in foreign postmarketing surveillance, but not in US clinical trials. In some of these cases, clomipramine had been administered with other epileptogenic agents, while in other cases the patients had possible predisposing medical conditions. Thus, a causal relationship between clomipramine therapy and these fatalities has not been established. (See Cautions: Precautions and Contraindications.)

Withdrawal Effects Withdrawal syndrome has been reported rarely in patients receiving clomipramine. In a limited number of patients, abrupt discontinuance of clomipramine resulted in a variety of withdrawal manifestations, including dizziness, nausea, vomiting, headache, malaise, sleep disturbance, hyperthermia, sweating, and irritability. Abrupt discontinuance of the drug also reportedly has resulted in seizures. In addition, some patients have experienced a worsening of psychiatric status when the drug was discontinued abruptly. Therefore, abrupt discontinuance of clomipramine therapy should be avoided. (See Cautions: Precautions and Contraindications.)

Serotonin Syndrome The manifestation of a group of adverse effects (e.g., tremor, myoclonus, diaphoresis, shivering, restlessness, fever, mental status changes, diarrhea) that resembles the serotonin syndrome observed in animals has been reported with clomipramine monotherapy. In an open study in which patients received clomipramine 150 mg daily for about 4 weeks for the treatment of depression, tremor of the tongue and myoclonus occurred most commonly (42 and 36% of patients, respectively). Tremor of the tongue or fingers and myoclonus were accompanied by diaphoresis and shivering in over a quarter of the patients. In most cases, these manifestations were transient and resolved despite continued therapy. More severe and sometimes fatal reactions resembling the serotonin syndrome have been reported when clomipramine has been given concurrently with other serotonergic agents such as MAO inhibitors, fluoxetine, lithium, or alprazolam. (See Drug Interactions.)

Other Nervous System Effects In controlled trials, somnolence, dizziness, or tremor was each reported in about 54% of adults and in about 46, 41, or 33%, respectively, of children and adolescents receiving clomipramine. Headache occurred in about 52% of adults and 28% of children and adolescents receiving clomipramine. Fatigue occurred in about 39% of adults and 35% of children and adolescents receiving the drug. Insomnia occurred in about 25% of adults and 11% of children and adolescents and nervousness occurred in about 18% of adults and 4% of children and adolescents treated with clomipramine.

Myoclonus occurred in about 13% of adults and 2% of children and adolescents receiving clomipramine. Motor hyperactivity that included jerking of the arms and legs during nocturnal sleep also has been reported. Memory impairment occurred in about 9 or 7% of adults or children and adolescents, respectively, receiving clomipramine. Paresthesia and anxiety each occurred in about 9 or 2% of adults or children and adolescents, respectively, receiving the drug. Twitching occurred in about 7 or 4% of adults or children and adolescents, respectively, receiving clomipramine. Impaired concentration and depression each occurred in about 5% of adults receiving clomipramine. Sleep disorder occurred in about 4 or 9% of adults or children and adolescents, respectively, treated with the drug. Disturbance of sleep by fright that was accompanied by myoclonus also has been reported in association with clomipramine therapy. Hypertonia occurred in about 4 or 2% of adults or children and adolescents, respectively, receiving the drug.

Confusion occurred in about 3 or 2% of adults or children and adolescents, respectively, receiving clomipramine. Psychosomatic disorder, speech disorder, dream abnormalities, agitation, or migraine occurred in about 3% of adults treated with the drug. Depersonalization or irritability occurred in about 2% of both adults and children or adolescents receiving clomipramine. Emotional lability occurred in about 2% of adults and aggressive reaction occurred in about 2% of children and adolescents treated with the drug. Paresis and asthenia each occurred in about 2% of children and adolescents and panic reaction occurred in about 1 or 2% of adults or children and adolescents, respectively, receiving clomipramine.

During premarketing clinical trials in patients with affective disorder, hypomania or mania was precipitated infrequently in patients receiving clomipramine therapy. Activation of mania or hypomania also has been reported in patients treated with other tricyclic antidepressants.

More than 30 cases of hyperthermia with clomipramine have been reported by foreign postmarketing surveillance systems. Most of these cases occurred in patients receiving clomipramine in combination with other drugs (e.g., antipsychotic agents). When clomipramine and an antipsychotic agent were used concomitantly, the cases sometimes were considered to be examples of neuroleptic malignant syndrome (NMS).

Abnormal thinking and vertigo each occurred in 1% or more of patients receiving clomipramine; however, a causal relationship to the drug has not been established.

Dyskinesia occurred in less than 1% of patients receiving clomipramine, although a causal relationship to the drug has not been established. Persistent tardive dyskinesia has been reported after initiation of clomipramine in a patient who was already receiving dextroamphetamine. A severe tardive dyskinesia-like syndrome consisting of orobuccal movements, choreoathetosis of the arms and other abnormal movements of the extremities, motor restlessness, and incoordination has been reported in another patient who was receiving clomipramine concurrently with thiothixene, buspirone, and trihexyphenidyl.

Other adverse nervous system effects occurring in less than 1% of clomipramine-treated patients include apathy, ataxia, coma, abnormal coordination, delirium, delusions, dysphonia, EEG abnormalities, encephalopathy, euphoria, extrapyramidal disorder, abnormal gait, hallucinations, hostility, hyperkinesia, hypnagogic hallucinations, hypokinesia, neuralgia, paranoia, phobic disorder, psychosis, sensory disturbance, somnambulism, stimulation, and teeth grinding; however, a causal relationship to the drug has not been established.

Rarely reported adverse nervous system effects for which a causal relationship to clomipramine has not been established include anticholinergic syndrome, aphasia, apraxia, catalepsy, cholinergic syndrome, choreoathetosis, hemiparesis, hyperesthesia, hyperreflexia, hypoesthesia, illusion, impaired im-

pulse control, indecisiveness, mutism, neuropathy, nystagmus, oculogyric crisis, oculomotor nerve paralysis, schizophrenic reaction, generalized spasm, stupor, and torticollis. Dystonia has been reported rarely in clomipramine-treated patients, although a causal relationship to the drug has not been established. Acute dystonia that included oculogyric crisis, torticollis, and lead-pipe rigidity has occurred in a patient receiving clomipramine. Exacerbation of motor tics and development of vocal tics also have been reported in a patient receiving the drug.

Suicidal ideation and suicide attempt have been reported in less than 1% of patients receiving clomipramine and suicide has been reported rarely. (See Cautions: Precautions and Contraindications.)

■ **Cardiovascular Effects** During clinical trials, modest orthostatic decreases in blood pressure and modest tachycardia each occurred in about 20% of patients receiving clomipramine, although patients frequently were asymptomatic. Postural hypotension occurred in about 6 or 4% of adults or children and adolescents, respectively, and tachycardia occurred in about 4 or 2% of adults or children and adolescents, respectively, receiving clomipramine in controlled clinical trials. Flushing occurred in about 8 or 7% of adults or children and adolescents, respectively, treated with the drug in controlled clinical trials.

Palpitations occurred in about 4% of both adults and children or adolescents receiving clomipramine in controlled clinical trials. Chest pain occurred in about 4 or 7% of adults or children and adolescents, respectively, and syncope occurred in about 2% of children and adolescents receiving clomipramine in controlled clinical trials.

Among approximately 1400 patients who received clomipramine during the premarketing evaluation, ECG abnormalities were observed in about 1.5% of the patients compared with 3.1% of those who received an active control and 0.7% of those receiving placebo. The most commonly observed ECG changes were ventricular premature contractions, ST-T wave changes, and intraventricular conduction abnormalities. These changes rarely were associated with clinically important symptoms; nevertheless, caution is necessary when treating patients with known cardiovascular disease with clomipramine, and gradual dosage titration is recommended in such patients.

Arrhythmia, bradycardia, cardiac arrest, extrasystoles, and pallor occurred in less than 1% of patients receiving clomipramine, although a causal relationship to the drug has not been established. Aneurysm, atrial flutter, bundle-branch block, cardiac failure, cerebral hemorrhage, heart block, myocardial infarction, myocardial ischemia, peripheral ischemia, thrombophlebitis, vasospasm, and ventricular tachycardia have occurred rarely, but these adverse effects also have not been attributed definitely to the drug. Hypertension also has been reported.

General edema, greater susceptibility to infection, malaise, and parosmia have been reported in less than 1% of clomipramine-treated patients and dependent edema has been reported rarely, although these adverse effects have not been attributed definitely to the drug.

There have been reports of fatigue and dizziness during physical exertion in children and adolescents receiving clomipramine. Because the cardiovascular effects of the drug have not been studied during such stress in this age group, some clinicians state that clomipramine should be used with caution in children and adolescents who participate in active sports.

■ **GI Effects** Adverse GI effects are encountered commonly during initial clomipramine therapy and in some cases can lead to early withdrawal of the drug. Dry mouth occurs in about 84 or 63% of adults or children and adolescents, respectively, and constipation occurs in about 47 or 22% of adults or children and adolescents, respectively, receiving clomipramine.

