

Paroxetine

SELECTIVE SEROTONIN-REUPTAKE INHIBITORS

28:16.04.20

Preparations

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

Paroxetine Hydrochloride

Oral		
Suspension	10 mg (of paroxetine) per 5 mL	Paxil [®] , GlaxoSmithKline
Tablets, extended-release, film-coated	12.5 mg (of paroxetine)	Paxil CR [®] , GlaxoSmithKline
	25 mg (of paroxetine)	Paxil CR [®] , GlaxoSmithKline
	37.5 mg (of paroxetine)	Paxil CR [®] , GlaxoSmithKline
Tablets, film-coated	10 mg (of paroxetine)*	Paroxetine Hydrochloride Film-coated Tablets Paxil [®] (scored), GlaxoSmithKline
	20 mg (of paroxetine)*	Paroxetine Hydrochloride Film-coated Tablets Paxil [®] (scored), GlaxoSmithKline
	30 mg (of paroxetine)*	Paroxetine Hydrochloride Film-coated Tablets Paxil [®] , GlaxoSmithKline
	40 mg (of paroxetine)*	Paroxetine Hydrochloride Film-coated Tablets Paxil [®] , GlaxoSmithKline

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

Paroxetine Mesylate

Oral		
Tablets, film-coated	10 mg (of paroxetine)	Pexeva [®] , JDS Pharmaceuticals
	20 mg (of paroxetine)	Pexeva [®] (scored), JDS Pharmaceuticals
	30 mg (of paroxetine)	Pexeva [®] , JDS Pharmaceuticals
	40 mg (of paroxetine)	Pexeva [®] , JDS Pharmaceuticals

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

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Sertraline Hydrochloride

■ Sertraline, a selective serotonin-reuptake inhibitor (SSRI), is an antidepressant agent.

Uses

■ **Major Depressive Disorder** Sertraline is used in the treatment of major depressive disorder. A major depressive episode implies a prominent and relatively persistent depressed or dysphoric mood that usually interferes with daily functioning (nearly every day for at least 2 weeks). According to DSM-IV criteria, a major depressive episode includes at least 5 of the following 9 symptoms (with at least one of the symptoms being either depressed mood or loss of interest or pleasure): depressed mood most of the day as indicated by subjective report (e.g., feels sad or empty) or observation made by others; markedly diminished interest or pleasure in all, or almost all, activities most of the day; significant weight loss (when not dieting) or weight gain (e.g., a change of more than 5% of body weight in a month), or decrease or increase in appetite; insomnia or hypersomnia; psychomotor agitation or retardation (observable by others, not merely subjective feelings of restlessness or being slowed down); fatigue or loss of energy; feelings of worthlessness or excessive or inappropriate guilt (not merely self-reproach or guilt about being sick); diminished ability to think or concentrate or indecisiveness (either by subjective account or as observed by others); and recurrent thoughts of death, recurrent suicidal ideation without a specific plan, or a suicide attempt or specific plan for committing suicide.

Treatment of major depressive disorder generally consists of an acute phase (to induce remission), a continuation phase (to preserve remission), and a maintenance phase (to prevent recurrence). Various interventions (e.g., psychotherapy, antidepressant drug therapy, electroconvulsive therapy [ECT]) are used alone or in combination to treat major depressive episodes. Treatment should be individualized and the most appropriate strategy for a particular patient is determined by clinical factors such as severity of depression (e.g., mild, moderate, severe), presence or absence of certain psychiatric features (e.g., suicide risk, catatonia, psychotic or atypical features, alcohol or substance abuse or dependence, panic or other anxiety disorder, cognitive dysfunction, dysthymia, personality disorder, seasonal affective disorder), and concurrent illness (e.g., asthma, cardiac disease, dementia, seizure disorder, glaucoma, hypertension). Demographic and psychosocial factors as well as patient preference also are used to determine the most effective treatment strategy.

While use of psychotherapy alone may be considered as an initial treatment strategy for patients with mild to moderate major depressive disorder (based on patient preference and presence of clinical features such as psychosocial stressors), combined use of antidepressant drug therapy and psychotherapy may be useful for initial treatment of patients with moderate to severe major depressive disorder with psychosocial issues, interpersonal problems, or a comorbid axis II disorder. In addition, combined use of antidepressant drug therapy and psychotherapy may be beneficial in patients who have a history of poor compliance or only partial response to adequate trials of either antidepressant drug therapy or psychotherapy alone.

Antidepressant drug therapy can be used alone for initial treatment of patients with mild major depressive disorder (if preferred by the patient) and usually is indicated alone or in combination with psychotherapy for initial treatment of patients with moderate to severe major depressive disorder (unless ECT is planned). ECT is not generally used for initial treatment of uncomplicated major depression, but is recommended as first-line treatment for severe major depressive disorder when it is coupled with psychotic features, catatonic stupor, severe suicidality, food refusal leading to nutritional compromise, or other situations when a rapid antidepressant response is required. ECT also is recommended for patients who have previously shown a positive response or a preference for this treatment modality and can be considered for patients with moderate or severe depression who have not responded to or cannot receive antidepressant drug therapy. In certain situations involving depressed patients unresponsive to adequate trials of several individual antidepressant agents, adjunctive therapy with another agent (e.g., buspirone, lithium) or concomitant use of a second antidepressant agent (e.g., bupropion) has been used; however, such combination therapy is associated with an increased risk of adverse reactions, may require dosage adjustments, and (if not contraindicated) should be undertaken only after careful consideration of the relative risks and benefits. (See Drug Interactions: Serotonergic Drugs, Drug Interactions: Tricyclic and Other Antidepressants, and Drug Interactions: Lithium.)

The efficacy of sertraline for the acute treatment of major depression has been established by 2 placebo-controlled studies in adult outpatients who met DSM-III criteria for major depression. In the first study of 8 weeks' duration, sertraline was administered with flexible dosing in a range of 50–200 mg daily; the mean daily dosage for patients completing the study was 145 mg daily. In the second study of 6 weeks' duration, sertraline was administered in fixed doses of 50, 100, and 200 mg daily. Overall, these 2 studies demonstrated that sertraline was superior to placebo in improving scores on the Hamilton Depression Rating Scale and the Clinical Global Impression Severity and Improvement Scales. However, the second study was not readily interpretable regarding whether there was a dose-response relationship for the drug's efficacy.

In a third study, depressed outpatients who had responded by the end of an initial 8-week open treatment phase to sertraline 50–200 mg daily were randomized to continue sertraline in the same dosage range or placebo for 44 weeks in a double-blind manner. The mean daily dosage of sertraline in those who completed this long-term study was 70 mg daily, and the relapse rate in the sertraline-treated patients was substantially lower than in those who received placebo.

An analysis of these 3 controlled studies for possible gender-related effects on treatment outcome did not suggest any difference in efficacy based on the gender of the patient.

While the optimum duration of sertraline therapy has not been established, many experts state that acute depressive episodes require several months or longer of sustained antidepressant therapy. In addition, some clinicians recommend that long-term antidepressant therapy be considered in certain patients at risk for recurrence of depressive episodes (such as those with highly recurrent unipolar depression). The efficacy of sertraline in maintaining an antidepressant response for up to 1 year without increased toxicity has been demonstrated in a controlled setting. The manufacturers state that the usefulness of the drug in patients receiving prolonged therapy should be reevaluated periodically. (See Dosage and Administration: Dosage.)

The manufacturers state that the drug's antidepressant efficacy in hospital settings has not been adequately studied to date.

As with certain other antidepressants, the possibility that sertraline may precipitate hypomanic or manic attacks in patients with bipolar or other major affective disorder should be considered. Sertraline is *not* approved for use in treating bipolar depression in adults.

Considerations in Choosing an Antidepressant A variety of antidepressant drugs is available for the treatment of major depressive disorder, including selective serotonin-reuptake inhibitors (SSRIs; e.g., citalopram, escitalopram, fluoxetine, paroxetine, sertraline), selective serotonin- and norepinephrine-reuptake inhibitors (SNRIs; e.g., desvenlafaxine, duloxetine, venlafaxine), tricyclic antidepressants (e.g., amitriptyline, amoxapine, desipramine, doxepin, imipramine, nortriptyline, protriptyline, trimipramine), monoamine oxidase (MAO) inhibitors (e.g., phenelzine, tranylcypromine), and other antidepressants (e.g., bupropion, maprotiline, nefazodone, trazodone). Most clinical studies have shown that the antidepressant effect of usual dosages of sertraline in patients with depression is greater than that of placebo and comparable to that of usual dosages of tricyclic antidepressants (e.g., amitriptyline), other SSRIs (e.g., fluoxetine), and other antidepressants (e.g., nefazodone). In geriatric patients with major depression, sertraline appears to be as effective as amitriptyline. The onset of action of sertraline appears to be comparable to that of tricyclic antidepressants.

In general, response rates in patients with major depression are similar for currently available antidepressants, and the choice of antidepressant agent for a given patient depends principally on other factors such as potential adverse effects, safety or tolerability of these adverse effects in the individual patient, psychiatric and medical history, patient or family history of response to specific therapies, patient preference, quantity and quality of available clinical data, cost, and relative acute overdose safety. No single antidepressant can be recommended as optimal for all patients because of substantial heterogeneity in individual responses and in the nature, likelihood, and severity of adverse effects. In addition, patients vary in the degree to which certain adverse effects and other inconveniences of drug therapy (e.g., cost, dietary restrictions) affect their preferences.

In the large-scale Sequenced Treatment Alternatives to Relieve Depression (STAR*D) effectiveness trial, patients with major depressive disorder who did not respond to or could not tolerate therapy with one SSRI (citalopram) were randomized to switch to extended-release ("sustained-release") bupropion, sertraline, or extended-release venlafaxine as a second step of treatment (level 2). Remission rates as assessed by the 17-item Hamilton Rating Scale for Depression (HRSD-17) and the Quick Inventory of Depressive Symptomatology—Self Report (QIDS-SR-16) were approximately 21 and 26% for extended-release bupropion, 18 and 27% for sertraline, and 25 and 25% for extended-release venlafaxine therapy, respectively; response rates as assessed by the QIDS-SR-16 were 26, 27, and 28% for extended-release bupropion, sertraline, and extended-release venlafaxine therapy, respectively. These results suggest that after unsuccessful initial treatment of depressed patients with an SSRI, approximately 25% of patients will achieve remission after the therapy is switched to another antidepressant and that either another SSRI (e.g., sertraline) or an agent from another class (e.g., bupropion, venlafaxine) may be reasonable alternative antidepressants in patients not responding to initial SSRI therapy.

Patient Tolerance Considerations. Because of differences in the adverse effect profile between SSRIs and tricyclic antidepressants, particularly less frequent anticholinergic effects, cardiovascular effects, and weight gain with SSRIs, these drugs may be preferred in patients in whom such effects are not tolerated or are of potential concern. The decreased incidence of anticholinergic effects associated with sertraline and other SSRIs compared with tricyclic antidepressants is a potential advantage, since such effects may result in discontinuance of the drug early during therapy in unusually sensitive patients. In addition, some anticholinergic effects may become troublesome during long-term tricyclic antidepressant therapy (e.g., persistent dry mouth may result in tooth decay). Although SSRIs share the same overall tolerability profile, certain patients may tolerate one drug in this class better than another. In an open study, most patients who had discontinued fluoxetine therapy because of adverse effects subsequently tolerated sertraline therapy. Antidepressants other than SSRIs may be preferred in patients in whom certain adverse GI effects (e.g., nausea, anorexia), nervous system effects (e.g., anxiety, nervousness, insomnia), and/or weight loss are not tolerated or are of concern, since such effects appear to occur more frequently with this class of drugs.

Pediatric Considerations. The clinical presentation of depression in children and adolescents can differ from that in adults and generally varies with the age and developmental stages of the child. Younger children may exhibit behavioral problems such as social withdrawal, aggressive behavior, apathy, sleep disruption, and weight loss; adolescents may present with somatic complaints, self-esteem problems, rebelliousness, poor performance in school, or a pattern of engaging in risky or aggressive behavior.

Only limited data are available to date from controlled clinical studies evaluating various antidepressant agents in children and adolescents, and many of these studies have methodologic limitations (e.g., nonrandomized or uncontrolled, small sample size, short duration, nonspecific inclusion criteria). However, there is some evidence that the response to antidepressants in pediatric patients may differ from that seen in adults, and caution should be used in extrapolating data from adult studies when making treatment decisions for pediatric patients. Results of several studies evaluating tricyclic antidepressants (e.g., amitriptyline, desipramine, imipramine, nortriptyline) in preadolescent and adolescent patients with major depression indicate a lack of overall efficacy in this age group. Based on the lack of efficacy data regarding use of tricyclic antidepressants and MAO inhibitors in pediatric patients and because of the potential for life-threatening adverse effects associated with the use of these drugs, many experts consider selective serotonin-reuptake inhibitors, including sertraline, the drugs of choice when antidepressant therapy is indicated for the treatment of major depressive disorder in children and adolescents. However, the US Food and Drug Administration (FDA) states that, while efficacy of fluoxetine has been established in pediatric patients, efficacy of other newer antidepressants (i.e., sertraline, citalopram, desvenlafaxine, duloxetine, escitalopram, fluvoxamine, mirtazapine, nefazodone, paroxetine, venlafaxine) was not conclusively established in clinical trials in pediatric patients with major depressive disorder. In addition, FDA now warns that antidepressants increase the risk of suicidal thinking and behavior (suicidality) in children and adolescents with major depressive disorder and other psychiatric disorders. (See Cautions: Pediatric Precautions.) FDA currently states that anyone considering using an antidepressant in a child or adolescent for any clinical use must balance the potential risk of therapy with the clinical need. (See Cautions: Precautions and Contraindications.)

Geriatric Considerations. The response to antidepressants in depressed geriatric patients without dementia is similar to that reported in younger adults,

but depression in geriatric patients often is not recognized and is not treated. In geriatric patients with major depressive disorder, selective serotonin-reuptake inhibitors (SSRIs) appear to be as effective as tricyclic antidepressants (e.g., amitriptyline) but generally are associated with fewer overall adverse effects than these other agents. Geriatric patients appear to be especially sensitive to anticholinergic (e.g., dry mouth, constipation, vision disturbance), cardiovascular, orthostatic hypotensive, and sedative effects of tricyclic antidepressants. The low incidence of anticholinergic effects associated with sertraline and other SSRIs compared with tricyclic antidepressants also is a potential advantage in geriatric patients, since such effects (e.g., constipation, dry mouth, confusion, memory impairment) may be particularly troublesome in these patients. However, SSRI therapy may be associated with other troublesome adverse effects (e.g., nausea and vomiting, agitation and akathisia, parkinsonian adverse effects, sexual dysfunction, weight loss, hyponatremia). Some clinicians state that SSRIs such as sertraline may be preferred for treating depression in geriatric patients in whom the orthostatic hypotension associated with many antidepressants (e.g., tricyclics) potentially may result in injuries (such as severe falls). However, despite the fewer cardiovascular and anticholinergic effects associated with SSRIs, these drugs did not show any advantage over tricyclic antidepressants with regard to hip fracture in a case-control study. In addition, there was little difference in the rates of falls between nursing home residents receiving SSRIs and those receiving tricyclic antidepressants in a retrospective study. Therefore, all geriatric individuals receiving either type of antidepressant should be considered at increased risk of falls and appropriate measures should be taken. In addition, clinicians prescribing SSRIs in geriatric patients should be aware of the many possible drug interactions associated with these drugs, including those involving metabolism of the drugs through the cytochrome P-450 system. (See Drug Interactions.)

