preparations. Although no interactions with nonprescription medications have been reported to date, the potential for such adverse drug interactions exists. Therefore, the use of any nonprescription medication should be initiated cautiously according to the directions of use provided on the nonprescription medication. Although sertraline has not been shown to potentiate the impairment of mental and motor skills caused by alcohol, the manufacturers recommend that patients be advised to avoid alcohol while receiving the drug.

Sertraline generally is less sedating than most other currently available antidepressants and does not appear to produce substantial impairment of cognitive or psychomotor function. However, patients should be cautioned that sertraline may impair their ability to perform activities requiring mental alertness or physical coordination (e.g., operating machinery, driving a motor vehicle) and to avoid such activities until they experience how the drug affects them. Because the risk of using sertraline concomitantly with other CNS active drugs has not been evaluated systematically to date, the manufacturers recommend that such therapy be employed cautiously.

Seizures have been reported in patients receiving therapeutic dosages of sertraline. Because of limited experience with sertraline in patients with a history of seizures, the drug should be used with caution in such patients.

Activation of mania and hypomania has occurred in patients receiving therapeutic dosages of sertraline. The drug should be used with caution in patients with a history of mania or hypomania.

Altered platelet function has been reported rarely in patients receiving sertraline. In addition, use of the drug has been associated with several reports of abnormal bleeding or purpura. While a causal relationship to sertraline remains to be established, pending such establishment, the drug should be used with caution in patients with an underlying coagulation defect since the possible effects on hemostasis may be exaggerated in such patients. (See Cautions: Hematologic Effects.)

Hyponatremia has been reported in several patients receiving sertraline, principally in geriatric patients but also in those concurrently receiving diuretics or who were otherwise volume depleted. Hyponatremia associated with sertraline therapy appears to be reversible following discontinuance of the drug.

Sertraline has a weak uricosuric effect. (See Cautions: Metabolic Effects.) Pending further elucidation of the clinical importance, if any, of this effect, the drug should be used with caution in patients who may be adversely affected (e.g., those at risk for acute renal failure).

Because sertraline therapy has been associated with anorexia and weight loss (see Cautions: Metabolic Effects), the drug should be used with caution in patients who may be adversely affected by these effects (e.g., underweight patients).

Like many other antidepressant drugs, sertraline has been associated with hypothyroidism, elevated serum thyrotropin, and/or reduced serum thyroxine concentrations in a limited number of patients. Because of reports with other antidepressant agents and the complex interrelationship between the hypothalamic-pituitary-thyroid axis and affective (mood) disorders, at least one manufacturer recommends that thyroid function be reassessed periodically in patients with thyroid disease who are receiving sertraline.

Potentially life-threatening serotonin syndrome may occur during therapy with selective serotonin-reuptake inhibitors (SSRIs), including sertaline, or selective serotonin- and norepinephrine-reuptake inhibitors (SNRIs), particularly with concurrent administration of other serotonergic drugs (e.g., serotonin [5-hydroxytryptamine; 5-HT] type 1 agonists ["triptans"]) or drugs that impair serotonin metabolism (e.g., monoamine oxidase [MAO] inhibitors). Symptoms of serotonin syndrome may include mental status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g., hyperreflexia, incoordination), and/or GI symptoms (e.g., nausea, vomiting, diarrhea). Patients should be cautioned about the risk of serotonin syndrome with the concomitant use of sertraline and 5-HT_1 receptor agonists (triptans), tramadol, or other serotonergic agents. Because of the risk of serotonin syndrome, caution also is advised when sertraline is concurrently administered with drugs affecting serotonergic neurotransmission, including linezolid, lithium, tramadol, and St. John's wort (*Hypericum perforatum*). If concurrent therapy with sertraline and a 5-HT_1 receptor agonist is clinically warranted, the patient should be observed carefully, particularly during initiation of therapy, when the dosage is increased, or when another serotonergic agent is initiated. Concomitant use of sertraline and serotonin precursors (e.g., tryptophan) is not recommended. (See Drug Interactions: Drugs Associated with Serotonin Syndrome.)