Nausea has been reported in about 33 or 9% of adults or children and adolescents, respectively, receiving clomipramine. Dyspepsia occurred in about 22 or 13% of adults or children and adolescents, respectively, and diarrhea occurred in about 13 or 7% of adults or children and adolescents, respectively, receiving the drug. Anorexia occurred in about 12 or 22% of adults or children and adolescents, respectively, receiving the drug. Abdominal pain occurred in about 11 or 13% of adults or children and adolescents, respectively, receiving clomipramine. Increase in appetite occurred in 11% of adults treated with the drug. Taste perversion occurred in about 8 or 4% of adults or children and adolescents, respectively, receiving clomipramine. Vomiting occurred in about 7% of clomipramine-treated adults, children, and adolescents. Flatulence has been reported in about 6% of adults receiving the drug. GI disorder or dysphagia occurred in about 2% of clomipramine-treated adults, and eructation, ulcerative stomatitis, or halitosis occurred in about 2% of children and adolescents receiving the drug. Esophagitis occurred in about 1% of adults receiving clomipramine.

Blood in stool, colitis, duodenitis, gastric ulcer, gastritis, gastroesophageal reflux, gingivitis, glossitis, hemorrhoids, increased salivation, irritable bowel syndrome, peptic ulcer, rectal hemorrhage, taste loss, and tongue ulceration were reported in less than 1% of patients receiving clomipramine, but a causal relationship to the drug has not been established. Cheilitis, chronic enteritis, discolored feces, gastric dilatation, gingival bleeding, intestinal obstruction, oral/pharyngeal edema, paralytic ileus, and salivary gland enlargement have occurred rarely but have not been attributed definitely to clomipramine.

■ **Dermatologic and Sensitivity Reactions** In controlled trials, increased sweating occurred in about 29 or 9% of adults or children and adolescents, respectively, receiving clomipramine. Rash occurred in about 8% of adults and 4% of children and adolescents treated with the drug. Pruritus occurred in about 6% of adults and 2% of children and adolescents receiving clomipramine. Dermatitis, acne, or dry skin occurred in about 2% of clomipramine-treated adults. Abnormal skin odor occurred in about 2% of children and adolescents receiving clomipramine therapy. Urticaria occurred in about 1% of adults and allergy occurred in about 3% of adults and 7% of children and adolescents treated with the drug.

Alopecia, cellulitis, cyst, eczema, genital pruritus, psoriasis, and rash that was erythematous, maculopapular, or pustular have been reported in less than 1% of patients receiving clomipramine, but these effects have not been attributed definitely to the drug. Lupus erythematosus rash has occurred rarely. Photosensitivity reaction or skin discoloration has occurred in less than 1% of patients receiving clomipramine, although a causal relationship to the drug has not been established. Pseudocyanotic (e.g., slate-gray, blue-black, purplish) pigmentation that affected areas of the body exposed to sunlight and therefore may have been a photosensitivity reaction also has occurred with clomipramine. Chloasma has been reported rarely. Folliculitis, hypertrichosis, pilocrection, polyarteritis nodosa, seborrhea, skin hypertrophy, or skin ulceration has been reported rarely in patients receiving clomipramine, although a causal relationship has not been established.

■ **Metabolic and Electrolyte Effects** In controlled studies, weight gain occurred in about 18% of adults who received clomipramine therapy for the treatment of obsessive-compulsive disorder compared with 1% of those receiving placebo. In these studies, a weight gain of at least 7% of initial body weight occurred in about 28% of clomipramine-treated patients compared with 4% of those receiving placebo. In several patients, weight gain exceeded 25% of the initial body weight. Conversely, weight losses of at least 7% of initial body weight occurred in about 5% of clomipramine-treated patients compared with 1% of those who received placebo. In controlled studies, weight gain or weight loss occurred in about 2 or 7% of children and adolescents, respectively, receiving clomipramine.

Thirst occurred in about 2% of adults receiving clomipramine. Dehydration, gout, hypercholesterolemia, hyperglycemia, hyperuricemia, and hypokalemia have been reported in less than 1% of patients receiving clomipramine, although a causal relationship to the drug has not been established. Fat intolerance and glycosuria have been reported rarely in patients receiving clomipramine, although these adverse effects have not been attributed definitely to the drug.

■ **Ocular and Otic Effects** Abnormal vision occurred in about 18 or 7% of adults or children and adolescents, respectively, receiving clomipramine. Abnormal lacrimation, mydriasis, and conjunctivitis occurred in about 3, 2, and 1% of adults, respectively, receiving the drug. Anisocoria, blepharospasm, and ocular allergy occurred in about 2% of children and adolescents receiving clomipramine. Adverse ocular effects reported in less than 1% of clomipramine-treated patients include abnormal accommodation, diplopia, ocular pain, foreign body sensation, photophobia, and scleritis; however, a causal relationship to the drug has not been established.

Glaucoma has been reported rarely in patients receiving clomipramine, although a causal relationship to the drug has not been established. Angle-closure glaucoma that presented clinically as amaurosis fugax (transient monocular blindness) attacks that were precipitated by rising from a sitting or supine position has been reported in at least one female patient treated with the drug. Although the precise mechanism is unclear, it was suggested that an abnormally large fall in blood pressure upon standing up combined with an increase in intraocular pressure may have been responsible. Blepharitis, chromatopsia, conjunctival hemorrhage, exophthalmos, keratitis, night blindness, retinal disorder, strabismus, and visual field defect occurred rarely in patients receiving clomipramine, but have not been attributed definitely to the drug.

Tinnitus occurred in about 6 or 4% of adults or children and adolescents, respectively, receiving clomipramine. Otitis media or vestibular disorder occurred in about 4 or 2% of children and adolescents, respectively, receiving clomipramine. Adverse otic effects reported in less than 1% of clomipramine-treated patients include hyperacusis, deafness, earache, and labyrinth disorder; however, these effects have not been attributed definitely to the drug.

■ **Musculoskeletal Effects** Myalgia occurred in about 13% of adults receiving clomipramine. Back pain and arthralgia occurred in about 6 and 3% of adults, respectively, receiving clomipramine. Muscle weakness occurred in about 1 or 2% of adults or children and adolescents, respectively, receiving clomipramine. Arthrosis and leg cramps have been reported in less than 1% of patients receiving clomipramine, although a causal relationship to the drug has not been established. Exostosis, bruising, myopathy, and myositis have been reported rarely in clomipramine-treated patients, although these effects have not been attributed definitely to the drug.

■ **Hematologic Effects** Purpura has been reported in about 3% of adults receiving clomipramine. Although no cases of severe hematologic toxicity were reported during the premarketing evaluation of clomipramine, there subsequently have been rare reports of bone marrow depression in patients receiving the drug, including leukopenia, agranulocytosis, thrombocytopenia, anemia, and pancytopenia. In controlled trials, anemia occurred in about 2% of children and adolescents receiving the drug.

■ **Respiratory Effects** Pharyngitis occurred in about 14% of adults receiving clomipramine. Rhinitis occurred in about 12 or 7% of adults or children and adolescents, respectively, receiving clomipramine. Cough occurred in about 6 or 4% of adults or children and adolescents, respectively, receiving clomipramine. Sinusitis occurred in about 6 or 2% of adults or children and

adolescents, respectively, treated with the drug. Yawning occurred in about 3% of adults receiving clomipramine. Bronchospasm occurred in about 2 or 7% of adults or children and adolescents, respectively, receiving clomipramine.

Epistaxis occurred in about 2% of adults receiving clomipramine. Dyspnea or laryngitis occurred in about 2% of clomipramine-treated children and adolescents. The development of adverse respiratory effects (e.g., dry sore throat, cough) severe enough to result in aphonia also has been reported.

Although a causal relationship has not been established, bronchitis, hyperventilation, increased sputum, and pneumonia have been reported in less than 1% of patients receiving clomipramine, and cyanosis, hemoptysis, hiccup, hypoventilation, and laryngismus have been reported rarely.

■ **Genitourinary Effects** ***Sexual Dysfunction*** One characteristic of clomipramine therapy that may be troublesome to some patients is its relatively high incidence of sexual dysfunction. The incidence of sexual dysfunction in male patients receiving clomipramine therapy for obsessive-compulsive disorder during premarketing clinical trials was substantially higher than in those receiving placebo. Normal sexual functioning usually returns within a few days after discontinuing clomipramine therapy.

Libido change occurred in about 21% of adults receiving clomipramine. Ejaculatory failure occurred in about 42% of adult males treated with clomipramine compared with 2% of those receiving placebo, and impotence occurred in 20% of clomipramine-treated adult males compared with about 3% of those receiving placebo. Approximately 85% of adult males who experienced sexual dysfunction during clomipramine therapy chose to continue therapy with the drug. About 6% of adolescent males experienced ejaculation failure while receiving clomipramine. Premature ejaculation has been reported rarely but has not been attributed definitely to the drug. On the other hand, clomipramine has been used in the treatment of premature ejaculation† in a limited number of patients. Painful ejaculation or orgasm has been reported in a limited number of male patients receiving the drug.

Anorgasmy has been reported in both male and female patients receiving clomipramine. In u controlled trial, difficulty or inability to reach orgasm was the most common adverse sexual effect in clomipramine-treated patients; sexual function generally returned to normal within 3 days after discontinuance of the drug. Anorgasmy associated with clomipramine has responded to anticipatory administration of yohimbine in several patients. Orgasm during yawning also has been reported in a limited number of patients receiving clomipramine.