Patients with dementia of the Alzheimer's type (Alzheimer's disease, presenile or senile dementia) often present with depressive symptoms, such as depressed mood, appetite loss, insomnia, fatigue, irritability, and agitation. Most experts recommend that patients with dementia of the Alzheimer's type who present with clinically important and persistent depressive symptoms be considered as candidates for pharmacotherapy even if they fail to meet the criteria for a major depressive syndrome. The goals of such therapy are to improve mood, functional status (e.g., cognition), and quality of life. Treatment of depression also may reduce other neuropsychiatric symptoms associated with depression in patients with dementia, including aggression, anxiety, apathy, and psychosis. Although patients may present with depressed mood alone, the possibility of more extensive depressive symptomatology should be considered. Therefore, patients should be evaluated and monitored carefully for indices of major depression, suicidal ideation, and neurovegetative signs since safety measures (e.g., hospitalization for suicidality) and more vigorous and aggressive therapy (e.g., relatively high dosages, multiple drug trials) may be needed in some patients.

Although placebo-controlled trials of antidepressants in depressed patients with concurrent dementia have shown mixed results, the available evidence and experience with the use of antidepressants in patients with dementia of the Alzheimer's type and associated depressive manifestations indicate that depressive symptoms (including depressed mood alone and with neurovegetative changes) in such patients are responsive to antidepressant therapy. In some patients, cognitive deficits may partially or fully resolve during antidepressant therapy, but the extent of response will be limited to the degree of cognitive impairment that is directly related to depression. SSRIs such as sertraline, citalopram, escitalopram, fluoxetine, or paroxetine are generally considered as first-line agents in the treatment of depressed patients with dementia since they are better tolerated than some other antidepressants (e.g., tricyclic antidepressants, monoamine oxidase inhibitors). Some possible alternative agents to SSRIs include bupropion, mirtazapine, and venlafaxine. Some geriatric patients with dementia and depression may be unable to tolerate the antidepressant dosages needed to achieve full remission. When a rapid antidepressant response is not critical, some experts therefore recommend a very gradual dosage increase to increase the likelihood that a therapeutic dosage of the SSRI or other antidepressant will be reached and tolerated. In a randomized, placebo-controlled study in a limited number of patients with major depression and Alzheimer's disease, sertraline was found to be superior to placebo; depression reduction in this study was accompanied by lessened behavior disturbance and improved activities of daily living but not improved cognition.

Cardiovascular Considerations. The relatively low incidence of adverse cardiovascular effects, including orthostatic hypotension and conduction disturbances, associated with sertraline and other selective serotonin-reuptake inhibitors may be advantageous in patients in whom the cardiovascular effects associated with tricyclic antidepressants may be hazardous. Patients with a recent history of myocardial infarction or unstable cardiovascular disease were excluded from premarketing clinical studies with sertraline. However, the cardiovascular safety of sertraline (50–200 mg daily for 24 weeks; mean dosage of 89 mg daily) was evaluated in a postmarketing, double-blind, placebo-controlled study in adult outpatients with major depressive disorder and a recent history of myocardial infarction or unstable angina pectoris requiring hospitalization but who were otherwise free of life-threatening medical conditions. When therapy was initiated during the acute phase of recovery (within 30 days after a myocardial infarction or hospitalization for unstable angina), sertraline therapy did not differ from placebo on the following cardiovascular end points at week 16: left ventricular ejection fraction and total cardiovascular events (angina, chest pain, edema, palpitations, syncope, postural dizziness, chronic

heart failure, myocardial infarction, tachycardia, bradycardia, blood pressure changes). Although not statistically significant, approximately 20% fewer major cardiovascular events involving death or requiring hospitalization (e.g., for myocardial infarction, chronic heart failure, stroke, angina) occurred in the sertraline-treated patients compared with those receiving placebo. (See Cautions: Cardiovascular Effects and see also Cautions: Precautions and Contraindications.)

Sedative Considerations. Because sertraline and other SSRIs are generally less sedating than some other antidepressants (e.g., tricyclics), some clinicians state that these drugs may be preferable in patients who do not require the sedative effects associated with many antidepressant agents; however, an antidepressant with more prominent sedative effects (e.g., trazodone) may be preferable in certain patients (e.g., those with insomnia).

Suicidal Risk Considerations. 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 suicidal thinking and behavior (suicidality) in certain patients during the early phases of treatment. FDA states that antidepressants increased the risk of suicidality in short-term studies in children, adolescents, and young adults (18–24 years of age) with major depressive disorder and other psychiatric disorders. (See Cautions: Pediatric Precautions.) 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 antidepressant 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. Because the risk of suicidality in depressed patients may persist until substantial remission of depression occurs, appropriate monitoring and close observation of all patients who are receiving antidepressant therapy is recommended. (See Cautions: Precautions and Contraindications.)

Other Considerations. Sertraline has been effective in patients with moderate to severe depression.

In the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) level 2 trial, patients with major depressive disorder who did not respond to or could not tolerate therapy with citalopram (another SSRI) were randomized to receive either extended-release ("sustained-release") bupropion or bupropion therapy in addition to citalopram. Although both extended-release bupropion and bupropion were found to produce similar remission rates, extended-release bupropion produced a greater reduction in the number and severity of symptoms and a lower rate of drug discontinuance than bupropion in this large-scale, effectiveness trial. These results suggest that augmentation of SSRI therapy with extended-release bupropion may be useful in some patients with refractory depression.

Sertraline has been effective in patients with depression and concurrent human immunodeficiency virus (HIV) infection and depression with anxiety.

In a double-blind, placebo-controlled study, both sertraline or imipramine were found to be more effective than placebo in reducing the depressive symptoms and improving psychosocial functioning in patients with dysthymia without concurrent major depression; moreover, fewer patients treated with sertraline than those treated with imipramine or placebo discontinued therapy because of adverse effects. The results of several other studies, both controlled and uncontrolled, also suggest that sertraline may be effective in patients with dysthymia. Because dysthymia is a chronic condition and requires prolonged antidepressant therapy, the good tolerability demonstrated in clinical studies to date may be advantageous. Sertraline also has been used in the treatment of anger attacks associated with atypical depression and dysthymia in a limited number of patients.

■ Obsessive-Compulsive Disorder Sertraline is used in the treatment of obsessive-compulsive disorder when the 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 ideas, 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, intentional 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 a recognition.

The efficacy of sertraline for the management of obsessive-compulsive disorder has been established in several multicenter, placebo-controlled studies, including one study of 8 weeks' duration and 2 studies of 12 weeks' duration in adults and one study of 12 weeks' duration in children and adolescents 6–17 years of age. Patients in these studies had moderate to severe obsessive-compulsive disorder with mean baseline total scores on the Yale-Brown Obsessive-Compulsive Scale (YBOCS) of 23–25 in adults and 22 in children and

adolescents (measured in the Children's Yale-Brown Obsessive-Compulsive Scale [CY-BOCS]). In the 8-week study with flexible dosing, adult patients received sertraline in dosages ranging from 50–200 mg daily; the mean dosage for those completing the study was 186 mg daily. Total scores on the YBOCS decreased by an average of approximately 4 points in sertraline-treated patients and 2 points in patients receiving placebo; this difference was statistically significant.

In a fixed-dose study of 12 weeks' duration involving sertraline dosages of 50, 100, and 200 mg daily, adult patients receiving 50 and 200 mg of the drug daily experienced substantially greater reductions in the YBOCS total score than those receiving placebo (approximately 6 to approximately 3 points, respectively). In a 12-week study with flexible dosing in the range of 50–200 mg daily, the mean sertraline dosage in adult patients completing the study was 185 mg daily. YBOCS total scores in the sertraline-treated patients were reduced by a mean of approximately 7 points, which was better than the mean reduction of approximately 4 points reported in the placebo-treated patients.

In a 12-week study with flexible dosing, sertraline therapy was initiated at dosages of 25 or 50 mg daily in children 6–12 years of age or adolescents 13–17 years of age, respectively. Subsequent dosage was titrated according to individual tolerance over the first 4 weeks to a maximum dosage of 200 mg daily; the mean dosage for those completing the study was 178 mg daily. The drug produced substantially greater reductions in scores in the Children's Yale-Brown Obsessive-Compulsive Scale (CY-BOCS), the National Institute of Mental Health Global Obsessive-Compulsive Scale (NIMH-OC), and the Clinical Global Impressions (CGI) Improvement Scale; total scores on the CY-BOCS decreased by an average of approximately 7 units in sertraline-treated patients and 3 units in patients receiving placebo. An analysis of these controlled studies for possible age- and gender-related effects on treatment outcome did not suggest any difference in efficacy based on either the age or gender of the patient.

In addition, in an uncontrolled, 6-week study with flexible dosing (50–200 mg daily) in children or adolescents 6–17 years of age with obsessive-compulsive disorder or major depression, those with a diagnosis of obsessive-compulsive disorder had mean baseline total scores on the CY-BOCS, NIMH-OC, and CGI of about 24.9, 10.2, and 5.2, respectively. Sertraline produced substantial reductions in all 3 of the scales; total scores on CY-BOCS, NIMH-OC, and CGI decreased to 12.9, 6.7, and 3.4, respectively. In another uncontrolled, 6-week study employing a sertraline dosage that was escalated from 25 to 200 mg daily over 3 weeks, the drug combined with behavioral therapy was effective in a limited number of adolescents 13–17 years of age with obsessive-compulsive disorder refractory to other therapies; total scores on the CY-BOCS at the end of the study decreased by 11 points (from 25.4 to 14.4).

Results from comparative studies to date suggest sertraline and other selective serotonin-reuptake inhibitors (SSRIs; e.g., fluoxetine, fluvoxamine, paroxetine) are as effective or somewhat less effective than clomipramine and more effective than tricyclic antidepressants (e.g., amitriptyline, desipramine, imipramine, nortriptyline) 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 SSRIs, although all drugs were superior to placebo. Like clomipramine, SSRIs reduce but do not completely eliminate obsessions and compulsions.

Many clinicians consider an SSRI (e.g., sertraline, fluoxetine, fluvoxamine, paroxetine) or clomipramine to be the drugs of choice for the pharmacologic treatment of obsessive-compulsive disorder. The decision whether to initiate therapy with an SSRI or clomipramine 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 SSRIs (nausea, headache, overstimulation, sleep disturbances) while SSRIs 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), pharmacokinetics of the drug, potential drug interactions, and cost of therapy may also influence clinicians when selecting between SSRIs and clomipramine as first-line therapy in patients with obsessive-compulsive disorder. Although not clearly established, it has been suggested that the mechanism of action of sertraline and other potent serotonin-reuptake inhibitors (e.g., clomipramine, fluoxetine, fluvoxamine, paroxetine) used in the management of obsessive-compulsive disorder may be related to their serotonergic activity.

■ Panic Disorder Sertraline is used in the treatment of panic disorder with or without agoraphobia. Panic disorder is characterized by the occurrence of unexpected panic attacks and associated concern about having additional attacks; worry about the implications or consequences of the attacks; and/or a clinically important change in behavior related to the attacks.

According to DSM-IV, panic disorder is characterized by recurrent unexpected panic attacks, which consist of a discrete period of intense fear or discomfort in which 4 (or more) of the following symptoms develop abruptly and reach a peak within 10 minutes: palpitations, pounding heart, or accelerated heart rate; sweating; trembling or shaking; sensations of shortness of breath or smothering; feeling of choking; chest pain or discomfort; nausea or abdominal distress; feeling dizzy, unsteady, lightheaded, or faint; derealization (feelings of unreality) or depersonalization (being detached from oneself); fear of losing control; fear of dying; paresthesias (numbness or tingling sensations); and chills or hot flashes.

The efficacy of sertraline for the management of panic disorder has been established by 3 double-blind, placebo-controlled studies in adult outpatients who met DSM-III-R criteria for panic disorder with or without agoraphobia. The first 2 studies were of 10 weeks' duration and used a flexible dosing schedule. Sertraline therapy was initiated in a dosage of 25 mg daily for the first week and then dosage was escalated to 50–200 mg daily depending on clinical response and tolerability. The mean sertraline dosages for completers were 131 and 144 mg daily for the first 2 studies. Overall, these 2 studies demonstrated that sertraline was superior to placebo in decreasing the frequency of panic attacks and in improving scores on the Clinical Global Impression Severity of Illness and Global Improvement Scales. The difference between sertraline and placebo in reduction in the number of full panic attacks per week compared with baseline was approximately 2 in both studies.

The third study was a fixed-dose study of 12 weeks' duration. Sertraline was given in dosages of 50, 100, and 200 mg daily. The patients receiving sertraline demonstrated a substantially greater reduction in panic attack frequency than patients receiving placebo. However, the results of this study were not readily interpretable regarding a dose-response relationship for efficacy in this condition.

An analysis of these 3 controlled studies for possible age-, race-, or gender-related effects on treatment outcome did not suggest any difference in efficacy based on these patient characteristics.

Panic disorder can be treated with cognitive and behavioral psychotherapy and/or pharmacologic therapy. There are several classes of drugs that appear to be effective in the pharmacologic management of panic disorder, including tricyclic antidepressants, MAO inhibitors (e.g., phenelzine), selective serotonin-reuptake inhibitors (SSRIs; e.g., citalopram, fluoxetine, paroxetine, sertraline), and benzodiazepines (e.g., alprazolam, clonazepam). When choosing among the available drugs, clinicians should consider their acceptance and tolerability by patients; their ability to reduce or eliminate panic attacks, reduce clinically important anxiety and disability secondary to phobic avoidance, and ameliorate other common comorbid conditions (such as depression); and their ability to prevent relapse during long-term therapy. Because of their better tolerability when compared with other agents (such as the tricyclic antidepressants and benzodiazepines), the lack of physical dependence problems commonly associated with benzodiazepines, and efficacy in panic disorder with comorbid conditions (e.g., depression, other anxiety disorders such as obsessive-compulsive disorder, alcoholism), many clinicians prefer SSRIs as first-line therapy in the management of panic disorder. If SSRI therapy is ineffective or not tolerated, use of a tricyclic antidepressant or a benzodiazepine is recommended.

Sertraline has improved chronic idiopathic urticaria[†] associated with panic disorder in at least one patient, but further study is needed to determine whether serotonin is involved in the pathogenesis of urticaria and whether SSRIs are effective in this condition.

■ **Posttraumatic Stress Disorder** Sertraline is used in the treatment of posttraumatic stress disorder (PTSD). PTSD is an anxiety disorder that involves the development of certain characteristic symptoms following personal exposure to an extreme traumatic stressor. According to DSM-IV, PTSD requires exposure to a traumatic event(s) that involved actual or threatened death or serious injury, or threat to the physical integrity of self or others, and the response to the event must involve intense fear, helplessness, or horror (In children the response may be expressed by disorganized or agitated behavior). PTSD is characterized by persistent symptoms of *reexperiencing* the trauma (e.g., intrusive distressing recollections of the event; recurrent distressing dreams of the event; acting or feeling as if the event were recurring including illusions, hallucinations, or flashbacks; intense distress at exposure to internal or external cues that symbolize or resemble an aspect of the event; physiologic reactivity on exposure to internal or external cues that symbolize or resemble an aspect of the event), persistent *avoidance* of stimuli associated with the trauma and numbing of general responsiveness (e.g., efforts to avoid thoughts, feelings, or conversations related to the event; efforts to avoid activities, places, or people that arouse recollections of the event; inability to recall an important aspect of the event; markedly diminished interest or participation in significant activities; feeling of detachment or estrangement from others; restricted emotions and/or range of affect not present before the event; sense of a foreshortened future), and persistent symptoms of *increased arousal* (e.g., difficulty sleeping; irritability/outbursts of anger; difficulty concentrating; hypervigilance; exaggerated startle response). According to DSM-IV, a PTSD diagnosis requires the presence of 1 or more symptoms of *reexperiencing*, 3 or more symptoms of *avoidance*, and 2 or more symptoms of *increased arousal*, all of which must be present for at least one month and cause clinically important distress or impairment in social, occupational, or other important areas of functioning. PTSD, like other anxiety disorders, rarely occurs alone, and patients with PTSD often present with comorbid disorders (e.g., major depressive disorder, substance abuse disorders, panic disorder, generalized anxiety disorders, obsessive-compulsive disorder, social phobia); it is unknown whether these comorbid disorders precede or follow the onset of PTSD.