Sertraline is contraindicated in patients receiving pimozide or MAO inhibitor therapy; at least 2 weeks should elapse between discontinuance of MAO inhibitor therapy and initiation of sertraline therapy and vice versa. (See Drug Interactions: Pimozide, and also see Monamine Oxidase Inhibitors under Drug Interactions: Drugs Associated with Serotonin Syndrome.)

Commercially available sertraline hydrochloride oral solution (Zoloft®) contains alcohol. Therefore, concomitant use of sertraline hydrochloride oral solution and disulfiram is contraindicated.

Sertraline also is contraindicated in patients who are hypersensitive to the drug or any ingredient in the formulation.

■ **Pediatric Precautions** The manufacturer states that safety and efficacy of sertraline in children with obsessive-compulsive disorder (OCD) younger than 6 years of age have not been established. Safety and efficacy of sertraline in children with other disorders (e.g., major depressive disorder, panic disorder, posttraumatic stress disorder, premenstrual dysphoric disorder, social phobia) have not been established. The overall adverse effect profile of sertaline in over 600 pediatric patients who received sertaline in controlled clinical trials was generally similar to that seen in the adult clinical studies. However, adverse effects reported in at least 2% of the sertraline-treated pediatric patients in these trials and that occurred at least twice as frequently as in pediatric patients receiving placebo included fever, hyperkinesia, urinary incontinence, aggressive reaction, sinusitis, epistaxis, and purpura.

Efficacy of sertraline in pediatric patients with major depressive disorder was evaluated in 2 randomized, 10-week, double-blind, placebo-controlled, flexible-dose (50–200 mg daily) trials in 373 children and adolescents with major depressive disorder, but data from these studies were not sufficient to establish efficacy in pediatric patients. In a safety analysis of the pooled data from these 2 studies, a difference in weight change between the sertraline and placebo groups was noted of approximately 1 kg for both pediatric patients (6–11 years of age) and adolescents (12–17 years of age) representing a slight weight loss for those receiving sertraline and a slight weight gain for those receiving placebo. In addition, a larger difference was noted in children than in adolescents between the sertraline and placebo groups in the proportion of outliers for clinically important weight loss; about 7% of the children and about 2% of the adolescents receiving sertraline in these studies experienced a weight loss of more than 7% of their body weight compared with none of those receiving placebo.

A subset of patients who completed these controlled trials was continued into a 24-week, flexible-dose, open-label, extension study. A mean weight loss of approximately 0.5 kg was observed during the initial 8 weeks of treatment for those pediatric patients first exposed to sertraline during the extension study, which was similar to the weight loss observed among sertraline-treated patients during the first 8 weeks of the randomized controlled trials. The patients continuing in the extension study began gaining weight relative to their baseline weight by week 12 of sertraline therapy, and patients who completed the entire 34 weeks of therapy with the drug had a weight gain that was similar to that expected using data from age-adjusted peers. The manufacturers state that periodic monitoring of weight and growth is recommended in pediatric patients receiving long-term therapy with sertraline or other selective serotonin-reuptake inhibitors (SSRIs).

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., sertraline, bupropion, citalopram, fluoxetine, fluvoxamine, mirtazapine, nefazodone, paroxetine, 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). (See Suicidality, under Cautions: Nervous System Effects, in Paroxetine 28:16.04.20.)

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. Caregivers of pediatric patients whose depression is persistently worse or who are experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidality during antidepressant therapy should consult their clinician regarding the best course of action (e.g., whether the therapeutic regimen should be changed or the drugs discontinued). *Patients should not discontinue use of selective serotonin-reuptake inhibitors without first consulting their clinician; it is very important that the drugs not be abruptly discontinued (see Dosage and Administration: Dosage), as withdrawal effects may occur.*

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