Other Genitourinary Effects Micturition disorder occurred in about 14 or 4% of adults or children and adolescents, respectively, receiving clomipramine. Urinary tract infection and frequent micturition occurred in about 6 and 5%, respectively, of adults receiving the drug. Urinary retention occurred in about 2 or 7% of adults or children and adolescents, respectively, receiving clomipramine while dysuria, including painful urination in men, and cystitis have been reported in about 2% of adults receiving clomipramine.

Dysmenorrhea has been reported in about 12 and 10% of adult and adolescent females, respectively, receiving clomipramine, and menstrual disorder (including irregular menstruation) has been reported in about 4% of adult females receiving the drug. Vaginitis and leukorrhea each occurred in about 2% of adult females receiving clomipramine therapy. Amenorrhea occurred in about 1% of adult females receiving clomipramine.

Although not attributed definitely to the drug, endometriosis, epididymitis, hematuria, nocturia, oliguria, ovarian cyst, perineal pain, polyuria, prostatic disorder, urethral disorder, urinary incontinence, uterine hemorrhage, or vaginal hemorrhage has been reported in less than 1% of clomipramine-treated patients. Albuminuria, cervical dysplasia, endometrial hyperplasia, pyuria, uterine inflammation, and vulvar disorder have occurred rarely; however, a causal relationship to the drug has not been established.

■ **Hepatic Effects** During premarketing evaluation, potentially clinically important elevations in serum ALT (SGOT) and AST (SGPT) concentrations exceeding 3 times the upper limit of normal were reported in approximately 1 and 3%, respectively, of patients receiving clomipramine. In most cases, these elevations in hepatic enzyme concentrations were not associated with other clinical findings suggestive of hepatic injury, and jaundice was not observed. Severe hepatic injury that was fatal in some cases has been reported rarely in foreign postmarketing experience. (See Cautions: Precautions and Contraindications.) Abnormal hepatic function and hepatitis have been reported in less than 1% of patients receiving clomipramine, although a causal relationship to the drug has not been established. Cross hepatotoxicity (e.g., elevated values on hepatic function tests, abdominal pain) involving different tricyclic antidepressants including clomipramine also has been reported.

■ **Other Adverse Effects** Hot flushes occurred in about 5% of adults and 2% of children and adolescents receiving clomipramine. Fever occurred in about 4% of adults and 2% of children and adolescents treated with the drug. Pain has been reported in about 3% of adults and 4% of children and adolescents receiving clomipramine therapy. Chills and local edema each occurred in about 2% of adults receiving the drug.

Tooth disorder occurred in about 5% of clomipramine-treated adults, and dental caries has been reported in less than 1% of patients receiving the drug. Although the exact mechanism for these effects is unclear, it has been suggested that long-term therapy with clomipramine or other antidepressants with prominent anticholinergic activity can lead to dental caries through inhibition of saliva secretion.

Elevations in serum prolactin concentrations have been reported following single and multiple doses of clomipramine. Nonpuerperal lactation has been reported in about 4% of adult females receiving clomipramine therapy. Breast enlargement and breast pain have been reported in about 2 and 1% of adult females, respectively, receiving the drug. Breast engorgement, breast fibroadenosis, and gynecomastia have been reported rarely in patients receiving clomipramine; however, these effects have not been attributed definitely to the drug.

Lymphadenopathy has been reported in less than 1% of clomipramine-treated patients, and leukemoid reaction and lymphoma-like disorder have been reported rarely, although a causal relationship to the drug has not been established.

Diabetes mellitus and hypothyroidism each have been reported in less than 1% of patients receiving clomipramine, and goiter and hyperthyroidism have been reported rarely; however, these effects have not been attributed definitely to the drug.

Oliguria, renal calculus, and renal pain have been reported in less than 1% of patients receiving clomipramine, and pyelonephritis and renal cyst have been reported rarely; however, a causal relationship to the drug has not been established. Hyponatremia also has occurred with clomipramine.

■ **Precautions and Contraindications**

[redacted] changes in behavior may occur in both adult and pediatric (see Cautions: Pediatric Precautions) patients with major depressive disorder or other psychiatric disorders, whether or not they are taking antidepressants. This risk may persist until clinically important remission occurs. Suicide is a known risk of depression and certain other psychiatric disorders, and these disorders themselves are the strongest predictors of suicide. However, there has been a long-standing concern that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients during the early phases of treatment. Pooled analyses of short-term, placebo-controlled studies of antidepressants (i.e., selective serotonin-reuptake inhibitors and other antidepressants) have shown an increased risk of suicidality in children, adolescents, and young adults (18–24 years of age) with major depressive disorder and other psychiatric disorders. An increased suicidality risk was not demonstrated with antidepressants compared with placebo in adults older than 24 years of age, and a reduced risk was observed in adults 65 years of age or older. It currently is unknown whether the suicidality risk extends to longer-term use (i.e., beyond several months); however, there is substantial evidence from placebo-controlled maintenance trials in adults with major depressive disorder that antidepressants can delay the recurrence of depression.

The US Food and Drug Administration (FDA) recommends that all patients being treated with antidepressants for any indication be appropriately monitored and closely observed for clinical worsening, suicidality, and unusual changes in behavior, particularly during initiation of therapy (i.e., the first few months) and during periods of dosage adjustments. Families and caregivers of patients being treated with antidepressants for major depressive disorder or other indications, both psychiatric and nonpsychiatric, also should be advised to monitor patients on a daily basis for the emergence of agitation, irritability, or unusual changes in behavior as well as the emergence of suicidality, and to report such symptoms immediately to a health-care provider.

Although a causal relationship between the emergence of symptoms such as anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia, hypomania, and/or mania and either the worsening of depression and/or the emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality. Consequently, consideration should be given to changing the therapeutic regimen or discontinuing therapy in patients whose depression is persistently worse or in patients experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidality, particularly if such manifestations are severe, abrupt in onset, or were not part of the patient's presenting symptoms. If a decision is made to discontinue therapy, clomipramine dosage should be tapered as rapidly as is feasible but with recognition of the risks of abrupt discontinuance. (See Dosage and Administration.) FDA also recommends that the drugs be prescribed in the smallest quantity consistent with good patient management, in order to reduce the risk of overdosage.

It is generally believed (though not established in controlled trials) that treating a major depressive episode with an antidepressant alone may increase the likelihood of precipitating a mixed or manic episode in patients at risk for bipolar disorder. Therefore, patients should be adequately screened for bipolar disorder prior to initiating treatment with an antidepressant; such screening should include a detailed psychiatric history (e.g., family history of suicide, bipolar disorder, and depression). Clomipramine is *not* approved for use in treating bipolar depression.

As with closely related tricyclic antidepressants, clomipramine should be used with caution in patients with concurrent cardiovascular disease; hyperthyroidism; increased intraocular pressure, a history of angle-closure glaucoma, or urinary retention; tumors of the adrenal medulla; clinically important renal impairment; or hepatic disease.

In patients with cardiovascular disease, gradual dosage titration of clomipramine is recommended. In hyperthyroid patients or patients receiving thyroid agents, the possibility of cardiac toxicity also should be considered. The manufacturers state that clomipramine should be used with caution in patients with increased intraocular pressure, a history of angle-closure glaucoma, or urinary retention, since its anticholinergic effects may exacerbate these conditions. Caution also should be exercised in patients with tumors of the adrenal medulla

(e.g., pheochromocytoma, neuroblastoma), since hypertensive crises may be provoked by clomipramine.

Clomipramine should be used with caution in patients with known hepatic disease, and the manufacturers recommend periodic monitoring of hepatic enzyme concentrations in such patients.

A variety of neuropsychiatric manifestations, including delusions, hallucinations, psychotic episodes, confusion, and paranoia, have been reported in patients receiving clomipramine. (See Cautions: Nervous System Effects.) However, because of the uncontrolled design of many of these studies, it is not possible to provide a precise estimate of the extent of the risk of such effects in clomipramine-treated patients. In patients whose schizophrenia has been unrecognized, an acute psychotic episode may be precipitated by clomipramine or other antidepressants. Another possibility is that clomipramine, like other antidepressants, may precipitate mania or hypomania in patients with affective disorder.

As with other tricyclic antidepressants, the development of fever and sore throat in any patient receiving clomipramine therapy should prompt the clinician to obtain leukocyte and differential blood cell counts. (See Cautions: Hematologic Effects.)

Male patients for whom clomipramine therapy is considered should be informed about the relatively high incidence of sexual dysfunction associated with the drug. Sexual dysfunction occurred in more males with obsessive-compulsive disorder treated with clomipramine than with placebo in premarketing experience. (See Cautions: Genitourinary Effects.)

As with closely related tricyclic antidepressants, the risks associated with electroconvulsive therapy (ECT) may be increased during concurrent clomipramine therapy. Because of the limited clinical experience to date, the manufacturers recommend that the combination of clomipramine and ECT be limited to those patients for whom it is essential.