■ Psychotherapy alone or in combination with pharmacotherapy generally is considered the treatment of choice for PTSD. Pharmacologic therapy may be indicated in addition to psychotherapy for initial treatment of PTSD in patients who have comorbid disorders (e.g., major depressive disorder, bipolar disorder, other anxiety disorders) and also may be indicated in those who do not respond to initial treatment with psychotherapy alone. If pharmacotherapy is indicated in patients with PTSD, selective serotonin-reuptake inhibitors (SSRIs; e.g., ser-

traline, fluoxetine, paroxetine) usually are considered the drugs of choice (except in patients with bipolar disorder who require treatment with mood stabilizing agents).

The efficacy of sertraline for the management of PTSD has been established in 2 placebo-controlled studies of 12 weeks' duration in adult outpatients (76% women) who met DSM-III-R criteria for chronic PTSD (duration of symptoms 3 months or longer). The mean duration of PTSD for these patients was approximately 12 years and 44% of patients had secondary depressive disorders. Sertraline therapy was initiated at a dosage of 25 mg daily for the first week and then dosage was escalated (using a flexible dosage schedule) to 50–200 mg daily based on clinical response and tolerability. The mean sertraline dosage for patients who completed studies 1 and 2 was 146 mg and 151 mg daily, respectively. Overall, these 2 studies showed that sertraline was superior to placebo in improving scores on the Clinician-Administered PTSD Scale Part 2 total severity scale (a measure of the intensity and frequency of all 3 PTSD diagnostic symptom clusters [reexperiencing/intrusion, avoidance/numbing, and hyperarousal]), Impact of Event Scale (a patient rated measurement of the intrusion and avoidance symptoms), and the Clinical Global Impressions Severity of Illness and Global Improvement Scales.

However, in 2 additional placebo-controlled studies of similar design and duration, the difference in response to treatment on key assessment scales between patients receiving sertraline and those receiving placebo was not statistically significant. In one study of mostly female patients who met the DSM-III-R criteria for PTSD related to sexual/physical trauma, those receiving placebo experienced substantially greater improvement on the Impact of Event Scale than those receiving sertraline therapy. Although this study enrolled a higher proportion of patients with comorbid anxiety disorders and a higher proportion of patients receiving placebo with a successful response to previous psychotropic therapies than the studies demonstrating efficacy of the drug, it is unknown whether these factors alone account for the high placebo response in the study.

Efficacy of sertraline for the management of PTSD related to war or combat was evaluated in a study involving primarily white men in a VA medical center outpatient setting (mean duration of PTSD approximately 18 years). At the end of this study, patients receiving sertraline did not differ from those receiving placebo on any of the key efficacy assessment scales (e.g., Clinician-Administered PTSD scale, Davidson Self-Rating Trauma scale, Impact of Event Scale). In addition, the mean change from baseline for both treatment groups in this study was of a lesser magnitude than those of patients receiving placebo in the other reported studies. The lack of response to sertraline treatment in these combat veterans is consistent with controlled studies evaluating other selective serotonin-reuptake inhibitors (e.g., fluoxetine, brofaromine [not commercially available in the US]) in Vietnam veterans with PTSD. Some experts suggest that patients with combat- or war-related PTSD may be less responsive to treatment than patients with PTSD related to other traumatic events (e.g., sexual assault, accidents, natural disasters) because of some factor inherent in combat- or war-related trauma. However, other experts suggest that the poor treatment response in studies evaluating use in veterans may be the result of sampling error since veterans receiving treatment at VA hospitals may constitute a self-selected group of patients with chronic PTSD who have multiple impairments (comorbid disorders, substance abuse) that make them less responsive to treatment.

Since PTSD is a more common disorder in women than men, the majority (76%) of patients in reported studies were women. A retrospective analysis of pooled data has shown a substantial difference between sertraline and placebo on key efficacy assessment scales (e.g., Clinician-Administered PTSD scale, Impact of Event Scale, Clinical Global Impressions Severity of Illness Scale) in women (regardless of a baseline diagnosis of comorbid depression), but essentially no effect in the limited number of men studied. The clinical importance of this apparent gender effect is unknown; however, only limited data are available to date regarding use of SSRIs in men who have PTSD related to noncombat-related trauma (e.g., sexual assault, accidents, natural disasters). There are insufficient data to date to determine whether race or age has any effect on the efficacy of sertraline in the management of PTSD.

■ **Premenstrual Dysphoric Disorder** Sertraline is used in the treatment of premenstrual dysphoric disorder (previously late luteal phase dysphoric disorder). DSM-IV criteria for premenstrual dysphoric disorder (PMDD) requires that in most menstrual cycles of the previous year at least 5 of the following 11 symptoms must have been present for most of the time during the last week of the luteal phase (with at least one of the symptoms being one of the first 4 listed): marked depressed mood, feelings of hopelessness, or self-deprecating thoughts; marked anxiety, tension; feelings of being "keyed up" or on "edge"; marked affective lability (e.g., feeling suddenly sad or tearful or increased sensitivity to rejection); persistent and marked anger or irritability or increased interpersonal conflicts; decreased interest in usual activities (e.g., work, school, friends, hobbies); a subjective sense of difficulty in concentrating; lethargy, easy fatigability, or marked lack of energy; marked change in appetite, overeating, or specific food cravings; hypersomnia or insomnia; a subjective sense of being overwhelmed or out of control; and other physical symptoms, such as breast tenderness or swelling, headaches, joint or muscle pain, or a sensation of "bloating" or weight gain. Such symptoms should begin to remit within a few days of the onset of menses (follicular phase) and are always absent in the week following menses. The presence of this cyclical pattern of symptoms must be confirmed by at least 2 consecutive months of prospective daily symptom ratings. PMDD should be distinguished from the more common

premenstrual syndrome (PMS) by prospective daily ratings and the strict criteria listed above.

The efficacy of sertraline for the management of PMDD has been established in 2 randomized, placebo-controlled studies over 3 menstrual cycles in adult women who met DSM-III-R or DSM-IV criteria for PMDD. In these studies, flexible dosages (range: 50–150 mg daily) of sertraline administered continuously throughout the menstrual cycle or during the luteal phase only (i.e., for 2 weeks prior to the onset of menses) were shown to be substantially more effective than placebo in improving scores from baseline on the Daily Record of Severity of Problems (DRSP), the Clinical Global Impression of Severity of Illness (CGI-S) and Improvement (CGI-I), and/or the Hamilton Depression Rating Scales (HAM-D-17). The mean dosage of sertraline in patients completing these trials was 102 or 74 mg daily, for those receiving continuous or luteal-phase dosing of the drug, respectively.

When given in a flexible dosage of 50–150 mg daily in a separate double-blind, placebo-controlled study, sertraline was substantially better than placebo in improving symptoms (depressive symptoms, physical symptoms, anger/irritability) and functional impairment associated with this disorder. The beneficial effect of the drug was apparent by the first treatment cycle. In an open study comparing sertraline and desipramine in the treatment of premenstrual dysphoric disorder, sertraline and possibly desipramine were found to be effective; however, sertraline was better tolerated than desipramine. Additional controlled studies are needed to determine whether the efficacy of the drug is sustained during longer-term, maintenance therapy in women with this condition. In addition, efficacy of sertraline used in conjunction with oral contraceptives for the treatment of PMDD has not been determined since patients receiving oral contraceptives were excluded from most clinical studies, to date.

■ Social Phobia Sertraline is used in the treatment of social phobia (social anxiety disorder). According to DSM-IV, social phobia is characterized by a marked and persistent fear of one or more social or performance situations in which the person is exposed to unfamiliar people or to possible scrutiny by others. Exposure to the feared situation almost invariably provokes anxiety, which may approach the intensity of a panic attack. The feared situations are avoided or endured with intense anxiety or distress. The avoidance, fear, or anxious anticipation of encountering the social or performance situation interferes significantly with the person's daily routine, occupational or academic functioning, or social activities or relationships, or there is marked distress about having the phobias. Lesser degrees of performance anxiety or shyness generally do not require psychotherapy or pharmacologic treatment.

The efficacy of sertraline in the treatment of social phobia has been established in 2 multicenter, placebo-controlled studies in adult outpatients who met DSM-IV criteria for social phobia. In one study of 12 weeks' duration, 47% of patients receiving flexible dosages of sertraline (50–200 mg daily; mean dosage of 144 mg daily) were characterized as responders (defined as a score of 1 or 2 on the Clinical Global Impressions [CGI] Global Improvement Scale) compared with 26% of those receiving placebo (intent-to-treat analysis). Sertraline also was found to be superior to placebo on the Liebowitz Social Anxiety Scale (LSAS), a 24-item clinician administered measure of fear, anxiety, and avoidance of social and performance situation, and on most secondary efficacy measures, including the Duke Brief Social Phobia Scale (BSPS) total score, fear and avoidance subscales of BSPS, and fear/anxiety and avoidance subscales of LSAS. These results were similar to those seen in a flexible-dose study of 20 weeks' duration, in which a score of 1 ("very much improved") or 2 ("much improved") on the CGI Global Improvement Scale was attained by the end of the treatment period by 53 or 29% of patients receiving sertraline (50–200 mg daily; mean dosage of 147 mg daily) or placebo, respectively (intent-to-treat analysis). Sixty-five patients in this study subsequently were enrolled in a separate controlled study, including 50 patients who had responded to sertraline in the initial study and then were randomized to receive either continued treatment with sertraline or placebo in the subsequent study and 15 patients who had responded to placebo in the initial study and continued to receive placebo in the subsequent study. Based on an intent-to-treat analysis, 4% of patients who continued treatment with sertraline, 36% of patients randomized to receive placebo, and 27% of those who continued treatment with placebo relapsed (defined as an increase of 2 or more points from baseline in the CGI Severity of Illness score or discontinuance of the study drug because of lack of efficacy) at the end of the 24-week treatment period. Similar to results of pivotal, short-term clinical studies, sertraline also was shown to be substantially more effective than placebo on the CGI Severity of Illness Scale, Marks Fear Questionnaire (MFQ) Social Phobia subscale, and BSPS total score.

Subgroup analysis of short-term, controlled studies in adult outpatients with social anxiety disorder did not reveal any evidence of gender-related differences in treatment outcome. There was insufficient information to determine the effect of race or age on treatment outcome. Safety and efficacy of sertraline for the treatment of social phobia in children or adolescents have not been established to date.

■ Premature Ejaculation Like some other serotonin-reuptake inhibitors, sertraline has been used with some success in the treatment of premature ejaculation. In a placebo-controlled study, sertraline produced substantial improvements compared with placebo in time to ejaculation, number of successful attempts at intercourse, and incidence of ejaculation during foreplay, as well as overall clinical judgment of improvement. In addition, the drug was well tolerated in most patients. 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.

■ Other Uses Sertraline has been used in a limited number of patients with various types of headache with variable results; however, its use in this condition may be limited by frequent adverse effects.

Dosage and Administration

■ Administration Sertraline is administered orally. The drug usually is administered once daily in the morning or evening. The extent of GI absorption of sertraline reportedly may be increased slightly, the peak concentration increased by about 25%, and the time to peak concentration after a dose decreased from about 8 to 5.5 hours when the drug is administered with food, but such changes do not appear to be clinically important.

When sertraline hydrochloride concentrate for oral solution (Zoloft[®]) is used, doses of the drug should be measured carefully using the calibrated dropper provided by the manufacturer. The appropriate dose of the oral solution should be diluted in 120 mL of water, ginger ale, lemon/lime soda, lemonade, or orange juice before administration. The diluted solution containing sertraline hydrochloride should be mixed and administered immediately and should not be allowed to stand before administration. A slight haze may occasionally appear in the diluted oral solution, but the manufacturer states that this is normal.

■ Dosage Dosage of sertraline hydrochloride is expressed in terms of sertraline.

Patients receiving sertraline 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.)

Abrupt discontinuance of sertraline therapy should be avoided because of the potential for withdrawal reactions. (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 several weeks) and the patient monitored carefully when sertraline therapy is discontinued.

The manufacturers recommend that an interval of at least 2 weeks elapse when switching a patient from a monoamine oxidase (MAO) inhibitor to sertraline or when switching from sertraline to an MAO inhibitor. For additional information on potentially serious drug interactions that may occur between sertraline and MAO inhibitors or other serotonergic agents, see Cautions: Precautions and Contraindications and see also Drug Interactions: Serotonergic Drugs.

Clinical experience regarding the optimal timing of switching from other drugs used in the treatment of major depressive disorder, obsessive-compulsive disorder, panic disorder, posttraumatic stress disorder, premenstrual dysphoric disorder, and social anxiety disorder to sertraline therapy is limited. Therefore, the manufacturers recommend that care and prudent medical judgment be exercised when switching from other drugs to sertraline, particularly from long-acting agents (such as fluoxetine). Because some adverse reactions resembling serotonin syndrome have developed when fluoxetine therapy was discontinued abruptly and sertraline therapy was initiated immediately afterward, a washout period appears to be advisable when transferring a patient from fluoxetine to sertraline therapy. However, the appropriate duration of the washout period when switching from one selective serotonin-reuptake inhibitor to another has not been clearly established. Pending further experience in patients being transferred from therapy with another antidepressant to sertraline, it generally is recommended that the previous antidepressant be discontinued according to the recommended guidelines for the specific antidepressant prior to initiation of sertraline therapy. (See Drug Interactions: Serotonergic Drugs and see Drug Interactions: Tricyclic and Other Antidepressants.)

Major Depressive Disorder For the management of major depressive disorder in adults, the recommended initial dosage of sertraline is 50–100 mg once daily. If no clinical improvement is apparent, dosage may be increased at intervals of not less than 1 week up to a maximum of 200 mg daily. Clinical experience with the drug to date suggests that many patients will respond to 50–100 mg of the drug once daily. While a relationship between dose and antidepressant effect has not been established, efficacy of the drug was demonstrated in clinical trials employing 50–200 mg daily.

While the optimum duration of sertraline therapy has not been established, many experts state that acute depressive episodes require several months or longer of sustained antidepressant therapy. In addition, some clinicians recommend that long-term antidepressant therapy be considered in certain patients at risk for recurrence of depressive episodes (such as those with highly recurrent unipolar depression). Whether the dose of sertraline required to induce remission is identical to the dose needed to maintain and/or sustain euthymia is unknown. Systematic evaluation of sertraline has shown that its antidepressant efficacy is maintained for periods of up to 1 year in patients receiving 50–200 mg daily (mean dose of 70 mg daily). The usefulness of the drug in patients receiving prolonged therapy should be reevaluated periodically.

Obsessive-Compulsive Disorder For the management of obsessive-compulsive disorder in adults and adolescents 13–17 years of age, the recommended initial dosage of sertraline is 50 mg once daily. In children 6–12 years of age, the recommended initial dosage of sertraline is 25 mg once daily. If no clinical improvement is apparent, dosage may be increased at intervals of not less than 1 week up to a maximum of 200 mg daily. However, it should be considered that children usually have a lower body weight than adults and

particular care should be taken to avoid excessive dosage in children. While a relationship between dose and efficacy in obsessive-compulsive disorder has not been established, efficacy of the drug was demonstrated in clinical trials employing 50–200 mg daily in adults and 25–200 mg daily in children and adolescents.

While the optimum duration of sertraline therapy required to prevent recurrence of obsessive-compulsive symptoms has not been established to date, the manufacturer and many experts state that this disorder is chronic and requires several months or longer of sustained therapy. Whether the dose of sertraline required to induce remission is identical to the dose needed to maintain and/or sustain remission in patients with this disorder is unknown. Systematic evaluation of sertraline has shown that its efficacy in the management of obsessive-compulsive disorder is maintained for periods of up to 28 weeks in patients receiving 50–200 mg daily. The usefulness of the drug in patients receiving prolonged therapy should be reevaluated periodically.

Panic Disorder For the management of panic disorder in adults, the recommended initial dosage of sertraline is 25 mg once daily. After 1 week, the dosage should be increased to 50 mg once daily. If no clinical improvement is apparent, dosage may then be increased at intervals of not less than 1 week up to a maximum of 200 mg daily.

