changing the ...ing therapy in patients whose depression is ...ssibility 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 ...daily dose of clomipramine to a max- ...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.