Prior to elective surgery with general anesthetics, the manufacturers state that clomipramine therapy should be discontinued for as long as is clinically feasible, and the anesthetist should be so advised.

The withdrawal effects of clomipramine have not been systematically evaluated in controlled studies, although such effects have been reported following abrupt withdrawal of closely related tricyclic antidepressants. (See Cautions: Nervous System Effects and also see Chronic Toxicity in the Tricyclic Antidepressants General Statement 28:16.04.28.) Therefore, gradual tapering of clomipramine dosage and careful monitoring of the patient is recommended during discontinuance of clomipramine therapy.

Clomipramine can produce somnolence and impaired concentration, and patients should be cautioned that the drug may impair the mental and/or physical abilities required for the performance of these complex tasks. Patients also should be cautioned about the use of alcohol, barbiturates, or other CNS depressants because the effects of these agents may be exaggerated during concurrent clomipramine therapy.

The possibility of seizure is the most clinically important risk associated with clomipramine therapy (see Cautions: Nervous System Effects), and the drug should be used with caution in patients with a history of seizures or other predisposing factors (e.g., brain damage of various etiology, alcoholism, concurrent use of other drugs that lower the seizure threshold). The ability to predict the occurrence of seizures with daily doses exceeding 250 mg is limited because plasma concentrations may be dose dependent and may vary considerably among individuals administered the same dosage. Nevertheless, the manufacturers recommend limiting the daily dose of clomipramine to a maximum of 250 mg in adults or 3 mg/kg (up to 200 mg) in children and adolescents. Patients receiving clomipramine should be informed about the risk of seizures associated with the drug. In addition, physicians should discuss with patients the risk and the possibility of serious injury to themselves or other people resulting from sudden loss of consciousness while engaged in certain complex and hazardous activities (e.g., operation of complex machinery, driving a motor vehicle, swimming, climbing).

Clomipramine is contraindicated in patients with known hypersensitivity to the drug or other tricyclic antidepressants. The drug also is contraindicated in patients currently receiving, or having recently received (i.e., within 2 weeks), monoamine oxidase (MAO) inhibitor therapy. (See Drugs Associated with Serotonin Syndrome: Monoamine Oxidase Inhibitors, under Drug Interactions.) Clomipramine also is contraindicated during the acute recovery phase following myocardial infarction.

■ **Pediatric Precautions** Safety and efficacy of clomipramine in children younger than 10 years of age have not been established. Therefore, the manufacturers state that no specific recommendations can be made for the use of the drug in this age group.

Safe use of clomipramine in pediatric patients 10 years of age or older for the treatment of obsessive-compulsive disorder (OCD) is based on relatively short-term studies in this patient population and from extrapolation of experience gained with adult patients. The potential risks associated with long-term clomipramine therapy have not been systematically evaluated in children and adolescents. Although there is no evidence that the drug adversely affects growth, development, or maturation in these patients, the absence of such findings does not rule out a potential for such effects with long-term use.

In a controlled study, clomipramine has been administered for up to 8 weeks to 46 children and adolescents 10–17 years of age. In addition, 150 adolescent patients have received clomipramine therapy for periods ranging from several months to several years in uncontrolled studies. Out of a total of 196 children and adolescents studied, 50 patients were 13 years of age or younger and 146 patients were 14–17 years of age. The adverse effect profile in this age group is similar to that observed in adults.

FDA warns that antidepressants increase the risk of suicidal thinking and behavior (suicidality) in children and adolescents with major depressive disorder and other psychiatric disorders. The risk of suicidality for these drugs was identified in a pooled analysis of data from a total of 24 short-term (4–16 weeks), placebo-controlled studies of 9 antidepressants (i.e., bupropion, citalopram, fluoxetine, fluvoxamine, mirtazapine, nefazodone, paroxetine, sertraline, venlafaxine) in over 4400 children and adolescents with major depressive disorder, OCD, or other psychiatric disorders. The analysis revealed a greater risk of adverse events representing suicidal behavior or thinking (suicidality) during the first few months of treatment in pediatric patients receiving antidepressants than in those receiving placebo. The average risk of such events was 4% among children and adolescents receiving these drugs, twice the risk (2%) that was observed among those receiving placebo. However, a more recent meta-analysis of 27 placebo-controlled trials of 9 antidepressants (SSRIs and others) in patients younger than 19 years of age with major depressive disorder, OCD, or non-OCD anxiety disorders suggests that the benefits of antidepressant therapy in treating these conditions may outweigh the risks of suicidal behavior or suicidal ideation. No suicides occurred in these pediatric trials.

The risk of suicidality in FDA's pooled analysis differed across the different psychiatric indications, with the highest incidence observed in the major depressive disorder studies. In addition, although there was considerable variation in risk among the antidepressants, a tendency toward an increase in suicidality risk in younger patients was found for almost all drugs studied. It is currently unknown whether the suicidality risk in pediatric patients extends to longer-term use (i.e., beyond several months).

As a result of this analysis and public discussion of the issue, FDA has directed manufacturers of all antidepressants to add a boxed warning to the labeling of their products to alert clinicians of this suicidality risk in children and adolescents and to recommend appropriate monitoring and close observation of patients receiving these agents. (See Cautions: Precautions and Contraindications.) The drugs that are the focus of the revised labeling are all drugs included in the general class of antidepressants, including those that have not been studied in controlled clinical trials in pediatric patients, since the available data are not adequate to exclude any single antidepressant from an increased risk. In addition to the boxed warning and other information in professional labeling on antidepressants, FDA currently recommends that a patient medication guide explaining the risks associated with the drugs be provided to the patient each time the drugs are dispensed.

Anyone considering the use of clomipramine in a child or adolescent for any clinical use must balance the potential risk of therapy with the clinical need.

■ **Geriatric Precautions** The manufacturers state that clinical studies with clomipramine did not include sufficient numbers of patients 65 years of age or older to determine whether they respond differently than younger patients. No unusual age-related adverse effects were identified in 152 patients at least 60 years of age participating in US clinical studies who received the drug for periods of several months to several years. In addition, other clinical experience revealed no evidence of age-related differences in response to clomipramine.

In pooled data analyses, a *reduced* risk of suicidality was observed in adults 65 years of age or older with antidepressant therapy compared with placebo. (See Cautions: Precautions and Contraindications.)

Clomipramine is eliminated more slowly in geriatric patients. In addition, older patients may not tolerate the drug's adverse effects as well as younger patients. The manufacturers and some clinicians recommend cautiously selecting a clomipramine dosage regimen in geriatric patients, usually starting at the lower end of the recommended dosage range, since decreased hepatic, renal, or cardiac function and concomitant illnesses and medications are more frequent in this population.

■ **Mutagenicity and Carcinogenicity** No clear evidence of carcinogenicity was seen in rats receiving oral clomipramine hydrochloride dosages of 20 times the maximum recommended human daily dosage in a 2-year bioassay. Hemangioendothelioma was observed in 3 out of 235 rats administered clomipramine; the relationship between this rare tumor and the drug is not known.

■ **Pregnancy, Fertility, and Lactation** Teratogenic effects were not observed in rats and mice receiving clomipramine hydrochloride dosages up to 20 times the maximum human daily dosage. Slight, nonspecific fetotoxic effects were observed in the offspring of pregnant mice receiving 10 times the maximum human daily dosage. Slight, nonspecific embryotoxicity occurred in rats receiving 5–10 times the maximum human daily dosage.

There are no adequate and controlled studies using clomipramine in pregnant women, and the drug should be used during pregnancy only if the possible benefits justify the potential risk to the fetus. Women should be advised to notify their physician if they are or plan to become pregnant during clomipramine therapy. Neonates whose mothers had received clomipramine throughout pregnancy in dosages of 75–250 mg daily have exhibited withdrawal manifestations or adverse effects, including jitteriness, tremor, seizures, twitching, hypertonia, hypotonia, tachypnea, respiratory acidosis, cyanosis, feeding difficulties, hypothermia, lethargy, and diaphoresis. Phenobarbital has been recommended by some clinicians for the management of neurologic withdrawal

symptoms. Abrupt discontinuance of clomipramine at 32 weeks of pregnancy resulted in premature birth of a neonate who developed seizures soon after delivery. Because of the risk of neonatal withdrawal, some clinicians state that clomipramine therapy particularly should be avoided during late pregnancy.

Reproduction studies in rats using clomipramine hydrochloride dosages approximately 5 times the maximum human daily dosage have not revealed evidence of impaired fertility.

Clomipramine is distributed into milk. (See Pharmacokinetics: Distribution.) Adverse effects were absent in an infant who was breast-feeding from a woman who continued treatment with clomipramine at a dosage of 150 mg daily. However, because of the potential for adverse reactions, including concern about the potential for tricyclic antidepressants to affect development of the CNS of infants, a decision should be made whether to discontinue nursing or clomipramine, taking into account the importance of the drug to the woman. Women should be advised to notify their physician if they are breast-feeding.

Drug Interactions

Because of the similarity of clomipramine to other tricyclic antidepressants, all drug interactions that may occur with this class of drugs should be considered when clomipramine is used. (See Drug Interactions in the Tricyclic Antidepressants General Statement 28:16.04.28.) In addition, the possibility that clomipramine may interact with any concomitantly administered drug has not been evaluated systematically but should be considered.