While the optimum duration of sertraline therapy required to prevent recurrence of panic disorder has not been established to date, the manufacturer and many experts state that this disorder is chronic and requires several months or longer of sustained therapy. Whether the dose of sertraline required to induce remission is identical to the dose needed to maintain and/or sustain remission in patients with this disorder is unknown. Systematic evaluation of sertraline has shown that its efficacy in the management of panic disorder is maintained for periods of up to 28 weeks in patients receiving 50–200 mg daily. The usefulness of the drug in patients receiving prolonged therapy should be reevaluated periodically.

Posttraumatic Stress Disorder For the management of posttraumatic stress disorder (PTSD) in adults, the recommended initial dosage of sertraline is 25 mg once daily. After 1 week, dosage should be increased to 50 mg once daily. If no clinical improvement is apparent, dosage may then be increased at intervals of not less than 1 week up to a maximum of 200 mg daily.

While the optimum duration of sertraline therapy required to prevent recurrence of PTSD has not been established to date, this disorder is chronic and it is reasonable to continue therapy in responding patients. Whether the dose of sertraline required to induce remission is identical to the dose needed to maintain and/or sustain remission in patients with this disorder is unknown. Systematic evaluation of sertraline has shown that its efficacy in the management of posttraumatic stress disorder is maintained for periods of up to 28 weeks in patients receiving 50–200 mg daily. The usefulness of the drug in patients receiving prolonged therapy should be reevaluated periodically.

Premenstrual Dysphoric Disorder For the treatment of premenstrual dysphoric disorder (previously late luteal-phase dysphoric disorder), the recommended initial dosage of sertraline is 50 mg daily given continuously throughout the menstrual cycle or given during the luteal-phase only (i.e., starting 2 weeks prior to the anticipated onset of menstruation and continuing through the first full day of menses). If no clinical improvement is apparent, dosage may be increased in 50-mg increments at the onset of each new menstrual cycle up to a maximum of 150 mg daily when administered continuously or 100 mg daily when administered during the luteal-phase only. If a dosage of 100 mg daily has been established with luteal phase dosing, dosages should be increased gradually over the first 3 days of each luteal phase dosing period. While a relationship between dose and effect in premenstrual dysphoric disorder (PMDD) has not been established, efficacy of the drug was demonstrated in clinical trials employing 50–150 mg daily.

The optimum duration of sertraline therapy required to treat PMDD has not been established to date. The manufacturer states that the efficacy of sertraline therapy beyond 3 menstrual cycles has not been demonstrated in controlled studies. However, because women commonly report that symptoms of PMDD worsen with age until relieved by the onset of menopause, the manufacturer recommends that long-term sertraline therapy be considered in responding women. Dosage adjustments, which may include transfers between dosing regimens (e.g., continuous versus luteal phase dosing), may be needed to maintain the patient on the lowest effective dosage, and patients should be periodically reassessed to determine the need for continued treatment.

Social Phobia For the management of social phobia in adults, the recommended initial dosage of sertraline is 25 mg once daily. After 1 week, the dosage should be increased to 50 mg once daily. If no clinical improvement is apparent, dosage may then be increased at intervals of not less than 1 week up to a maximum of 200 mg daily.

While the optimum duration of sertraline therapy required to prevent recurrence of social phobia symptoms has not been established to date, the manufacturer states that this disorder is chronic and requires several months or longer of sustained therapy. Whether the dose of sertraline required to induce remission is identical to the dose needed to maintain and/or sustain remission in patients with this disorder is unknown. Systematic evaluation of sertraline has shown that its efficacy in the management of social phobia is maintained for periods of up to 24 weeks following 20 weeks of therapy at dosages of 50–200 mg daily. Dosages should be adjusted so that the patient is maintained on the lowest effective dosage, and patients should be reassessed periodically to determine the need for continued therapy.

Premature Ejaculation For the management of premature ejaculation, sertraline has been given in a dosage of 25–50 mg daily. Alternatively, patients have taken sertraline on an “as needed” basis using doses of 25–50 mg daily.

Dosage in Geriatric Patients Major Depressive Disorder For the management of depressive symptoms associated with dementia of the Alzheimer’s type in geriatric patients, some experts recommend an initial sertraline dosage of 12.5–25 mg once daily. The dosage may then be gradually increased at intervals of 1–2 weeks up to a maximum dosage of 150–200 mg once daily.

Dosage in Renal and Hepatic Impairment The manufacturers state that, based on the pharmacokinetics of sertraline, there is no need for dosage adjustment in patients with renal impairment. Because sertraline does not appear to be removed substantially by dialysis, supplemental doses of the drug probably are unnecessary after dialysis.

Because sertraline is metabolized extensively by the liver, hepatic impairment can affect the elimination of the drug. (See Pharmacokinetics: Elimination.) Therefore, the manufacturers recommend that sertraline be administered with caution and in a reduced dosage or less frequently in patients with hepatic impairment.

Treatment of Pregnant Women during the Third Trimester Because some neonates exposed to sertraline and other SSRIs or selective serotonin- and norepinephrine-reuptake inhibitors (SNRIs) late in the third trimester of pregnancy have developed severe complications, consideration may be given to cautiously tapering sertraline therapy in the third trimester prior to delivery if the drug is administered during pregnancy. (See Pregnancy, under Cautions: Pregnancy, Fertility, and Lactation.)

Cautions

The adverse effect profile of sertraline is similar to that of other selective serotonin-reuptake inhibitors (SSRIs) (e.g., citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine). Because sertraline is a highly selective serotonin-reuptake inhibitor with little or no effect on other neurotransmitters, the incidence of some adverse effects commonly associated with tricyclic antidepressants, such as anticholinergic effects (dry mouth, constipation), adverse cardiovascular effects, drowsiness, and weight gain, is lower in patients receiving sertraline. However, certain adverse GI (e.g., nausea, diarrhea, anorexia) and nervous system (e.g., tremor, insomnia) effects appear to occur more frequently with sertraline and other SSRIs than with tricyclic antidepressants.

Overall, the adverse effect profile of sertraline in adults with depression, obsessive-compulsive disorder, or panic disorder appears to be similar. In controlled studies, the most common adverse effects occurring more frequently in adults receiving sertraline than in those receiving placebo included GI effects such as nausea, diarrhea or loose stools, dyspepsia, and dry mouth; nervous system effects such as somnolence, dizziness, insomnia, and tremor; sexual dysfunction in males (principally ejaculatory delay); and sweating. Discontinuation of sertraline therapy was required in about 15% of adults in clinical trials, principally because of adverse psychiatric (e.g., somnolence, insomnia, agitation, tremor), other nervous system (e.g., dizziness, headache), GI (e.g., nausea, diarrhea or loose stools, anorexia), or male sexual dysfunction (e.g., ejaculatory delay) effects or because of fatigue.

Nervous System Effects Headache is the most common adverse nervous system effect of sertraline, occurring in approximately 26% of patients receiving the drug in controlled clinical trials; headache occurred in 23% of those receiving placebo in these trials. Somnolence or drowsiness occurred in about 14% of patients receiving sertraline in controlled clinical trials. Headache or somnolence each required discontinuation of therapy in about 2% of patients. Fatigue has been reported in approximately 12% of patients receiving the drug in clinical trials and required discontinuation of therapy in about 1% of patients; this effect was reported in 8% of those receiving placebo in these trials.

Dizziness occurred in about 13% of patients receiving sertraline in controlled clinical trials and required discontinuation of therapy in less than 1% of patients. Insomnia occurred in about 22% of patients receiving the drug in controlled clinical trials. However, because insomnia is a symptom also associated with depression, relief of insomnia and improvement in sleep patterns may occur when clinical improvement in depression becomes apparent during antidepressant therapy. In clinical trials, about 2% of patients discontinued sertraline because of insomnia.

Tremor occurred in about 9%, nervousness in about 6%, anxiety (which occasionally may be severe [e.g., panic]) in about 4%, paresthesia in about 3%, and agitation in about 6% of patients receiving sertraline in controlled clinical trials. Tremor, agitation, and nervousness resulted in discontinuation of sertraline in about 1% of patients while anxiety resulted in discontinuation in less than 1% of patients in clinical trials. Agitation and anxiety may subside with continued therapy. Hypoesthesia, hypertonia, or malaise occurred in at least 1% of patients receiving sertraline in clinical trials. Impaired concentration, dystonia, or twitching occurred in approximately 0.1–1% of patients receiving sertraline, although these adverse effects have not been definitely attributed to the drug.

The incidence of seizures during sertraline therapy appears to be similar to or less than that observed during therapy with most other currently available antidepressants. Seizures occurred in less than 0.1% of patients receiving sertraline in clinical trials. (See Cautions: Precautions and Contraindications.)

Hypomania and mania have been reported in approximately 0.4% of patients receiving sertraline in controlled clinical trials, which is similar to the incidence reported in patients receiving active control agents (i.e., other antidepressants). In at least 2 patients, hypomanic symptoms occurred after they were receiving sertraline 200 mg daily for approximately 9 weeks. In both patients, the adverse reaction was obviated by a reduction in sertraline dosage. (See Cautions: Precautions and Contraindications.) Such reactions have occurred in patients receiving other antidepressant agents and may be caused by antidepressant-induced functional increases in catecholamine activity within the CNS, resulting in a "switch" from depressive to manic behavior. There is some evidence that patients with bipolar disorder may be more likely to experience antidepressant-induced hypomanic or manic reactions than patients without evidence of this disorder. In addition, limited evidence suggests that such reactions may occur more frequently in bipolar depressed patients receiving tricyclics and tetracyclics (e.g., maprotiline, mianserin [not commercially available in the US]) than in those receiving SSRIs (e.g., citalopram, escitalopram, fluoxetine, paroxetine, sertraline). However, further studies are needed to confirm these findings.

Asthenia has been reported in at least 1% of patients receiving sertraline; however, a causal relationship to the drug has not been established. Confusion, migraine, abnormal coordination, abnormal gait, hyperesthesia, ataxia, depersonalization, hallucinations, hyperkinesia, hypokinesia, nystagmus, vertigo, abnormal dreams, aggressive reaction, amnesia, apathy, paranoia, delusion, depression or aggravated depression, emotional lability, euphoria, abnormal thinking, or paranoid reaction have been reported in 0.1–1% of patients receiving the drug; although these adverse effects have not been definitely attributed to sertraline.

Adverse nervous system effects reported in less than 0.1% of patients receiving sertraline include dysphoria, choreoathetosis, dyskinesia, coma, dysphonia, hyporeflexia, hypoonia, prosis, somnambulism, and illusion; these effects have not been definitely attributed to the drug. Although a causal relationship has not been established, psychosis, extrapyramidal symptoms, and oculogyric crisis have been reported during postmarketing surveillance. Serotonin syndrome and neuroleptic malignant syndrome (NMS)-like reactions also have been reported in patients receiving sertraline, other SSRIs, and selective serotonin- and norepinephrine-reuptake inhibitors. (See Cautions: Precautions and Contraindications, Drug Interactions: Serotonergic Drugs, and Acute Toxicity.)

A withdrawal syndrome, which also has not been definitely attributed to the drug, has been reported in less than 0.1% of sertraline-treated patients. Fatigue, severe abdominal cramping, memory impairment, and influenza-like symptoms were reported 2 days following the abrupt discontinuance of sertraline in one patient; when sertraline was restarted, the symptoms remitted. Electric shock-like sensations occurred in another patient 1 day after the last administered dose of sertraline; these sensations became less intense and eventually disappeared 13 weeks after sertraline therapy was discontinued. (See Chronic Toxicity.) Forgetfulness, panic attacks, and unspecified pain also have been reported rarely, although a causal relationship to sertraline has not been established. Sertraline also has been reported to precipitate or exacerbate "flashbacks" in patients who previously had used lysergic acid diethylamide (LSD).

Extrapyramidal reactions, including akathisia, stuttering (which may be a speech manifestation of akathisia), bilateral jaw stiffness, and torticollis, have been reported rarely with sertraline use, and such reactions appear to be a class effect of SSRIs and dose related. Reactions occurring early during therapy with these drugs may be secondary to preexisting parkinsonian syndrome and/or concomitant therapy.

Suicidality Suicidal ideation has been reported in less than 0.1% of adults receiving sertraline. The US Food and Drug Administration (FDA) has determined that antidepressants increase the risk of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults (18–24 years of age) with major depressive disorder and other psychiatric disorders. (See Suicidality, under Cautions: Nervous System Effects, in Paroxetine 28:16.04.20.) Patients, therefore, should be appropriately monitored and closely observed for clinical worsening, suicidality, and unusual changes in behavior, particularly during initiation of sertraline therapy (i.e., the first few months) and during periods of dosage adjustments. (See Cautions: Precautions and Contraindications and Cautions: Pediatric Precautions.)

GI Effects Like other selective serotonin-reuptake inhibitors (e.g., citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine), sertraline therapy is associated with a relatively high incidence of GI disturbances, principally nausea, dry mouth, and diarrhea/loose stools. The most frequent adverse effect associated with sertraline therapy is nausea, which occurred in about 28% of patients receiving the drug in controlled clinical trials. In clinical trials, nausea required discontinuance of sertraline in about 4% of patients. In general, the incidence of nausea associated with selective serotonin-reuptake inhibitors appears to be higher when therapy is initiated with high doses but decreases as therapy with these drugs is continued. While the mechanism(s) of sertraline-induced GI effects has not been fully elucidated, they appear to arise at least in part because of increased serotonergic activity in the GI tract (which may result in stimulation of small intestine motility and inhibition of gastric and large intestine motility) and possibly because of the drug's effect on central serotonergic type-3 (5-HT₃) receptors.

Diarrhea or loose stools occurred in about 20%, dry mouth in about 15%, constipation in about 7%, dyspepsia in about 8%, or anorexia in about 6% of

patients receiving sertraline in controlled clinical trials. Other adverse GI effects associated with sertraline therapy include vomiting which occurred in about 4% and flatulence which occurred in about 3% of patients receiving the drug in controlled clinical trials. Abdominal pain was reported in approximately 2% and taste perversion in about 1% of patients receiving sertraline. In clinical trials, diarrhea or loose stools required discontinuance of sertraline in about 3% of patients and dry mouth required discontinuance of therapy in about 1% of patients.

Epidemiologic case-control and cohort design studies have suggested that selective serotonin-reuptake inhibitors may increase the risk of upper GI bleeding. Although the precise mechanism for this increased risk remains to be clearly established, serotonin release by platelets is known to play an important role in hemostasis, and selective serotonin-reuptake inhibitors decrease serotonin uptake from the blood by platelets thereby decreasing the amount of serotonin in platelets. In addition, concurrent use of aspirin or other nonsteroidal anti-inflammatory drugs was found to substantially increase the risk of GI bleeding in patients receiving selective serotonin-reuptake inhibitors in 2 of these studies. Although these studies focused on upper GI bleeding, there is some evidence suggesting that bleeding at other sites may be similarly potentiated. Further clinical studies are needed to determine the clinical importance of these findings. (See Cautions: Hematologic Effects, and see also Drug Interactions: Drugs Affecting Hemostasis.)

Although a causal relationship to sertraline has not been established, dysphagia, esophagitis, aggravation of dental caries, gastroenteritis, eructation, and increased salivation have been reported in 0.1–1% of patients receiving the drug. Aphthous stomatitis, ulcerative stomatitis, stomatitis, tongue ulceration or edema, glossitis, diverticulitis, gastritis, hemorrhagic peptic ulcer, rectal hemorrhage, colitis, proctitis, fecal incontinence, melena, or tenesmus has been reported in less than 0.1% of patients receiving sertraline; however, these adverse effects have not been definitely attributed to the drug. Pancreatitis also has been reported rarely in association with sertraline; however, a causal relationship to the drug has not been clearly established.