■ **Drugs Associated with Serotonin Syndrome** ***Serotonin Syndrome*** Use of clomipramine concurrently or in close succession with other serotonergic drugs may result in serotonin syndrome. Although the syndrome appears to be relatively uncommon and usually mild in severity, serious complications, including seizures, disseminated intravascular coagulation, respiratory failure, severe hyperthermia, and death occasionally have been reported.

The syndrome most commonly occurs when 2 or more serotonergic agents with different mechanisms of action are administered either concurrently or in close succession. Serotonergic agents include those that increase serotonin synthesis (e.g., the serotonin precursor tryptophan), stimulate synaptic serotonin release (e.g., some amphetamines, dexfenfluramine, fenfluramine), inhibit the reuptake of serotonin after release (e.g., selective serotonin-reuptake inhibitors, tricyclic antidepressants, trazodone, dextromethorphan, meperidine, tramadol), decrease the metabolism of serotonin (e.g., monoamine oxidase [MAO] inhibitors), have direct serotonin postsynaptic receptor activity (e.g., buspirone), or nonspecifically induce increases in serotonergic neuronal activity (e.g., lithium salts).

The combination of selective serotonin-reuptake inhibitors and MAO inhibitors appears to be responsible for most of the recent case reports of serotonin syndrome. The syndrome also has been reported when MAO inhibitors have been combined with tricyclic antidepressants such as clomipramine, tryptophan, meperidine, or dextromethorphan. In rare cases, the serotonin syndrome reportedly has occurred with the recommended dosage of a single serotonergic agent (e.g., clomipramine) or during accidental overdosage (e.g., sertraline intoxication in a child). Some other drugs that have been implicated in certain circumstances include buspirone, bromocriptine, dextropropoxyphene, methylenedioxymethamphetamine (MDMA; ecstasy), selegiline (a selective MAO-B inhibitor), and sumatriptan. Other drugs that have been associated with the syndrome but for which less convincing data are available include carbamazepine, fentanyl, and pentazocine.

Clinicians should be aware of the potential for serious, possibly fatal reactions associated with the serotonin syndrome in patients receiving 2 or more drugs that increase the availability of serotonin in the CNS, even if no such interactions with the specific drugs have been reported to date in the medical literature. Pending further accumulation of data, all drugs with serotonergic activity should be used cautiously in combination and such combinations avoided whenever clinically possible. Some clinicians state that patients who have experienced serotonin syndrome may be at higher risk for recurrence of the syndrome upon reinitiation of serotonergic drugs. Pending further experience in such cases, some clinicians recommend that therapy with serotonergic agents be limited following recovery. In cases in which the potential benefit of the drug is thought to outweigh the risk of serotonin syndrome, lower potency agents and reduced dosages should be used, combination serotonergic therapy should be avoided, and patients should be monitored carefully for symptoms of serotonin syndrome.

For further information on serotonin syndrome, including manifestations and treatment, see Serotonin Syndrome under Drug Interactions: Drugs associated with Serotonin Syndrome, in Fluoxetine Hydrochloride 28:16.04.20.

Monoamine Oxidase Inhibitors Concomitant administration of clomipramine and MAO inhibitors is contraindicated, and at least 2 weeks elapse between discontinuance of clomipramine therapy and initiation of MAO inhibitor therapy and vice versa. Concomitant administration of clomipramine and an MAO inhibitor is potentially hazardous and may result in severe adverse effects associated with serotonin syndrome such as hyperpyrexia, seizures, and coma. Other adverse effects that have occurred with this combination of drugs include confusion, agitation, myoclonus, tremor, diaphoresis, shivering, rigors, rigidity, hypotension, tachycardia, cardiac arrhythmia, and disseminated intravascular coagulation. Some reactions occurring in patients receiving clomipramine and an MAO inhibitor have been fatal.

Clonus, hyperreflexia, tremor, rigidity, and diaphoresis were observed in some patients after administration of clomipramine about 1 month after discontinuance of a selective inhibitor of monoamine oxidase-A. Status epilepticus developed in a patient after treatment with clomipramine was started approximately 24 hours after discontinuance of phenelzine sulfate. Although the mechanism has not been clearly established, the reactions resemble serotonin syndrome and may be caused by excessive serotonergic activity in the CNS.

Other Serotonergic Agents Concurrent administration of clomipramine and other serotonergic drugs (e.g., lithium, alprazolam) has resulted in the development of adverse effects similar to those reported with the combination of clomipramine and an MAO inhibitor and which resemble the serotonin syndrome.

Concurrent administration of clomipramine and fluoxetine has resulted in seizures. Concurrent administration of clomipramine and fluvoxamine has resulted in a severalfold elevation of the plasma clomipramine concentration.

■ **CNS Depressants** Like other tricyclic antidepressants, clomipramine may be additive with or may potentiate the action of other CNS depressants such as alcohol and barbiturates. In addition, concomitant administration of clomipramine with phenobarbital reportedly resulted in an increase in the plasma concentration of phenobarbital.

■ **Drugs Affecting the Seizure Threshold** Caution should be observed with concurrent administration of clomipramine and drugs (e.g., other antidepressants, antipsychotic agents) that lower the seizure threshold. (See Cautions: Nervous System Effects.)

■ **Haloperidol** Concomitant administration of clomipramine with haloperidol reportedly resulted in increases in the plasma concentrations of clomipramine, presumably because of haloperidol-induced inhibition of clomipramine metabolism.

■ **Valproic Acid** The initiation of clomipramine therapy in a patient with a seizure disorder that was well controlled by valproic acid resulted in status epilepticus. The serum clomipramine concentration at the time of the seizures was elevated despite the relatively small dosage of clomipramine received (75 mg daily for 12 days). Although the mechanism has not been established clearly, it was suggested that valproic acid may have inhibited the metabolism and/or elimination of clomipramine. Pending further experience, it should be kept in mind that elevated serum concentrations of clomipramine and possibly its metabolites may occur when clomipramine and valproic acid are used concomitantly and that these changes may precipitate seizures in predisposed individuals.

■ **Other CNS Agents** The risks associated with concurrent administration of clomipramine and other CNS-active agents have not been fully evaluated to date; therefore, caution should be exercised when such agents are administered concomitantly.

■ **Oral Contraceptives** Limited data suggest that oral contraceptives do not interfere with the therapeutic effects of clomipramine. No difference in adverse effects or depression was observed in patients receiving clomipramine and oral contraceptives compared with those receiving clomipramine alone in one study. However, the clomipramine dosage given (25 mg daily) was lower than those commonly used in the treatment of obsessive-compulsive disorder or depression. Further study to confirm the safety and efficacy of combined clomipramine and oral contraceptive therapy is necessary.

■ **Smoking** Substantially lower plasma clomipramine concentrations have been reported in cigarette smokers receiving clomipramine when compared with nonsmokers. The presumed mechanism appears to be induction of clomipramine metabolism by nicotine or other substances present in cigarette smoke.

■ **Protein-bound Drugs** Clomipramine and its active metabolite, desmethylclomipramine, are highly protein bound; therefore, they theoretically could be displaced from binding sites by or could displace from binding sites other protein-bound drugs such as oral anticoagulants (e.g., warfarin) and digoxin. Pending further accumulation of data, patients receiving clomipramine with any highly protein-bound drug should be observed for potential adverse effects associated with combined therapy.

■ **Other Drugs** Concomitant use of clomipramine with anticholinergic or sympathomimetic drugs requires close supervision and careful adjustment of the dosage of clomipramine because of potential additive effects.

Consideration of the structural similarity of clomipramine with other tricyclic antidepressants would suggest that blockade of the pharmacologic effects (such as hypotension) and possibly the adverse effects of guanethidine, clonidine, or other similar hypotensive agents, as has been reported with several other tricyclic antidepressants, may be anticipated with clomipramine.

The plasma concentrations of several tricyclic antidepressants closely related to clomipramine reportedly were increased with concomitant administration of methylphenidate or drugs that inhibit hepatic microsomal enzyme systems (e.g., cimetidine, fluoxetine) and were decreased with concomitant administration of drugs that induce hepatic microsomal enzymes (e.g., barbiturates, phenytoin). Such effects also may be anticipated with clomipramine.

Acute Toxicity

Limited information is available on the acute toxicity of clomipramine.

■ **Pathogenesis** Postmarketing reports from the UK suggest that clomipramine overdosage results in lethality similar to that reported for other closely related tricyclic antidepressants.

In 10 out of 12 patients who overdosed on clomipramine taken alone or with other drugs during US clinical studies, complete recovery occurred with overdosages of up to 5 g that produced plasma concentrations of up to 1010 ng/mL. In the 2 remaining patients, who were suspected of ingesting overdosages of 7 g and 5.75 g, death occurred. Other fatalities have been reported after overdosages of clomipramine were ingested. The lowest dosage of clomipramine associated with fatality outside of the US is 750 mg.

■ **Manifestations** Overdosage with clomipramine produces signs and symptoms similar to that with other tricyclic antidepressants. (See Acute Toxicity: Manifestations, in the Tricyclic Antidepressants General Statement 28:16.04.28.) Acute pancreatitis accompanied by prolonged ileus has occurred following an overdose of clomipramine in one patient.