Although a causal relationship has not been established, nocturnal bruxism (clenching and/or grinding of the teeth during sleep) has developed within 2–4 weeks following initiation of sertraline or fluoxetine therapy in several patients. The bruxism remitted upon reduction in dosage of the serotonin-reuptake inhibitor and/or the addition of buspirone therapy.

Speech blockage also has been reported in at least one sertraline-treated patient.

Dermatologic and Sensitivity Reactions Sweating occurred in about 7% of patients receiving sertraline in controlled clinical trials.

Rash, which may be erythematous, follicular, maculopapular, or pustular, has been reported in about 3% of patients receiving sertraline in controlled clinical trials. Adverse dermatologic effects reported in 0.1–1% of patients receiving sertraline in controlled clinical trials include acne, alopecia, dry skin, urticaria, pruritus, and photosensitivity reaction (which may be severe); however, these adverse effects have not been definitely attributed to sertraline. Bullous eruption, eczema, contact dermatitis, skin discoloration, and hypertrichosis have been reported in less than 0.1% of patients receiving the drug, although a causal relationship to sertraline has not been established. Allergy, allergic reaction, and angioedema also have been reported rarely.

Other dermatologic and sensitivity events, which can be severe and potentially may be fatal, reported during the postmarketing surveillance of sertraline have included anaphylactoid reaction, angioedema, Stevens-Johnson syndrome, erythema multiforme, and vasculitis.

Metabolic Effects Thirst has been reported in 0.1–1% of patients receiving sertraline in controlled clinical trials.

Weight loss occurred in 0.1–1% of patients receiving sertraline. In controlled clinical trials, patients lost an average of about 0.45–0.9 kg while receiving sertraline. Rarely, weight loss has required discontinuance of therapy. Like fluoxetine, sertraline exhibits anorexigenic activity and can cause anorexia, which may be more pronounced in overweight patients and those with carbohydrate craving. Anorexia occurred in about 3% of patients receiving sertraline in controlled clinical trials and required discontinuance in at least 1% of patients. Increased appetite and weight gain have been reported in at least 1% of patients receiving sertraline in controlled clinical trials, although a causal relationship to the drug has not been established. (See Cautions: Pediatric Precautions.)

Sertraline use has been associated with small mean decreases (approximately 7%) in serum uric acid concentration as a result of a weak uricosuric effect; the clinical importance is not known and there have been no cases of acute renal failure associated with the drug. Small mean increases in serum total cholesterol (about 3%) and triglyceride (about 5%) concentrations also have been reported in patients receiving sertraline. Hypercholesterolemia has been reported in less than 0.1% of patients. Other adverse effects reported in less than 0.1% of patients receiving the drug include dehydration and hypoglycemia. These adverse effects have not been definitely attributed to sertraline.

Ocular and Otic Effects Abnormal vision (including blurred vision) occurred in about 4% of patients receiving sertraline in controlled clinical trials. Adverse ocular effects reported in 0.1–1% of patients receiving sertraline include abnormality of accommodation, conjunctivitis, mydriasis, and ocular pain. Although a causal relationship to sertraline has not been established, anisocoria, abnormal lacrimation, xerophthalmia, diplopia, scotoma, visual field defect, exophthalmos, hemorrhage of the anterior chamber of the eye,

Sertraline

SELECTIVE SEROTONIN-REUPTAKE INHIBITORS

glaucoma, or photophobia has been reported in less than 0.1% of patients receiving the drug. Other adverse ocular effects reported during postmarketing surveillance of sertraline have included blindness, optic neuritis, and cataract; however, a causal relationship to the drug has not been established.

Tinnitus occurred in at least 1% of patients receiving sertraline in controlled clinical trials. Earache has been reported in 0.1–1% of patients, and hyperacusis and labyrinthine disorder have been reported in less than 0.1% of patients.

■ Cardiovascular Effects Sertraline does not exhibit clinically important anticholinergic activity, and current evidence suggests that sertraline is less cardiotoxic than many antidepressant agents (e.g., tricyclic antidepressants, monoamine oxidase inhibitors). (See Cardiovascular Considerations in Uses: Major Depressive Disorder and see also Pharmacology: Cardiovascular Effects.) However, bradycardia, AV block, atrial arrhythmias, QT-interval prolongation, and ventricular tachycardia (including torsades de pointes-type arrhythmias) have been reported during postmarketing surveillance evaluations of the drug.

Hot flushes occurred in about 2% of patients receiving sertraline in controlled clinical trials. Palpitation and chest pain have been reported in at least 1% of patients receiving sertraline in controlled clinical trials. In one patient with underlying coronary artery disease, chest pain developed suddenly and was relieved with sublingual nitroglycerin but was not associated with ECG changes; the mechanism of this effect, particularly regarding any potential cardiovascular effect, is unclear and alternative mechanisms (e.g., GI) for the chest pain have been proposed.

Unlike tricyclic antidepressants, sertraline has been associated with hypotension (e.g., orthostatic) infrequently; in controlled clinical trials, postural effects (e.g., dizziness, hypotension [which can also be nonpostural]) occurred in 0.1–1% of patients receiving sertraline. Syncope also occurred in at least 0.1% of patients.

Hypertension, peripheral ischemia, and tachycardia have been reported in 0.1–1% of patients receiving the drug, although a definite causal relationship to sertraline has not been established. Precordial or substernal chest pain, aggravated hypertension, myocardial infarction, pallor, vasodilation, and cerebrovascular disorder have been reported in less than 0.1% of patients receiving sertraline; these adverse effects have not been definitely attributed to the drug.

Generalized, dependent, periorbital, or peripheral edema has been reported in at least 0.1% of patients receiving sertraline, and facial edema has been reported rarely. However, a causal relationship to the drug has not been established.

■ Musculoskeletal Effects Myalgia or back pain occurred in at least 1% of patients receiving sertraline in controlled clinical trials. Arthralgia, arthrosis, leg or other muscle cramps, or muscle weakness has been reported in 0.1–1% of patients receiving sertraline; these adverse effects have not been definitely attributed to the drug.

■ Hematologic Effects Purpura, aplastic anemia, pancytopenia, leukopenia, thrombocytopenia, and abnormal bleeding have been reported occasionally in patients receiving sertraline; however, these adverse effects have not been definitely attributed to the drug.

Altered platelet function and/or abnormal platelet-laboratory results have been reported rarely, but a causal relationship to sertraline remains to be established. In addition, in at least one patient with idiopathic thrombocytopenic purpura, sertraline therapy was associated with an increase in platelet counts. Anemia has been reported in less than 0.1% of patients receiving sertraline, although a causal relationship to the drug has not been established. Neutropenia also has been reported rarely with sertraline use and has been a reason for drug discontinuance. Agranulocytosis and septic shock developed in a geriatric woman who had been receiving sertraline for about 1 month in addition to atenolol, bendroflumethiazide, and thioridazine; the patient responded to anti-infective and granulocyte colony-stimulating factor therapy and made a full recovery within 10 days.

Bleeding complications (e.g., ecchymosis, purpura, menorrhagia, rectal bleeding) have been reported infrequently in patients receiving selective serotonin-reuptake inhibitors. Although the precise mechanism for these reactions has not been established, it has been suggested that impaired platelet aggregation and prolonged bleeding time may be due at least in part to inhibition of serotonin reuptake into platelets and/or that increased capillary fragility and vascular tone may contribute to these cases. (See Cautions: GI Effects and see also Drug Interactions: Drugs Affecting Hemostasis.)

■ Respiratory Effects Rhinitis or yawning has been reported in at least 1% of patients receiving sertraline in controlled clinical trials. Adverse respiratory effects reported in 0.1–1% of patients receiving the drug include bronchospasm, dyspnea, epistaxis, upper respiratory tract infection, sinusitis, and coughing; however, a definite causal relationship to sertraline has not been established. Adverse respiratory effects reported in less than 0.1% of patients receiving sertraline include bradypnea, hypoventilation, hyperventilation, apnea, stridor, hiccups, hemoptysis, bronchitis, laryngismus, and laryngitis. Pulmonary hypertension also has been reported during postmarketing surveillance evaluations of the drug. However, these adverse effects have not been definitely attributed to the drug.

■ Renal, Electrolyte, and Genitourinary Effects *Sexual Dysfunction* Like other selective serotonin-reuptake inhibitors, adverse effects on sexual function have been reported in both men and women receiving sertraline. Although changes in sexual desire, sexual performance, and sexual

satisfaction often occur as manifestations of a psychiatric disorder, they also may occur as the result of pharmacologic therapy. It is difficult to determine the true incidence and severity of adverse effects on sexual function during sertraline therapy, in part because patients and clinicians may be reluctant to discuss these effects. Therefore, incidence data reported in product labeling and earlier studies are most likely underestimates of the true incidence of adverse sexual effects. Recent reports indicate that up to 50% of patients receiving selective serotonin-reuptake inhibitors describe some form of sexual dysfunction during treatment and the actual incidence may be even higher.

Sexual dysfunction (principally ejaculatory delay) is the most common adverse urogenital effect of sertraline in males, occurring in about 14% of male patients receiving the drug in controlled clinical trials. In some cases, this effect has been used for therapeutic benefit in the treatment of premature ejaculation. (See Uses: Premature Ejaculation.) Impotence has occurred in at least 1% of male patients receiving sertraline in controlled trials, and priapism has been reported rarely. Female sexual dysfunction (e.g., anorgasmia) has been reported in at least 1% of female patients receiving the drug in controlled clinical trials. Decreased libido has been reported in males and females, occurring in 6% of patients in controlled clinical studies. Sexual dysfunction (principally ejaculatory delay) required discontinuance of therapy in at least 1% of patients in controlled clinical trials. Increased libido has been reported in less than 1% of patients receiving the drug.

Results of some (but not all) studies in men and women suggest that paroxetine may be associated with a higher incidence of sexual dysfunction than some other currently available selective serotonin-reuptake inhibitors, including sertraline and citalopram. Since it is difficult to know the precise risk of sexual dysfunction associated with serotonin-reuptake inhibitors, clinicians should routinely inquire about such possible adverse effects in patients receiving these drugs.

The long-term effects of selective serotonin-reuptake inhibitors on sexual function have not been fully determined to date. In a double-blind study evaluating 6 months of sertraline or citalopram therapy in depressed patients, sexual desire and overall sexual functioning (as measured on the UKU Side Effect Scale) substantially improved in women and sexual desire improved in men. In men, no change in orgasmic dysfunction, erectile dysfunction, or overall sexual functioning was reported after 6 months of therapy with sertraline or citalopram, although there was a trend toward worsening of ejaculatory dysfunction. However, in the subgroups of women and men reporting no sexual problems at baseline, approximately 12% of women reported decreased sexual desire and 14% reported orgasmic dysfunction after 6 months of citalopram therapy; the corresponding figures in the same subgroup of men were approximately 17 and 19%, respectively, and as many as 25% experienced ejaculatory dysfunction after 6 months. No substantial differences between sertraline and citalopram were reported in this study.

Management of sexual dysfunction caused by selective serotonin-reuptake inhibitor therapy includes waiting for tolerance to develop; using a lower dosage of the drug; using drug holidays; delaying administration of the drug until after coitus; or changing to another antidepressant. Although further study is needed, there is some evidence that adverse sexual effects of the selective serotonin-reuptake inhibitors may be reversed by concomitant use of certain drugs, including buspirone, 5-hydroxytryptamine-2 (5-HT₂) receptor antagonists (e.g., nefazodone), 5-HT₂ receptor inhibitors (e.g., granisetron), or α_2 -adrenergic receptor antagonists (e.g., yohimbine), selective phosphodiesterase (PDE) inhibitors (e.g., sildenafil), or dopamine receptor agonists (e.g., amantadine, dextroamphetamine, pemoline [no longer commercially available in the US], methylphenidate). In most patients, sexual dysfunction is fully reversed 1–3 days after discontinuance of the antidepressant.

Other Renal, Electrolyte, and Genitourinary Effects Although a definite causal relationship to sertraline has not been established, menstrual disorders, dysmenorrhea, intermenstrual bleeding, amenorrhea, vaginal hemorrhage, and leukorrhea have been reported in 0.1–1% of patients receiving sertraline. In addition, menorrhagia, breast enlargement, female breast pain or tenderness, acute mastitis in females, gynecomasia, and atrophic vaginitis have been reported in less than 0.1% of patients receiving sertraline; however, a causal relationship to the drug has not been clearly established.

Treatment with SSRIs, including sertraline, and selective serotonin- and norepinephrine-reuptake inhibitors (SNRIs) may result in hyponatremia. In many cases, this hyponatremia appears to be due to the syndrome of inappropriate antidiuretic hormone secretion (SIADH) and was reversible when the SSRI or SNRI was discontinued. Cases with serum sodium concentrations lower than 110 mEq/L have been reported. Hyponatremia and SIADH in patients receiving SSRIs usually develop an average of 2 weeks after initiating therapy (range: 3–120 days). Geriatric individuals and patients receiving diuretics or who are otherwise volume depleted may be at greater risk of developing hyponatremia during therapy with SSRIs or SNRIs. Discontinuance of sertraline should be considered in patients with symptomatic hyponatremia and appropriate medical intervention should be instituted. Because geriatric patients may be at increased risk for hyponatremia associated with these drugs, clinicians prescribing sertraline in such patients should be aware of the possibility that such reactions may occur. In addition, periodic monitoring of serum sodium concentrations (particularly during the first several months) in geriatric patients receiving SSRIs has been recommended by some clinicians.

A variety of urinary disorders, including urinary frequency, polyuria, urinary hesitancy and/or retention, dysuria, nocturia, and urinary incontinence, has been reported in 0.1–1% of patients receiving sertraline; however, these

effects have not been definitely attributed to the drug. In addition, cystitis, oliguria, pyelonephritis, hematuria, renal pain, strangury, and balanoposthitis have been reported in less than 0.1% of patients receiving sertraline, although a causal relationship to the drug has not been clearly established.

■ Hepatic Effects Impaired hepatic function has been reported in less than 1% of patients receiving sertraline in controlled clinical trials; in most cases, such reactions appeared to be reversible upon discontinuance of sertraline therapy. Asymptomatic elevations in serum AST (SGOT) and ALT (SGPT) concentrations have been reported in approximately 0.8% of patients receiving the drug and occasionally have been a reason for drug discontinuance. Elevations in aminotransferase concentrations usually occurred within the first 1–9 weeks of sertraline therapy and were rapidly reversible following discontinuance of the drug. In addition, in at least 2 patients, elevated liver enzymes returned to normal levels with continued therapy.

Increased serum alkaline phosphatase and bilirubin concentrations occurred rarely in patients receiving sertraline in clinical trials and required discontinuance of therapy in some cases. Other clinical features associated with adverse hepatic reactions that have been reported in at least one patient include hepatitis, hepatomegaly, jaundice, abdominal pain, vomiting, hepatic failure, and death. However, these effects have not been definitely attributed to the drug.

■ Endocrine Effects Low levels of total thyroxine developed in a depressed adolescent who had been receiving sertraline therapy; however, it appears that sertraline only displaced the bound fraction of total thyroxine but was not associated with true hypothyroidism. In a limited number of hypothyroid patients receiving thyroxine therapy, elevated serum thyrotropin and reduced serum thyroxine concentrations have been observed following the initiation of sertraline therapy. Hypothyroidism also has been reported. (See Cautions: Precautions and Contraindications.)

Hyperprolactinemia and galactorrhea also have been reported rarely; however, a causal relationship to the drug has not been established.

■ Other Adverse Effects Cold clammy skin, flushing, fever, or rigors has been reported in 0.1–1% of patients receiving the drug, although a causal relationship to sertraline has not been established. In addition, lupus-like syndrome and serum sickness have been reported during postmarketing surveillance evaluations of the drug; however, a causal relationship has not been definitively established.

■ Precautions and Contraindications Worsening of depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual 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 [SSRIs] 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 to 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. (See Suicidality under Cautions: Nervous System Effects, in Paroxetine, 28:16.04.20.)

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, sertraline dosage should be tapered as rapidly as is feasible but with recognition of the risks of abrupt discontinuance. (See Dosage and Administration: Dosage.) 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).

Potentially life-threatening serotonin syndrome or neuroleptic malignant syndrome (NMS)-like reactions have been reported with SSRIs, including sertraline, and selective serotonin- and norepinephrine-reuptake inhibitors (SNRIs) alone, but particularly with concurrent administration of other serotonergic drugs (including serotonin [5-hydroxytryptamine; 5-HT] type 1 receptor agonists ["triptans"]), drugs that impair the metabolism of serotonin (e.g., monoamine oxidase [MAO] inhibitors), or antipsychotic agents or other dopamine antagonists. 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). In its most severe form, serotonin syndrome may resemble NMS, which is characterized by hyperthermia, muscle rigidity, autonomic instability with possible rapid fluctuation in vital signs, and mental status changes. Patients receiving sertraline should be monitored for the development of serotonin syndrome or NMS-like signs and symptoms.

Concurrent or recent (i.e., within 2 weeks) therapy with MAO inhibitors used for treatment of depression is contraindicated in patients receiving sertraline and vice versa. If concurrent therapy with sertraline and a 5-HT₁ receptor agonist (triptan) is clinically warranted, the patient should be observed carefully, particularly during initiation of therapy, when dosage is increased, or when another serotonergic agent is initiated. Concomitant use of sertraline and serotonin precursors (e.g., tryptophan) is not recommended. If signs and symptoms of serotonin syndrome or NMS develop during sertraline therapy, treatment with sertraline and any concurrently administered serotonergic or antidopaminergic agents, including antipsychotic agents, should be discontinued immediately and supportive and symptomatic treatment should be initiated. (See Drug Interactions: Serotonergic Drugs.)

The dropper dispenser provided with Zoloft[®] oral solution contains natural latex proteins in the form of dry natural rubber which may cause sensitivity reactions in susceptible individuals.

Because clinical experience with sertraline in patients with certain concurrent systemic disease, including cardiovascular disease and renal impairment, is limited, caution should be exercised when sertraline is administered to patients with any systemic disease or condition that may alter metabolism of the drug or adversely affect hemodynamic function. (See Dosage and Administration: Dosage.)

Sertraline should be used with caution in patients with hepatic impairment, since prolonged elimination of the drug has been reported to occur in patients with liver cirrhosis. (See Pharmacokinetics: Elimination and see Dosage and Administration: Dosage in Renal and Hepatic Impairment.)

The manufacturers recommend that patients receiving sertraline be advised to notify their clinician if they are taking or plan to take nonprescription (over-the-counter) or prescription medications or alcohol-containing beverages or 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.

Treatment with SSRIs, including sertraline, and selective serotonin- and norepinephrine-reuptake inhibitors (SNRIs) may result in hyponatremia. In many cases, this hyponatremia appears to be due to the syndrome of inappropriate antidiuretic hormone secretion (SIADH) and was reversible when sertraline was discontinued. Cases with serum sodium concentrations lower than 110 mEq/L have been reported. Geriatric individuals and patients receiving diuretics or who are otherwise volume depleted may be at greater risk of developing hyponatremia during therapy with SSRIs or SNRIs. Signs and symptoms of hyponatremia include headache, difficulty concentrating, memory impairment, confusion, weakness, and unsteadiness, which may lead to falls; more severe and/or acute cases have been associated with hallucinations, syncope, seizures, coma, respiratory arrest, and death. Discontinuance of sertraline

should be considered in patients with symptomatic hyponatremia and appropriate medical intervention should be instituted. (See Cautions: Renal, Electrolyte, and Genitourinary Effects and see also Cautions: Geriatric Precautions.)

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.)

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.

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

Sertraline is contraindicated in patients concurrently receiving pimozide. (See Drug Interactions: Pimozide.)

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

■ Pediatric Precautions 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 sertraline in over 600 pediatric patients who received sertraline 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. 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.

■ Geriatric Precautions In clinical studies in geriatric patients, 660 patients receiving sertraline for the treatment of depression were 65 years of age or older, and 180 were 75 years of age or older. No overall differences in efficacy or adverse effects were observed for geriatric patients in these studies relative to younger patients, and other clinical experience has revealed no evidence of age-related differences in safety. In addition, no adverse effects on psychomotor performance were observed in geriatric individuals who received the drug in one controlled study. However, the possibility that older patients may exhibit increased sensitivity to the drug cannot be excluded. (See Dosage in Geriatric Patients under Dosage and Administration.)

Limited evidence suggests that geriatric patients may be more likely than younger patients to develop sertraline-induced hyponatremia and transient syndrome of inappropriate secretion of antidiuretic hormone (SIADH). Therefore, clinicians prescribing sertraline in geriatric patients should be aware of the possibility that such reactions may occur. Periodic monitoring (especially during the first several months) of serum sodium concentrations in geriatric patients receiving the drug has been recommended by some clinicians. (See Cautions: Precautions and Contraindications.)

As with other psychotropic drugs, geriatric patients receiving antidepressants appear to have an increased risk of hip fracture. Despite the fewer cardiovascular and anticholinergic effects associated with selective serotonin-reuptake inhibitors (SSRIs), these drugs did not show any advantage over tricyclic antidepressants with regard to hip fracture in a case-control study. In addition, there was little difference in the rates of falls between nursing home residents receiving SSRIs and those receiving tricyclic antidepressants in a retrospective study. Therefore, all geriatric individuals receiving either type of antidepressant should be considered to be at increased risk of falls and appropriate measures should be taken.

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.)

Plasma clearance of sertraline may be decreased in geriatric patients; plasma clearance of the less active metabolite, *N*-desmethylsertraline, also may be decreased in older males.

■ Mutagenicity and Carcinogenicity Sertraline was not mutagenic, with or without metabolic activation, in several in vitro tests including the bacterial mutation assay and the mouse lymphoma mutation assay. Sertraline also was not mutagenic in tests for cytogenetic aberrations in vivo in mouse bone marrow and in vitro in human lymphocytes.

Lifetime studies to determine the carcinogenic potential of sertraline were performed in CD-1 mice and Long-Evans rats receiving dosages up to 40 mg/kg daily. This dosage corresponded to 1 and 2 times the maximum recommended human dose on a mg/m² basis in mice and rats, respectively. There was a dose-related increase in the incidence of hepatic adenomas in male mice receiving sertraline dosages of 10–40 mg/kg (0.25–1 times the maximum recommended human dose on a mg/m² basis). No increase was seen in female mice or in rats of either gender receiving the same dosages, nor was there an increase in hepatocellular carcinomas. Hepatic adenomas have a variable rate of spontaneous occurrence in this strain of mice, and the relevance of this finding to humans is not known. There was an increase in follicular adenomas

of the thyroid, not accompanied by thyroid hyperplasia, in female rats receiving a sertraline dosage of 40 mg/kg (2 times the maximum recommended human dose on a mg/m² basis). There also was an increase in uterine adenocarcinomas in rats receiving sertraline dosages of 10–40 mg/kg (0.5–2 times the maximum recommended human dose on a mg/m² basis); however, this effect could not be directly attributed to the drug.

■ Pregnancy, Fertility, and Lactation *Pregnancy* Some neonates exposed to sertraline and other SSRIs or SNRIs late in the third trimester of pregnancy have developed complications that have sometimes been severe and required prolonged hospitalization, respiratory support, enteral nutrition, and other forms of supportive care in special-care nurseries. Such complications can arise immediately upon delivery and usually last several days or up to 2–4 weeks. Clinical findings reported to date in the neonates have included respiratory distress, cyanosis, apnea, seizures, temperature instability or fever, feeding difficulty, dehydration, excessive weight loss, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, lethargy, reduced or lack of reaction to pain stimuli, and constant crying. These clinical features appear to be consistent with either a direct toxic effect of the SSRI or SNRI or, possibly, a drug withdrawal syndrome. It should be noted that in some cases the clinical picture was consistent with serotonin syndrome (see Drug Interactions: Serotonergic Drugs). When treating a pregnant woman with sertraline during the third trimester of pregnancy, the clinician should carefully consider the potential risks and benefits of such therapy. Consideration may be given to cautiously tapering sertraline therapy in the third trimester prior to delivery if the drug is administered during pregnancy. (See Treatment of Pregnant Women during the Third Trimester under Dosage and Administration: Dosage.)

FDA states that decisions about management of depression in pregnant women are challenging and that the patient and her clinician must carefully consider and discuss the potential benefits and risks of SSRI therapy during pregnancy for the individual woman. Two recent studies provide important information on risks associated with discontinuing or continuing antidepressant therapy during pregnancy:

The first study, which was prospective, naturalistic, and longitudinal in design, evaluated the potential risk of relapsed depression in pregnant women with a history of major depressive disorder who discontinued or attempted to discontinue antidepressant (SSRIs, tricyclic antidepressants, or others) therapy during pregnancy compared with that in women who continued antidepressant therapy throughout their pregnancy; all women were euthymic while receiving antidepressant therapy at the beginning of pregnancy. In this study, women who discontinued antidepressant therapy were found to be 5 times more likely to have a relapse of depression during their pregnancy than were women who continued to receive their antidepressant while pregnant, suggesting that pregnancy does not protect against a relapse of depression.

The second study suggests that infants exposed to SSRIs in late pregnancy may have an increased risk of persistent pulmonary hypertension of the newborn (PPHN), which is associated with substantial neonatal morbidity and mortality. PPHN occurs at a rate of 1–2 neonates per 1000 live births in the general population in the US. In this retrospective case-control study of 377 women whose infants were born with PPHN and 836 women whose infants were born healthy, the risk for developing persistent pulmonary hypertension of the newborn was approximately sixfold higher for infants exposed to SSRIs after the twentieth week of gestation compared with infants who had not been exposed to SSRIs during this period. The study was too small to compare the risk of PPHN associated with individual SSRIs, and the findings have not been confirmed. Although the risk of PPHN identified in this study still is low (6–12 cases per 1000) and further study is needed, the findings add to concerns from previous reports that infants exposed to SSRIs late in pregnancy may experience adverse effects.

Most epidemiologic studies of pregnancy outcome following first-trimester exposure to SSRIs, including sertraline, conducted to date have not revealed evidence of an increased risk of major congenital malformations. In a prospective, controlled, multicenter study, maternal use of several SSRIs (sertraline, fluvoxamine, paroxetine) in a limited number of pregnant women did not appear to increase the risk of congenital malformation, miscarriage, stillbirth, or premature delivery when used during pregnancy at recommended dosages. Birth weight and gestational age in neonates exposed to the drugs were similar to those in the control group. In another small study based on medical records review, the incidence of congenital anomalies reported in infants born to women who were treated with sertraline and other SSRIs during pregnancy was comparable to that observed in the general population. However, the results of epidemiologic studies indicate that exposure to paroxetine during the first trimester of pregnancy may increase the risk for congenital malformations, particularly cardiovascular malformations. (See Cautions: Pregnancy, Fertility, and Lactation, in Paroxetine 28:16.04.20.) Additional epidemiologic studies are needed to more thoroughly evaluate the relative safety of sertraline and other SSRIs during pregnancy, including their potential teratogenic risks and possible effects on neurobehavioral development.

The manufacturers state that there are no adequate and controlled studies to date using sertraline in pregnant women, and the drug should be used during pregnancy only when the potential benefits justify the possible risks to the fetus. Women should be advised to notify their physician if they become pregnant or plan to become pregnant during therapy with the drug. FDA states that women who are pregnant or thinking about becoming pregnant should not discontinue any antidepressant, including sertraline, without first consulting

their clinician. The decision whether or not to continue antidepressant therapy should be made only after careful consideration of the potential benefits and risks of antidepressant therapy for each individual pregnant patient. If a decision is made to discontinue treatment with sertraline or other SSRIs before or during pregnancy, discontinuance of therapy should be done in consultation with the clinician in accordance with the prescribing information for the antidepressant and the patient should be closely monitored for possible relapse of depression.

Reproduction studies in rats using sertraline dosages up to 80 mg/kg daily and in rabbits using dosages up to 40 mg/kg daily have not revealed evidence of teratogenicity; these dosages correspond to approximately 4 times the maximum recommended human dosage on a mg/m² basis. No evidence of teratogenicity was observed at any dosage studied. When pregnant rats and rabbits were given sertraline during the period of organogenesis, delayed ossification was observed in fetuses at doses of 10 mg/kg (0.5 times the maximum recommended human dose on a mg/m² basis) in rats and 40 mg/kg (4 times the maximum recommended human dose on a mg/m² basis) in rabbits. When female rats received sertraline during the last third of gestation and throughout lactation, there was an increase in the number of stillborn pups and in the number of pups dying during the first 4 days after birth. The body weights of the pups also were decreased during the first 4 days after birth. These effects occurred at a dose of 20 mg/kg (approximately the same as the maximum recommended human dose on a mg/m² basis). At 10 mg/kg (0.5 times the maximum recommended human dose on a mg/m² basis), no effect on rat pup mortality was observed. The decrease in pup survival was shown to result from in utero exposure to the drug. The clinical importance of these effects is not known.

The effect of sertraline on labor and delivery is not known.

Fertility A decrease in fertility was observed in 1 of 2 reproduction studies in rats using sertraline dosages of 80 mg/kg (4 times the maximum recommended human dose on a mg/m² basis).

Lactation Sertraline and its principal metabolite, *N*-desmethylsertraline, are distributed into milk. Sertraline should be used with caution in nursing women, and women should be advised to notify their physician if they plan to breast-feed.

Drug Interactions

■ Serotonergic Drugs Use of selective serotonin-reuptake-inhibitors (SSRIs) such as sertraline concurrently or in close succession with other drugs that affect serotonergic neurotransmission may result in serotonin syndrome or neuroleptic malignant syndrome (NMS)-like reactions. 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). Although the syndrome appears to be relatively uncommon and usually mild in severity, serious and potentially life-threatening complications, including seizures, disseminated intravascular coagulation, respiratory failure, and severe hyperthermia as well as death occasionally have been reported. In its most severe form, serotonin syndrome may resemble NMS, which is characterized by hyperthermia, muscle rigidity, autonomic instability with possible rapid fluctuation in vital signs, and mental status changes. The precise mechanism of these reactions is not fully understood; however, they appear to result from excessive serotonergic activity in the CNS, probably mediated by activation of serotonin 5-HT_{1A} receptors. The possible involvement of dopamine and 5-HT₂ receptors also has been suggested, although their roles remain unclear.

Serotonin syndrome most commonly occurs when 2 or more drugs that affect serotonergic neurotransmission 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 [no longer commercially available in the US], fenfluramine [no longer commercially available in the US]), inhibit the reuptake of serotonin after release (e.g., SSRIs, selective serotonin- and norepinephrine-reuptake inhibitors [SNRIs]), tricyclic antidepressants, trazodone, dextromethorphan, meperidine, tramadol), decrease the metabolism of serotonin (e.g., MAO inhibitors), have direct serotonin postsynaptic receptor activity (e.g., buspirone), or nonspecifically induce increases in serotonergic neuronal activity (e.g., lithium salts). Selective agonists of serotonin (5-hydroxytryptamine; 5-HT) type 1 receptors ("triptans") and dihydroergotamine, agents with serotonergic activity used in the management of migraine headache, and St. John's wort (*Hypericum perforatum*) also have been implicated in serotonin syndrome.

The combination of SSRIs and MAO inhibitors may result in serotonin syndrome or NMS-like reactions. Such reactions have also been reported in patients receiving SSRIs concomitantly with tryptophan, lithium, dextromethorphan, sumatriptan, dihydroergotamine, or antipsychotics or other dopamine antagonists. In rare cases, serotonin syndrome reportedly has occurred in patients receiving 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 precipitating symptoms suggestive of serotonin syndrome or NMS-like reactions include buspirone, bromocriptine, dextropropoxyphene, linezolid, methylenedioxymethamphetamine (MDMA; "ecstasy"), selegiline (a selective MAO-B inhibitor), and sibutramine (an SNRI used for the management of obesity). 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 serotonin syndrome or NMS-like reactions in patients receiving 2 or more drugs that affect serotonergic neurotransmission, even if no such interactions with the specific drugs have been reported to date in the medical literature. Pending further accumulation of data, serotonergic drugs should be used cautiously in combination and such combinations avoided whenever clinically possible. Serotonin syndrome may be more likely to occur when initiating therapy, increasing the dosage, or following the addition of another serotonergic drug. 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 manifestations of serotonin syndrome. If signs and symptoms of serotonin syndrome or NMS develop during therapy, treatment with sertraline and any concurrently administered serotonergic or antidopaminergic agents, including antipsychotic agents, should be discontinued immediately and supportive and symptomatic treatment should be initiated.