The signs and symptoms of clomipramine overdosage vary in severity depending on a number of factors, including the amount of drug absorbed, the patient's age, and the amount of time elapsed since ingestion. Plasma concentrations of clomipramine should not guide management of the patient. However, they may be of qualitative value when the diagnosis is not clear. In addition, evidence from one patient who experienced biphasic absorption (delayed) and elimination of clomipramine in which, after an initial decline, the serum concentration of clomipramine and desmethylclomipramine increased to a peak and declined subsequently, suggests that monitoring such concentrations until the patient is stable may be of diagnostic benefit, since manifestations of severe toxicity and the need for aggressive management also were biphasic, recurring 3–4 days after the initial toxic episode. Although clomipramine and desmethylclomipramine have low cross-reactivity (e.g., 40–50% to antibody for clomipramine at concentrations of 189–472 ng/mL) with a fluorescent polarization immunoassay (FPIA) for tricyclic antidepressants, clomipramine concentrations of 100 ng/mL are detectable by the assay, and therefore this nonspecific assay may still be useful in diagnosing overdosage with the drug.

■ **Treatment** For information on the management of tricyclic antidepressant overdosage, see Acute Toxicity: Treatment, in the Tricyclic Antidepressants General Statement 28:16.04.28. In addition, clinicians should consult a poison control center for current information about therapy for overdoses of tricyclic antidepressants because such treatment is complex and changeable.

Chronic Toxicity

Clomipramine has not been evaluated systematically in animals or humans to determine its potential for abuse, tolerance, or physical dependence. Although discontinuance of therapy has been associated with a variety of withdrawal manifestations (see Cautions: Nervous System Effects), there is no evidence of drug-seeking behavior, except for one patient with a history of dependence on codeine, benzodiazepines, and multiple psychoactive drugs. This patient received clomipramine for depression and panic attacks and appeared to become dependent on the drug after hospital discharge.

Although foreign clinical experience has not revealed substantial evidence for abuse potential with clomipramine, it is impossible to predict the extent to which the drug may be misused or abused. Because of such uncertainty, clinicians should carefully evaluate patients for a history of substance abuse and such patients who receive clomipramine should be monitored closely.

Pharmacology

The pharmacology of clomipramine is complex and in many ways resembles that of other antidepressants, particularly those agents (e.g., selective serotonin-reuptake inhibitors, trazodone) that predominantly potentiate the pharmacologic effects of serotonin (5-HT). Although clomipramine's principal pharmacologic effect in vitro is the selective inhibition of serotonin reuptake, in vivo the drug's pharmacologic activity is not so selective because of the action of its demethylated metabolite, desmethylclomipramine, as an inhibitor of norepinephrine reuptake. As a result of this and other effects, clomipramine also shares the pharmacologic profile of other tricyclic antidepressants.

■ **Nervous System Effects** The precise mechanism of action that is responsible for the efficacy of clomipramine in the treatment of obsessive-compulsive disorder is unclear. However, because of its pronounced potency in blocking serotonin reuptake at the presynaptic neuronal membrane and its efficacy in the treatment of obsessive-compulsive disorder, a serotonin hypothesis has been developed to explain the pathogenesis of the condition. The hypothesis postulates that a dysregulation of serotonin is responsible for obsessive-compulsive disorder and that clomipramine is effective because it corrects this imbalance. The potency of clomipramine relative to other tricyclic antidepressants as a serotonin-reuptake inhibitor and its superiority in obsessive-compulsive disorder provide additional support to this hypothesis. Although the available evidence supports the serotonergic hypothesis of obsessive-compulsive disorder (see Pharmacology: Serotonergic Effects), additional studies are necessary to confirm this hypothesis.

Like other tricyclic antidepressants, the exact mechanism of clomipramine's antidepressant action is unclear. Clomipramine and its principal metabolite, desmethylclomipramine, have been shown to block the reuptake of serotonin and norepinephrine, respectively, at the presynaptic neuronal membrane. The effects of serotonin and norepinephrine may thus be potentiated. However, it has been suggested that postsynaptic receptor modification is mainly responsible for the antidepressant action observed during long-term administration of antidepressant agents. During long-term therapy with most antidepressants (e.g., tricyclic antidepressants, monoamine oxidase [MAO] inhibitors), these adaptive changes generally consist of subsensitivity of the noradrenergic adenylate cyclase system in association with a decrease in the number of β-adrenergic receptors; such effects on noradrenergic receptor function commonly are referred to as "down-regulation." In addition, some antidepressants reportedly decrease the number of 5-HT binding sites following chronic administration.

Like other tricyclic antidepressants, clomipramine may produce sedation. The drug also may lower the seizure threshold, particularly at relatively high dosages. (See Cautions: Nervous System Effects.)

Serotonergic Effects Clomipramine is a potent and somewhat selective inhibitor of serotonin reuptake at the presynaptic neuronal membrane. Clomipramine-induced inhibition of serotonin reuptake causes increased synaptic concentrations of the neurotransmitter, resulting in numerous functional changes associated with enhanced serotonergic neurotransmission.

Clomipramine is the most potent inhibitor of serotonin reuptake among currently available tricyclic antidepressants. Data from in vitro studies suggest that clomipramine is approximately equivalent to or more potent than fluoxetine as a serotonin-reuptake inhibitor; however, in vivo studies indicate that the serotonin-reuptake inhibiting effect of fluoxetine may be more potent than that of clomipramine on a weight as well as an equimolar basis. This apparent discrepancy may be explained at least in part by the relatively long elimination half-lives of fluoxetine and its principal metabolite, norfluoxetine. In addition, metabolism by *N*-demethylation decreases the potency and specificity of serotonin-reuptake inhibition by clomipramine but not fluoxetine.

Clomipramine appears to decrease the turnover of serotonin in the CNS, probably as a result of a decrease in the release and/or synthesis of serotonin. Several studies have investigated the effects of clomipramine on serotonin concentrations in patients with obsessive-compulsive disorder. The concentration of serotonin in platelets has been shown to be substantially lower in patients with obsessive-compulsive disorder treated with the drug, and this decrease has been shown to correlate with clinical improvement in obsessive-compulsive manifestations in these patients.

Clomipramine reportedly decreases the concentration of 5-hydroxyindoleacetic acid (5-HIAA), the principal metabolite of serotonin, in the CSF of patients with obsessive-compulsive disorder or depression. Limited data suggest a possible relationship between improvement of obsessive-compulsive manifestations and decreased concentrations of 5-HIAA in the CSF.

Manifestations of obsessive-compulsive disorder worsened after administration of a serotonin agonist, metachlorophenylpiperazine (mCPP), compared with placebo. Manifestations of obsessive-compulsive disorder also appeared to worsen after administration of a nonselective serotonin antagonist, metergoline, compared with placebo in patients receiving clomipramine. In contrast, such exacerbation was not observed with administration of mCPP in patients treated with clomipramine for several weeks or longer. If obsessive-compulsive disorder is related to increased serotonergic responsiveness, then these data suggest that clomipramine's efficacy following long-term administration may be related to induction of subsensitivity in the serotonergic system; such an effect has been referred to as "down-regulation" of serotonin receptors.

Effects on Other Neurotransmitters Clomipramine's principal metabolite, desmethylclomipramine, is an inhibitor of norepinephrine reuptake. Clomipramine decreases the concentration of 3-methoxy-4-hydroxyphenylglycol (MHPG), a metabolite of norepinephrine, in CSF in patients with obsessive-compulsive disorder. Patients with depressive affective (mood) disorders (e.g., major depressive episode) also exhibit decreases in concentrations of 5-HIAA and MHPG in CSF during treatment with clomipramine. The decrease in the concentration of 5-HIAA in CSF was correlated with inhibition of the in vitro uptake of ^{3}H-serotonin in plasma. The change in concentration of MHPG in CSF during clomipramine therapy was correlated with amelioration of depression.

Preliminary evidence suggests that clomipramine may inhibit dopaminergic activity. Unlike many other antidepressants, clomipramine exhibited extensive binding to postsynaptic receptors of dopamine antagonists (^{3}H-spiroperidol) in vitro. In animals, dopamine antagonism has been demonstrated by clomipramine's ability to reduce apomorphine-induced behavioral stereotypy. The drug also increases the CSF concentration of the dopamine metabolite homovanillic acid secondary to increased dopamine turnover. Because obsessive-compulsive disorder is common in patients with certain disorders of dopamine regulation (e.g., Sydenham's chorea, Tourette's disorder [Gilles de la Tourette's syndrome]), additional studies are needed to determine whether these initial findings are clinically important. (See Uses: Obsessive-Compulsive Disorder.)

Like other tricyclic antidepressants, clomipramine binds to cholinergic receptors and exhibits marked anticholinergic activity. As a result, clomipramine therapy may cause adverse effects commonly associated with blockade of muscarinic cholinergic receptors (e.g., dry mouth, blurred vision, urinary retention, constipation, confusion). In addition, clomipramine binds to α_1-adrenergic and histaminergic receptors and consequently exhibits α_1-adrenergic blocking and antihistaminic activity at usual therapeutic dosages. The drug also has been shown to bind to α_2-adrenoceptors and opiate receptors.