For further information on serotonin syndrome, including manifestations and treatment, see **Drug Interactions: Serotonergic Drugs, in Fluoxetine Hydrochloride** 28:16.04.20.

Monoamine Oxidase Inhibitors Potentially serious, sometimes fatal serotonin syndrome or NMS-like reactions have been reported in patients receiving SSRIs, including sertraline, in combination with an MAO inhibitor. Severe serotonin syndrome reaction developed several hours after initiating sertraline in a woman already receiving phenelzine, lithium, thioridazine, and doxepin. Such reactions also have been reported in patients who recently have discontinued an SSRI and have been started on an MAO inhibitor.

Because of the potential risk of serotonin syndrome or NMS-like reactions, concomitant use of sertraline and MAO inhibitors is contraindicated. At least 2 weeks should elapse between discontinuance of MAO inhibitor therapy and initiation of sertraline therapy and vice versa.

Linezolid Linezolid, an anti-infective agent that is a nonselective and reversible MAO inhibitor, has been associated with drug interactions resulting in serotonin syndrome, including some associated with SSRIs, and potentially may also cause NMS-like reactions. Therefore, some manufacturers of sertraline state that linezolid should be used with caution in patients receiving sertraline. The manufacturer of linezolid states that, unless patients are carefully observed for signs and/or symptoms of serotonin syndrome, the drug should not be used in patients receiving SSRIs. Some clinicians suggest that linezolid only be used with caution and close monitoring in patients concurrently receiving SSRIs, and some suggest that SSRI therapy should be discontinued before linezolid is initiated and not reinitiated until 2 weeks after linezolid therapy is completed.

Moclobemide Moclobemide (not commercially available in the US), a selective and reversible MAO-A inhibitor, has been associated with serotonin syndrome, and such reactions have been fatal in several cases in which the drug was given in combination with the SSRI citalopram or with clomipramine. Pending further experience with such combinations, some clinicians recommend that concurrent therapy with moclobemide and SSRIs be used only with extreme caution and that SSRIs should have been discontinued for some time (depending on the elimination half-lives of the drug and its active metabolites) before initiating moclobemide therapy.

Selegiline Selegiline, a selective MAO-B inhibitor used in the management of parkinsonian syndrome, has been reported to cause serotonin syndrome when given concurrently with SSRIs (e.g., fluoxetine, paroxetine, sertraline). Although selegiline is a selective MAO-B inhibitor at therapeutic dosages, the drug appears to lose its selectivity for the MAO-B enzyme at higher dosages (e.g., those exceeding 10 mg/kg), thereby increasing the risk of serotonin syndrome in patients receiving higher dosages of the drug either alone or in combination with other serotonergic agents. The manufacturer of selegiline recommends avoiding concurrent selegiline and SSRI therapy. In addition, the manufacturer of selegiline recommends that at least 2 weeks elapse between discontinuance of selegiline and initiation of SSRI therapy.

Isoniazid Isoniazid, an antituberculosis agent, appears to have some MAO-inhibiting activity. In addition, iproniazid (not commercially available in the US), another antituberculosis agent structurally related to isoniazid that also possesses MAO-inhibiting activity, reportedly has resulted in serotonin syndrome in at least 2 patients when given in combination with meperidine. Pending further experience, clinicians should be aware of the potential for serotonin syndrome when isoniazid is given in combination with SSRI therapy (such as sertraline) or other serotonergic agents.

Tryptophan and Other Serotonin Precursors Because of the potential risk of serotonin syndrome or NMS-like reactions, concurrent use of tryptophan or other serotonin precursors should be avoided in patients receiving sertraline.

5-HT₁ Receptor Agonists ("Triptans") Weakness, hyperreflexia, and incoordination have been reported rarely during postmarketing surveillance

in patients receiving sumatriptan concomitantly with an SSRI (e.g., citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline); these reactions resembled serotonin syndrome. Oral or subcutaneous sumatriptan and SSRIs were used concomitantly in some clinical studies without unusual adverse effects. However, an increase in the frequency of migraine attacks and a decrease in the effectiveness of sumatriptan in relieving migraine headache have been reported in a patient receiving subcutaneous injections of sumatriptan intermittently while undergoing fluoxetine therapy.

Clinicians prescribing 5-HT₁ receptor agonists, SSRIs, and SNRIs should consider that 5-HT₁ receptor agonists often are used intermittently and that either the 5-HT₁ receptor agonist, SSRI, or SNRI may be prescribed by a different clinician. Clinicians also should weigh the potential risk of serotonin syndrome or NMS-like reactions with the expected benefit of using a 5-HT₁ receptor agonist concurrently with SSRI or SNRI therapy. If concomitant treatment with sumatriptan or another 5-HT₁ receptor agonist and sertraline is clinically warranted, the patient should be observed carefully, particularly during treatment initiation, dosage increases, and following the addition of other serotonergic agents. Patients receiving concomitant 5-HT₁ receptor agonist and SSRI or SNRI therapy should be informed of the possibility of serotonin syndrome or NMS-like reactions and advised to immediately seek medical attention if they experience signs or symptoms of these syndromes.

Sibutramine Because of the possibility of developing potentially serious, sometimes fatal serotonin syndrome or NMS-like reactions, sibutramine should be used with caution in patients receiving sertraline.

Other Selective Serotonin-reuptake Inhibitors and Selective Serotonin- and Norepinephrine-reuptake Inhibitors Concomitant administration of sertraline with other SSRIs or SNRIs potentially may result in serotonin syndrome or NMS-like reactions and is therefore not recommended. (See Dosage and Administration: Dosage.)

Antipsychotic Agents and Other Dopamine Antagonists Concomitant use of antipsychotic agents and other dopamine antagonists with sertraline rarely may result in potentially serious, sometimes fatal serotonin syndrome or NMS-like reactions. If signs and symptoms of serotonin syndrome or NMS occur, treatment with sertraline and any concurrently administered antidopaminergic or serotonergic agents should be immediately discontinued and supportive and symptomatic treatment initiated. (See Drug Interactions: Clozapine and see also Drug Interactions: Pimozide.)

Tramadol and Other Serotonergic Drugs Because of the potential risk of serotonin syndrome or NMS-like reactions, caution is advised whenever SSRIs, including sertraline, and SNRIs are concurrently administered with other drugs that may affect serotonergic neurotransmitter systems, including tramadol and St. John's wort (*Hypericum perforatum*).

Drugs Undergoing Hepatic Metabolism or Affecting Hepatic Microsomal Enzymes Animal studies have demonstrated that sertraline induces hepatic microsomal enzymes. In humans, microsomal enzyme induction by sertraline was minimal as determined by a small (5%) but statistically significant decrease in antipyrine half-life following sertraline administration (200 mg daily) for 21 days. The manufacturers state that this small change in antipyrine half-life reflects a clinically unimportant change in hepatic metabolism. Nonetheless, caution should be exercised when sertraline is given to patients receiving drugs that are hepatically metabolized and that have a low therapeutic ratio, such as warfarin. (See Drug Interactions: Protein-bound Drugs and see also Anticoagulants under Drug Interactions: Drugs Affecting Hemostasis.)

Drugs Metabolized by Cytochrome P-450 (CYP) 2D6 Sertraline, like many other antidepressants (e.g., other SSRIs, many tricyclic antidepressants) is metabolized by the drug-metabolizing cytochrome P-450 (CYP) 2D6 isoenzyme (debrisoquine hydroxylase). In addition, like many other drugs metabolized by CYP2D6, sertraline inhibits the activity of CYP2D6 and potentially may increase plasma concentrations of concomitantly administered drugs that also are metabolized by this isoenzyme. Although similar interactions are possible with other SSRIs, there is considerable variability among the drugs in the extent to which they inhibit CYP2D6. At lower doses, sertraline has demonstrated a less prominent inhibitory effect on CYP2D6 than some other SSRIs. Nevertheless, even sertraline has the potential for clinically important CYP2D6 inhibition.

Concomitant use of sertraline with other drugs metabolized by CYP2D6 has not been systematically studied. The extent to which this potential interaction may become clinically important depends on the extent of inhibition of CYP2D6 by the antidepressant and the therapeutic index of the concomitantly administered drug. The drugs for which this potential interaction is of greatest concern are those that are metabolized principally by CYP2D6 and have a narrow therapeutic index, such as tricyclic antidepressants, class IC antiarrhythmics (e.g., propafenone, flecainide, encainide), and some phenothiazines (e.g., thioridazine).

Caution should be used whenever concurrent therapy with sertraline and other drugs metabolized by CYP2D6 is considered. Because concomitant use of sertraline and thioridazine may result in increased plasma concentrations of the phenothiazine and increase the risk of serious, potentially fatal, adverse cardiac effects (e.g., cardiac arrhythmias), the manufacturer of thioridazine states that the drug should not be used concomitantly with any drug that inhibits the CYP2D6 isozyme. The manufacturers of sertraline state that concurrent use of a drug metabolized by CYP2D6 may necessitate the administration of dos-

ages of the other drug that are lower than those usually prescribed. Furthermore, whenever sertraline therapy is discontinued (and plasma concentrations of sertraline are decreased) during concurrent therapy with another drug metabolized by CYP2D6, an increased dosage of the concurrently administered drug may be necessary.

Drugs Metabolized by Cytochrome P-450 (CYP) 3A4 Although sertraline can inhibit the cytochrome P-450 (CYP) 3A4 isoenzyme, results of *in vitro* and *in vivo* studies indicate that the drug is a much less potent inhibitor of this enzyme than many other drugs. In an *in vivo* drug interaction study, concomitant use of sertraline and the CYP3A4 substrate, carbamazepine, under steady-state conditions had no effect on plasma concentrations of carbamazepine. The manufacturers of sertraline state that these data suggest that the extent of sertraline's inhibition of CYP3A4 activity is unlikely to be of clinical importance. However, a marked increase in plasma concentrations (ranging from 80–250%) and bone marrow suppression developed within 1–2 months of initiating sertraline in a patient previously stabilized on carbamazepine and flecainide therapy. Although the precise mechanism for this possible interaction and the role of the cytochrome P-450 enzyme system are unclear, some clinicians recommend that carbamazepine concentrations be monitored during concomitant sertraline therapy.

Results of an *in vivo* drug interaction study with cisapride indicate that concomitant use of sertraline (200 mg daily) induces the metabolism of cisapride; peak plasma concentrations and area under the plasma concentration-time curve (AUC) of cisapride were decreased by about 35% in the study. However, the manufacturers of sertraline state that the extent of sertraline's inhibition of CYP3A4 activity is unlikely to be of clinical importance.

Results of another drug interaction study in which sertraline was used concomitantly with terfenadine (no longer commercially available in the US), a drug metabolized principally by the cytochrome P-450 microsomal enzyme system (mainly by the CYP3A4 isoenzyme), indicate that concurrent use of sertraline did not increase plasma concentrations of terfenadine and, therefore, the manufacturers state that these data suggest that the extent of sertraline's inhibition of CYP3A4 activity is unlikely to be of clinical importance. However, the manufacturer of astemizole (no longer commercially available in the US) and some clinicians state that until the clinical importance of these findings is established, concomitant use of sertraline with astemizole or terfenadine is not recommended since substantially increased plasma concentrations of unchanged astemizole or terfenadine could occur resulting in an increased risk of serious adverse cardiac effects.

Tricyclic and Other Antidepressants The extent to which SSRI interactions with tricyclic antidepressants may pose clinical problems depends on the degree of inhibition and the pharmacokinetics of the serotonin-reuptake inhibitor involved. In healthy individuals, sertraline has been shown to substantially reduce the clearance of two tricyclic antidepressants, desipramine and imipramine. This interaction appears to result from sertraline-induced inhibition of CYP2D6. Thus, the manufacturers and some clinicians recommend that caution be exercised during concurrent use of tricyclics with sertraline since sertraline may inhibit the metabolism of the tricyclic antidepressant. In addition, plasma tricyclic concentrations may need to be monitored and the dosage of the tricyclic reduced during concomitant administration. (See Dosage and Administration: Dosage and see also Drugs Metabolized by Cytochrome P-450 [CYP] 2D6 under Drug Interactions: Drugs Undergoing Hepatic Metabolism or Affecting Hepatic Microsomal Enzymes.)

Clinical experience regarding the optimal timing of switching from other antidepressants to sertraline therapy is limited. Therefore, the manufacturers recommend that care and prudent medical judgment be exercised when switching from other antidepressants to sertraline, particularly from long-acting agents (e.g., fluoxetine). Pending further experience in patients being transferred from therapy with another antidepressant to sertraline and as the clinical situation permits, it generally is recommended that the previous antidepressant be discontinued according to the recommended guidelines for the specific antidepressant prior to initiation of sertraline therapy. (See Drug Interactions: Serotonergic Drugs.)

Protein-bound Drugs Because sertraline is highly protein bound, the drug theoretically could be displaced from binding sites by, or it could displace from binding sites, other protein-bound drugs such as oral anticoagulants or digitoxin. *In vitro* studies to date have shown that sertraline has no effect on the protein binding of 2 other highly protein-bound drugs, propranolol or warfarin; these findings also have been confirmed in clinical studies. However, pending further accumulation of data, patients receiving sertraline concomitantly with any highly protein-bound drug should be observed for potential adverse effects associated with combined therapy. (See Anticoagulants under Drug Interactions: Drugs Affecting Hemostasis.)

Drugs Affecting Hemostasis **Anticoagulants** In a study comparing prothrombin time AUC (0–120 hour) following a dose of warfarin (0.75 mg/kg) or placebo prior to and after 21 days of either sertraline (50–200 mg daily) or placebo, prothrombin time increased by an average of 8% compared with baseline in the sertraline group and decreased by an average of 1% in those receiving placebo. In addition, the normalization of prothrombin time was slightly delayed in those receiving sertraline when compared with those receiving placebo. Because the clinical importance of these findings is not known, prothrombin time should be monitored carefully whenever sertraline therapy is initiated or discontinued in patients receiving anticoagulants. (See Drug Interactions: Protein-bound Drugs.)

Other Drugs That Interfere with Hemostasis Epidemiologic case-control and cohort design studies that have demonstrated an association between selective serotonin-reuptake inhibitor therapy and an increased risk of upper GI bleeding also have shown that concurrent use of aspirin or other nonsteroidal anti-inflammatory agents substantially increases the risk of GI bleeding. Although these studies focused on upper-GI bleeding, there is some evidence suggesting that bleeding at other sites may be similarly potentiated. The precise mechanism for this increased risk remains to be clearly established; however, serotonin release by platelets is known to play an important role in hemostasis, and selective serotonin-reuptake inhibitors decrease serotonin uptake from the blood by platelets, thereby decreasing the amount of serotonin in platelets. Patients receiving sertraline should be cautioned about the concomitant use of drugs that interfere with hemostasis, including aspirin and other nonsteroidal anti-inflammatory agents.

Alcohol Sertraline administration did not potentiate the cognitive and psychomotor effects induced by alcohol in healthy individuals. In addition, no apparent additive CNS depressant effects were observed in geriatric patients receiving sertraline together with moderate amounts of alcohol. Nonetheless, the manufacturers state that concurrent use of sertraline and alcohol is not recommended.

Electroconvulsive Therapy The effects of sertraline in conjunction with electroconvulsive therapy (ECT) have not been evaluated to date in clinical studies.