CNS Metabolic Effects Brain imaging studies using positron emission tomography (PET) have demonstrated metabolic abnormalities (usually hypermetabolism) in certain regions of the brain (including the orbitofrontal cortex, caudate nucleus, and prefrontal gyri) in patients with obsessive-compulsive disorder. Clomipramine appears to produce a return of metabolism to a more normal level in the regions of the brain that may be involved in the

pathology of obsessive-compulsive disorder (orbitofrontal cortex and the caudate nucleus). For example, the metabolic rate of glucose was decreased in regions of the orbitofrontal cortex and the left caudate nucleus and was increased in other areas of the basal ganglia, including the right anterior putamen, in patients with obsessive-compulsive disorder treated with clomipramine compared with pretreatment measurements.

Other limited data suggest a relationship between decreases in the metabolic rate of glucose in the orbitofrontal cortex and the efficacy of clomipramine in obsessive-compulsive disorder. The decrease from baseline in the metabolic rate of glucose in the left orbitofrontal region was greater in patients whose obsessive-compulsive symptoms improved during clomipramine or fluoxetine therapy than in nonresponders to such therapy. In these patients, the decrease from baseline in the metabolic rate of glucose in the right orbitofrontal region was correlated with improvement in the manifestations of obsessive-compulsive disorder.

Effects on Sleep Like tricyclic and most other antidepressants, clomipramine suppresses rapid eye movement (REM) sleep. The drug appears to be the most potent suppressor of REM sleep in the tricyclic antidepressant class. The REM-suppressing effect may be sustained following discontinuance of clomipramine therapy, and chronic therapy leads to substantial REM rebound upon withdrawal of the drug.

■ **Cardiovascular Effects** Clomipramine shares the cardiovascular effects of other tricyclic antidepressants (see Pharmacology in the Tricyclic Antidepressants General Statement 28:16.04.24) and may produce ECG changes (e.g., increases from baseline in QRS duration, QT interval corrected for rate [QT_c], and QRS axis; inversion or flattening of the T waves), cardiac urrhythmias, tachycardia, and postural hypotension.

■ **Neuroendocrine Effects** Clomipramine affects the endocrine system. IV administration of clomipramine produced a dose-related increase in plasma prolactin and corticotropin (ACTH) concentrations in healthy individuals; an increase in the plasma cortisol concentration also was observed. Patients with depressive affective (mood) disorders (e.g., major depressive episode) also exhibited increases in plasma prolactin, ACTH, and cortisol concentrations following IV administration of clomipramine; however, the increase in plasma prolactin noted in patients with a major depressive episode was less than in nondepressed individuals. Clomipramine-induced increases in prolactin secretion appear to be serotonergically mediated.

Clomipramine appears to affect the CSF concentration of neuropeptides that are elevated in patients with obsessive-compulsive disorder. The concentrations of such neuropeptides (e.g., corticotropin-releasing hormone, vasopressin) are decreased during long-term (e.g., 20 months) therapy with the drug. In addition, an increase in the CSF concentration, corrected for age, of oxytocin has been observed.

For further information on the pharmacology of clomipramine, see Pharmacology in the Tricyclic Antidepressants General Statement 28:16.04.24.

Pharmacokinetics

In all human studies described in the Pharmacokinetics section, clomipramine was administered as the hydrochloride salt.

■ **Absorption** Clomipramine hydrochloride appears to be well absorbed from the GI tract following oral administration. However, extensive first-pass metabolism decreases its oral bioavailability to about 50%. The oral capsules and solution of clomipramine hydrochloride reportedly are bioequivalent. Food does not appear to substantially affect the bioavailability of clomipramine from the capsules.

Peak plasma clomipramine concentrations of approximately 56–154 ng/mL (mean: 92 ng/mL) usually occur within 2–6 hours (mean: 4.7 hours) following oral administration of a single 50-mg dose of clomipramine hydrochloride. Like other tricyclic antidepressants, clomipramine exhibits considerable interindividual variation in plasma concentrations achieved with a given dose due, at least in part, to genetic differences in the metabolism of the drug. (See Pharmacokinetics: Elimination.)

Following multiple-dose oral administration of clomipramine, steady-state plasma concentrations of the drug generally are achieved within about 1–2 weeks. Steady-state plasma desmethylclomipramine (the principal metabolite) concentrations may be achieved at about the same time as steady-state plasma clomipramine concentrations or later. In some cases, plasma desmethylclomipramine concentrations have been observed to continue to increase during 4–6 weeks of administration of a constant dosage of clomipramine hydrochloride. Plasma concentrations of desmethylclomipramine generally exceed those of the parent drug following multiple daily dosing of clomipramine hydrochloride.

The manufacturers state that, after multiple daily dosing of clomipramine hydrochloride 150 mg, the accumulation factors for clomipramine and desmethylclomipramine are approximately 2.5 and 4.6, respectively. However, it may take 2 weeks or more to achieve this extent of accumulation at a constant dosage because of the relatively long elimination half-lives of clomipramine and desmethylclomipramine. At steady state, peak plasma concentrations of 94–339 (mean: 218) and 134–532 (mean: 274) ng/mL of clomipramine and desmethylclomipramine, respectively, were attained following multiple daily doses of 150 mg of clomipramine hydrochloride. Pharmacokinetic data in patients receiving clomipramine hydrochloride dosages ranging from 150–250 mg daily are lacking.

In a dose-proportionality study involving multiple dosing, steady-state plasma concentrations and the areas under the plasma concentration-time curve (AUCs) of clomipramine and desmethylclomipramine were not proportional to dose at dosages ranging from 25–150 mg daily. However, at dosages ranging from 100–150 mg daily there was an approximately linear relationship between these variables and dose. The manufacturers state that the relationship between dose and plasma clomipramine or desmethylclomipramine concentrations has not been systematically evaluated at higher dosages. However, if there is a substantial dose dependency at dosages exceeding 150 mg daily, the potential exists for dramatically higher steady-state plasma concentrations and AUCs of clomipramine and desmethylclomipramine even in patients receiving dosages within the recommended range. Such an effect may pose a potential risk in some patients. (See Cautions: Precautions and Contraindications.)

The effect of age on plasma concentrations of clomipramine and desmethylclomipramine is not fully known. However, substantially lower plasma concentrations of clomipramine and desmethylclomipramine have been reported in younger adults (18–40 years of age) compared with those obtained in individuals older than 65 years of age. Children younger than 15 years of age also had substantially lower plasma concentration-dose ratios of clomipramine when compared with adults. In addition, clomipramine appears to be better tolerated in younger than in older patients.

Substantially lower steady-state plasma clomipramine concentrations have been reported in smokers when compared with nonsmokers. However, smoking appears to have less effect on plasma concentrations of desmethylclomipramine.

The relationship between plasma clomipramine and desmethylclomipramine concentrations and the therapeutic and/or toxic effects of the drug has not been clearly established. The results of studies involving plasma concentration monitoring in patients with obsessive-compulsive disorder and/or depression have been equivocal. In some studies, the sum of plasma clomipramine and desmethylclomipramine concentrations has been used as the drug concentration. In depressed patients, preliminary evidence suggests that lower plasma concentrations of clomipramine plus desmethylclomipramine (less than 150 ng/mL) are associated with nonresponse while higher concentrations (exceeding 450 ng/mL) may be associated with an increased risk of adverse effects and perhaps nonresponse. In patients with obsessive-compulsive disorder, the results of 2 studies in which a relationship between plasma concentration and therapeutic response was found suggested that optimal therapeutic response may be obtained in patients with plasma clomipramine concentrations ranging from 100–250 ng/mL and plasma desmethylclomipramine concentrations ranging from 230–550 ng/mL.

■ **Distribution** Distribution of clomipramine and its metabolites into human body tissues and fluids has not been fully characterized. However, both clomipramine and desmethylclomipramine are highly lipophilic and are widely distributed in body tissues, with moderate to high concentrations occurring in organs such as the lungs, adrenals, kidneys, heart, and brain. The apparent volume of distribution of clomipramine in healthy adults averages 17 L/kg (range: 9–25 L/kg).

Both clomipramine and desmethylclomipramine cross the blood-brain barrier; the manufacturers state that desmethylclomipramine is distributed into CSF at a concentration about 2.6 times higher than in plasma. However, in one study of patients with depression or obsessive-compulsive disorder, the concentration of desmethylclomipramine in CSF was 2.6% that of the plasma concentration, corresponding to the fraction of desmethylclomipramine not bound to plasma proteins.

Clomipramine is approximately 97–98% bound to plasma proteins, principally to albumin and possibly to α_1-acid glycoprotein (α_1-AGP). The extent of protein binding of clomipramine appears to be independent of plasma concentration. Desmethylclomipramine is approximately 97–99% bound to plasma proteins. Because protein binding of both clomipramine and desmethylclomipramine is extensive, the manufacturers state that, while the possibility that clomipramine interacts with other highly protein-bound drugs has not been fully evaluated, such interactions may be important. (See Drug Interactions: Protein-bound Drugs.)

Clomipramine crosses the placenta and also is distributed into human milk. In one case report, plasma clomipramine concentrations were measured in an infant whose mother was receiving clomipramine hydrochloride 125 mg daily during pregnancy. The plasma clomipramine concentration in the infant was 267 ng/mL at birth; subsequently, the plasma concentration in the infant decreased although nursing began 7 days after delivery and continued. After the first week postpartum, the mother's dosage of clomipramine hydrochloride was increased to 150 mg daily and the concentration of clomipramine in milk was 80–160% of the concurrent plasma clomipramine concentration at steady state. The infant's plasma concentration of clomipramine was at the limit of detection (9.8 ng/mL) 35 days postpartum. Serum concentrations of clomipramine and its metabolites (i.e., desmethylclomipramine, 8-hydroxyclomipramine, 8-hydroxydesmethylclomipramine) were not observed or were below the limit of detection in a limited number of healthy, full-term neonates and infants who were breast-fed by mothers whose only medication was clomipramine administered at a constant dosage for at least 3 weeks.

■ **Elimination** Evidence that the steady-state plasma concentrations and AUCs of clomipramine and desmethylclomipramine may increase disproportionately with increasing oral doses of the drug suggests that the metabolism of clomipramine and desmethylclomipramine may be capacity-limited (saturable). The manufacturers caution that this fact should be considered when

evaluating the available data concerning the pharmacokinetic parameters of clomipramine as these data often were obtained in individuals receiving 150-mg daily doses. If clomipramine and desmethylclomipramine exhibit nonlinear pharmacokinetics at dosages exceeding 150 mg daily, their elimination half-lives may be considerably prolonged at dosages near the upper limit of the recommended dosage range (i.e., 200–250 mg daily). At such dosages, clomipramine and desmethylclomipramine may accumulate, which may increase the incidence of any dose- or plasma concentration-dependent adverse effects, particularly seizures.

The elimination half-life of clomipramine averages approximately 32 hours (range: 19–37 hours) and that of desmethylclomipramine averages about 69 hours (range: 54–77 hours) following a single, 150-mg oral dose of the drug.

The exact metabolic fate of clomipramine has not been fully elucidated. Clomipramine appears to be extensively metabolized to desmethylclomipramine and other metabolites and their glucuronide conjugates. Desmethylclomipramine, the principal metabolite, is formed by *N*-demethylation of clomipramine. Other metabolites of clomipramine include 8-hydroxyclomipramine, 2-hydroxyclomipramine, and clomipramine *N*-oxide, which appear to be formed via 8-hydroxylation, 2-hydroxylation, and *N*-oxidation, respectively. The metabolites of desmethylclomipramine include 8-hydroxydesmethylclomipramine and didesmethylclomipramine, which apparently are formed via 8-hydroxylation and *N*-demethylation, respectively. Although desmethylclomipramine is pharmacologically active, its efficacy in obsessive-compulsive disorder is not known. 8-Hydroxyclomipramine and 8-hydroxydesmethylclomipramine also are pharmacologically active but the clinical importance of their presence remains unknown.

The hydroxylation of clomipramine and desmethylclomipramine appears to be under genetic control (similar to that of debrisoquine and sparteine). In healthy adults who were phenotyped for debrisoquine hydroxylation, extensive metabolizers were distinguishable from poor metabolizers with regard to the extent of hydroxylation of desmethylclomipramine. Blood concentrations of desmethylclomipramine were higher than expected in a limited number of patients who subsequently were found to be poor metabolizers. Limited data suggest that CYP2D6, a cytochrome P-450 isoenzyme implicated in the sparteine/debrisoquine oxidation polymorphism, is involved in the 8-hydroxylation of clomipramine and desmethylclomipramine and in the 2-hydroxylation of clomipramine. In addition, demethylation of clomipramine may involve CYP2C, which is implicated in the *S*-mephenytoin oxidation polymorphism, and CYP1A2.

Possible differences in the metabolism of clomipramine among ethnic populations were suggested by a study in a limited number of healthy individuals that showed plasma clomipramine concentrations after a single oral dose of the drug to be higher in Asians (e.g., Indian, Pakistani) than in whites (e.g., British). In Japanese patients treated with clomipramine, substantial interindividual variation in demethylation and hydroxylation was observed; however, the prevalence of possibly poor demethylators and poor hydroxylators of clomipramine was estimated to be 0 and 1%, respectively. Further study is needed to clarify whether the pharmacokinetics of clomipramine truly differ in individuals of various ethnic backgrounds.

Following oral administration, clomipramine and its metabolites are excreted in urine and in feces (via biliary elimination). In 2 healthy individuals, approximately 51–60 and 24–32% of an orally administered, radiolabeled, 25-mg dose of clomipramine hydrochloride were excreted in urine and feces, respectively, after 14 days. Unchanged clomipramine and desmethylclomipramine were excreted in urine in quantities that together comprised approximately 0.8–1.3% of the dose. In a limited number of healthy individuals who received a single oral dose of clomipramine, 8-hydroxyclomipramine glucuronide was the principal metabolite found in urine. Although the urinary recovery of 8-hydroxyclomipramine glucuronide in these individuals who were phenotyped for metabolism of sparteine and mephenytoin was lower in poor metabolizers of sparteine compared with extensive metabolism of sparteine, estimates of clearance via glucuronidation did not differ between phenotypes, suggesting that the capacity for glucuronidation is not contingent on the capacity for 8-hydroxylation of clomipramine.

The effects of renal and hepatic impairment on the disposition of clomipramine have not been fully elucidated.

Limited data suggest that demethylation of clomipramine may be reduced with chronic alcohol consumption. In one study, the clearance of clomipramine via demethylation was decreased substantially and the ratio of blood clomipramine to desmethylclomipramine concentrations at steady state was higher in recently detoxified alcoholic patients (abstinence periods ranged from 4–20 weeks) compared with a control group of patients with no history of alcoholism.

Induction of drug-metabolizing enzymes (as measured by antipyrine half-life) does not appear to occur with clomipramine.

Hemodialysis, peritoneal dialysis, forced diuresis, and/or exchange transfusion are unlikely to remove clomipramine and desmethylclomipramine substantially because of the drug's rapid distribution into body tissues.

Chemistry and Stability

■ **Chemistry** Clomipramine, a dibenzazepine-derivative tricyclic antidepressant, is the 3-chloro analog of imipramine. Clomipramine is commercially available as the hydrochloride salt, which occurs as a white to off-white crystalline powder. The drug is freely soluble in water, methanol, and methylene chloride, and insoluble in ethyl ether and hexane. The drug has a pK_a of 9.5.

■ **Stability** Clomipramine hydrochloride capsules should be stored in tight containers at a temperature of 20–25°C and protected from moisture. When stored as directed, the capsules have an expiration date of 3 years following the date of manufacture.

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

Preparations

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

Clomipramine Hydrochloride

Oral		
Capsules	25 mg*	Anafranil*, Mallinckrodt
		Clomipramine Hydrochloride Capsules
	50 mg*	Anafranil*, Mallinckrodt
		Clomipramine Hydrochloride Capsules
	75 mg*	Anafranil*, Mallinckrodt
		Clomipramine Hydrochloride Capsules

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

Desipramine Hydrochloride

■ Desipramine is a dibenzazepine-derivative tricyclic antidepressant.

Dosage and Administration

■ **Administration** Desipramine hydrochloride is administered orally. Although desipramine has been administered in up to 3 divided doses throughout the day, it is long-acting and the entire daily dose may be administered at one time. Administration of the entire daily dose at bedtime may reduce daytime sedation; patients who experience insomnia and stimulation from the drug may receive the entire daily dose in the morning.

■ **Dosage** There is a wide range of dosage requirements, and dosage of desipramine hydrochloride must be carefully individualized. Initial dosages in adults should be low and generally range from 75–150 mg daily, depending on the severity of the condition being treated. Dosage may be gradually adjusted to the level that produces maximal therapeutic effect with minimal toxicity. In seriously ill patients, desipramine dosage may be gradually increased to 300 mg daily if necessary. Desipramine hydrochloride dosages exceeding 300 mg daily are not recommended. Hospitalized patients under close supervision may generally be given higher doses than outpatients. Geriatric and adolescent patients should usually be given lower than average doses. Manufacturers state that therapy should be initiated with 25–50 mg daily in these patients and that dosages greater than 100 mg daily are usually not necessary. In geriatric and adolescent patients who are seriously ill, desipramine dosage may be further increased to 150 mg daily if necessary. Desipramine hydrochloride dosages exceeding 150 mg daily are not recommended in these age groups. Maximum antidepressant effects may not occur for 2 or more weeks after therapy is begun.

After symptoms are controlled, dosage should be gradually reduced to the lowest level that will maintain relief of symptoms. To avoid the possibility of precipitating withdrawal symptoms, desipramine should not be terminated abruptly in patients who have received high dosages for prolonged periods.

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

Cautions

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

■ **Pediatric Precautions** Because collapse and sudden death occurred in at least one child (an 8-year-old boy) receiving desipramine for 2 years for attention deficit hyperactivity disorder (ADHD) and sudden death also has been reported in other children receiving the drug, at least one manufacturer of