Cimetidine In a study evaluating the effect of the addition of a single dose of sertraline (100 mg) on the second of 8 days of cimetidine administration (800 mg daily), the mean AUC, peak concentration, and elimination half-life of sertraline increased substantially (by 50, 24, and 26%, respectively) compared with the placebo group. The clinical importance of these changes is unknown.

Benzodiazepines In a study comparing the disposition of diazepam administered IV before and after 21 days of sertraline therapy (dosage titrated from 50–200 mg daily) or placebo, there was a 32% decrease in diazepam clearance in the sertraline recipients and a 19% decrease in those receiving placebo when compared with baseline. There was a 23% increase in the time to maximal plasma concentration for desmethyldiazepam in the sertraline group compared with a 20% decrease in the placebo group. The clinical importance of these findings is unknown; however, they suggest that sertraline and *N*-desmethylsertraline are not likely to substantially inhibit the CYP2C19 and CYP3A4 hepatic isoenzymes involved in the metabolism of diazepam.

Clozapine Concomitant use of SSRIs such as sertraline in patients receiving clozapine can increase plasma concentrations of the antipsychotic agent. In a study in schizophrenic patients receiving clozapine under steady-state conditions, initiation of paroxetine therapy resulted in only minor changes in plasma concentrations of clozapine and its metabolites; however, initiation of fluvoxamine therapy resulted in increases that were threefold compared with baseline. In other published reports, concomitant use of clozapine and SSRIs (fluvoxamine, paroxetine, sertraline) resulted in modest increases (less than twofold) in clozapine and metabolite concentrations. The manufacturer of clozapine states that caution should be exercised and patients closely monitored if clozapine is used in patients receiving SSRIs, and a reduction in clozapine dosage should be considered. (See Antipsychotic Agents and Other Dopamine Antagonists under Drug Interactions: Serotonergic Drugs.)

Lithium In a placebo-controlled trial, the administration of 2 doses of sertraline did not substantially alter steady-state plasma lithium concentrations or the renal clearance of lithium. Pending further accumulation of data, however, the manufacturers recommend that plasma lithium concentrations be monitored following initiation of sertraline in patients receiving lithium and that lithium dosage be adjusted accordingly. In addition, because of the potential risk of serotonin syndrome or NMS-like reactions, caution is advised during concurrent sertraline and lithium use. (See Drug Interactions: Serotonergic Drugs.)

Hypoglycemic Drugs In a placebo-controlled study in healthy male volunteers, sertraline administration for 22 days (including 200 mg daily for the final 13 days) caused a small but statistically significant decrease (16%) in the clearance of a 1-g IV dose of tolbutamide compared with baseline values and an increase in the terminal elimination half-life (from 6.9 to 8.6 hours). The decrease in clearance was not accompanied by any substantial changes in the plasma protein binding or the apparent volume of distribution of tolbutamide, which suggests that the change in tolbutamide clearance may be caused by a slight inhibition of the cytochrome P-450 isoenzyme CYP2C9/10 when sertraline is given in the maximum recommended dosage. The clinical importance of these findings remains to be determined.

Digoxin In a placebo-controlled trial in healthy volunteers, sertraline administration for 17 days (including 200 mg daily for the final 10 days) did not alter serum digoxin concentrations or renal clearance of digoxin. The results of this study suggest that dosage adjustment of digoxin may not be necessary in patients receiving concomitant sertraline.

Atenolol In a double-blind, placebo-controlled, randomized, crossover study, a single, 100-mg dose of sertraline had no effect on the β -adrenergic blocking activity of atenolol when administered to a limited number of healthy males.

■ Amiodarone A decrease in the plasma concentrations of amiodarone and its active metabolite, desmethylamiodarone, to 82 and 85% of the baseline values, respectively, occurred in one patient following the discontinuance of sertraline and carbamazepine therapy, suggesting that sertraline may have been inhibiting the metabolism of amiodarone by CYP3A4.

■ Phenytoin In a randomized, double-blind, placebo-controlled trial, chronic administration of high dosages of sertraline (200 mg daily) did not substantially affect the pharmacokinetics or pharmacodynamics of phenytoin when the 2 drugs were given concurrently in healthy volunteers. However, substantial reductions in plasma sertraline concentrations have been observed in sertraline-treated patients concurrently receiving phenytoin; it was suggested that induction of the cytochrome P-450 isoenzymes may be responsible. In addition, concurrent administration of sertraline and phenytoin reportedly resulted in elevated phenytoin concentrations in 2 geriatric patients. Pending further accumulation of data, the manufacturers and some clinicians recommend that plasma-phenytoin concentrations be monitored following initiation of sertraline therapy and that phenytoin dosage should be adjusted as necessary, particularly in patients with multiple underlying medical conditions and/or those receiving multiple concomitant drugs.

■ Pimozide Concomitant use of sertraline and pimozide has resulted in substantial increases in peak plasma concentrations and area under the plasma concentration-time curve (AUC) of pimozide. In one controlled study, administration of a single 2-mg dose of pimozide in individuals receiving sertraline 200 mg daily resulted in a mean increase in pimozide AUC and peak plasma concentrations of about 40%, but was not associated with changes in ECG parameters. The effects on QT interval and pharmacokinetic parameters of pimozide administered in higher doses (i.e., doses exceeding 2 mg) in combination with sertraline are as yet unknown. Concomitant use of sertraline and pimozide is contraindicated because of the low therapeutic index of pimozide and because the reported interaction between the 2 drugs occurred at a low dose of pimozide. The mechanism of this interaction is as yet unknown. (See Antipsychotic Agents and Other Dopamine Antagonists under Drug Interactions: Serotonergic Drugs.)

■ Valproic Acid The effect of sertraline on plasma valproic acid concentrations remains to be evaluated in clinical studies. In the absence of such data, the manufacturers recommend monitoring plasma valproic acid concentrations following initiation of sertraline therapy and adjusting the dosage of valproic acid as necessary.

Acute Toxicity

■ Pathogenesis The acute lethal dose of sertraline in humans is not known. One patient who ingested 13.5 g of sertraline alone subsequently recovered. However, death occurred in another patient who ingested 2.5 g of the drug alone.

In general, overdosage of sertraline may be expected to produce effects that are extensions of the drug's pharmacologic and adverse effects. The most common signs and symptoms associated with nonfatal sertraline overdosage include somnolence, nausea, vomiting, tachycardia, dizziness, agitation, and tremor. Other adverse events observed in patients who received overdosages of sertraline (alone or in combination with other drugs) include bradycardia, bundle branch block, coma, seizures, delirium, hallucinations, hypertension, hypotension, manic reaction, pancreatitis, QT-interval prolongation, serotonin syndrome, stupor, and syncope. Prolonged tachycardia, hypertension, hallucinations, hyperthermia, tremors of the extremities, and skin flushing have occurred in a child after accidental sertraline ingestion; the reaction resembled serotonin syndrome. Flushing, anger, emotional lability, and distractibility developed 1 hour after an adult female ingested 2 g of sertraline; recovery was uneventful apart from watery bowel movements.

■ Treatment Because fatalities and severe toxicity have been reported when sertraline was ingested alone or in combination with other drugs and/or alcohol, the manufacturers and some clinicians recommend that any overdosage involving sertraline be managed aggressively. Clinicians also should consider the possibility of serotonin syndrome or NMS-like reactions in patients presenting with similar clinical features and a recent history of sertraline and/or ingestion of other serotonergic agents and/or antipsychotic agents or other dopamine antagonists. (See Cautions: Precautions and Contraindications and see also Drug Interactions: Serotonergic Drugs.)

Management of sertraline overdosage generally involves symptomatic and supportive care. A patent airway should be established and maintained, and adequate oxygenation and ventilation should be ensured. ECG and vital sign monitoring is recommended following acute overdosage with the drug, although the value of ECG monitoring in predicting the severity of sertraline-induced cardiotoxicity is not known. (See Acute Toxicity: Manifestations, in the Tricyclic Antidepressants General Statement 28:16.04.28.) There is no specific antidote for sertraline intoxication. Because suicidal ingestion often involves more than one drug, clinicians treating sertraline overdosage should be alert to possible manifestations caused by drugs other than sertraline.

If the patient is comatose, having seizures, or lacks the gag reflex, gastric lavage may be performed if an endotracheal tube with cuff inflated is in place to prevent aspiration of gastric contents. Since administration of activated charcoal (which may be used in conjunction with sorbitol) may be as effective as or more effective than induction of emesis or gastric lavage, its use has been recommended either in the initial management of sertraline overdosage or fol-

lowing induction of emesis or gastric lavage in patients who have ingested a potentially toxic quantity of the drug.

Limited data indicate that sertraline is not appreciably removed by hemodialysis. Because of the large volume of distribution of sertraline and its principal metabolite, peritoneal dialysis, forced diuresis, hemoperfusion, and/or exchange transfusion also are likely to be ineffective in removing substantial amounts of sertraline and *N*-desmethylsertraline from the body.

Clinicians should consult a poison control center for additional information on the management of sertraline overdosage.

Chronic Toxicity

Sertraline has not been studied systematically in animals or humans to determine whether therapy with the drug is associated with abuse, tolerance, or physical dependence.

The premarketing clinical experience with sertraline did not reveal any tendency for a withdrawal syndrome or any drug-seeking behavior. However, fatigue, severe abdominal cramping, memory impairment, and influenza-like symptoms were reported 2 days following abrupt discontinuance of sertraline in one patient; when sertraline was restarted, the symptoms remitted. Electric shock-like sensations occurred in another patient 1 day after the last administered dose of sertraline; these sensations became less intense and eventually disappeared 13 weeks after sertraline therapy was discontinued. When evaluating these cases and those reported with other serotonin-reuptake inhibitors, it appears that a withdrawal syndrome may occur within several days following abrupt discontinuance of these drugs. The most commonly observed symptoms are those that resemble influenza, such as fatigue, stomach complaints (e.g., nausea), dizziness or lightheadedness, tremor, anxiety, chills, sweating, and incoordination. Other reported symptoms include memory impairment, insomnia, paresthesia, shock-like sensations, headache, palpitations, agitation, or aggression. Such reactions appear to be self-limiting and improve over 1 to several weeks. Pending further experience, sertraline therapy should be discontinued gradually to prevent the possible development of withdrawal reactions.

As with other CNS-active drugs, clinicians should carefully evaluate patients for a history of substance abuse prior to initiating sertraline therapy. If sertraline therapy is initiated in patients with a history of substance abuse, such patients should be monitored closely for signs of misuse or abuse of the drug (e.g., development of tolerance, use of increasing doses, drug-seeking behavior).

The potential for misuse of sertraline in patients with concurrent eating disorders and/or those who may seek the drug for its appetite-suppressant effects also may be considered.

Pharmacology

The pharmacology of sertraline is complex and in many ways resembles that of other antidepressant agents, particularly those agents (e.g., fluoxetine, fluvoxamine, paroxetine, clomipramine, trazodone) that predominantly potentiate the pharmacologic effects of serotonin (5-HT). Like other selective serotonin-reuptake inhibitors (SSRIs), sertraline is a potent and highly selective reuptake inhibitor of serotonin and has little or no effect on other neurotransmitters.

■ Nervous System Effects The precise mechanism of antidepressant action of sertraline is unclear, but the drug has been shown to selectively inhibit the reuptake of serotonin at the presynaptic neuronal membrane. Sertraline-induced inhibition of serotonin reuptake causes increased synaptic concentrations of serotonin in the CNS, resulting in numerous functional changes associated with enhanced serotonergic neurotransmission. Like other SSRIs (e.g., fluoxetine, fluvoxamine, paroxetine), sertraline appears to have only very weak effects on the reuptake of norepinephrine or dopamine and does not exhibit clinically important anticholinergic, antihistaminic, or adrenergic (α_1 , α_2 , β) blocking activity at usual therapeutic dosages.

Although the mechanism of antidepressant action of antidepressant agents may involve inhibition of the reuptake of various neurotransmitters (i.e., serotonin, norepinephrine) at the presynaptic neuronal membrane, 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 mainly 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 are commonly referred to as "down regulation." In animal studies, long-term administration of sertraline has been shown to downregulate noradrenergic receptors in the CNS as has been observed with many other clinically effective antidepressants. In addition, some antidepressants (e.g., amitriptyline) reportedly decrease the number of serotonergic (5-HT) binding sites following chronic administration. Although changes in the density of type 2 serotonergic (5-HT₂) binding sites were not observed during chronic administration of sertraline in animals in one study, the drug caused desensitization of the 5-HT₂ receptor transmembrane signaling system; the clinical importance of these findings requires further study.

The precise mechanism of action that is responsible for the efficacy of sertraline in the treatment of obsessive-compulsive disorder is unclear. However, because of the potency of clomipramine and other selective serotonin-reuptake inhibitors (e.g., fluoxetine, fluvoxamine, paroxetine) in inhibiting se-

rotonin reuptake and their 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 sertraline and these other agents are effective because they correct this imbalance. Although the available evidence supports the serotonergic hypothesis of obsessive-compulsive disorder, additional studies are necessary to confirm this hypothesis.

Serotonergic mechanisms also appear to be involved at least in part in a number of other pharmacologic effects associated with selective serotonin-reuptake inhibitors, including sertraline, such as decreased food intake and altered food selection as well as decreased alcohol intake.

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

Data from *in vitro* studies suggest that sertraline is more potent than fluvoxamine, fluoxetine, or clomipramine as a serotonin-reuptake inhibitor. Like some other serotonin-reuptake inhibitors, sertraline undergoes metabolism via *N*-demethylation to form *N*-desmethylsertraline, the principal metabolite. Data from *in vivo* and *in vitro* studies have shown that *N*-desmethylsertraline is approximately 5–10 times less potent as an inhibitor of serotonin reuptake than sertraline; however, the metabolite retains selectivity for serotonin reuptake compared with either norepinephrine or dopamine reuptake.

At therapeutic dosages (50–200 mg daily) in healthy individuals, sertraline has been shown to inhibit the reuptake of serotonin into platelets in a dose-dependent manner. Like other serotonin-reuptake inhibitors, sertraline inhibits the spontaneous firing of serotonergic neurons in the dorsal raphe nucleus. *In vitro* data have demonstrated that sertraline has substantial affinity for serotonergic (5-HT_{1A}, 5-HT_{1B}, 5-HT₂) receptors.

Effects on Other Neurotransmitters Like other serotonin-reuptake inhibitors, sertraline has been shown to have little or no activity in inhibiting the reuptake of norepinephrine. In addition, the drug has demonstrated a substantially higher selectivity ratio of serotonin-to-norepinephrine reuptake inhibiting activity than fluoxetine or tricyclic antidepressant agents, including clomipramine.

Although sertraline has only weak activity in inhibiting the reuptake of dopamine, the relative selectivity of sertraline for inhibiting serotonin reuptake relative to dopamine reuptake appears to be somewhat less than that of fluoxetine, fluvoxamine, zimelidine, or clomipramine. In addition, sertraline does not inhibit monoamine oxidase.

Unlike tricyclic and some other antidepressants, sertraline does not exhibit clinically important anticholinergic, α - or β -adrenergic blocking, or antihistaminic activity at usual therapeutic dosages. As a result, the incidence of adverse effects commonly associated with blockade of muscarinic cholinergic receptors (e.g., dry mouth, blurred vision, urinary retention, constipation, confusion), α -adrenergic receptors (e.g., orthostatic hypotension), and histamine H₁- and H₂-receptors (e.g., sedation) is lower in sertraline-treated patients. *In vitro* studies have demonstrated that sertraline does not possess clinically important affinity for α_1 - or α_2 -adrenergic, β -adrenergic, histaminergic, muscarinic, GABA, benzodiazepine, or dopamine receptors.

Effects on Sleep Like tricyclic and most other antidepressants, sertraline suppresses rapid eye movement (REM) sleep. Although not clearly established, there is some evidence that the REM-suppressing effects of antidepressant agents may contribute to the antidepressant activity of these drugs. In animal studies, sertraline suppressed REM sleep; the drug appears to reduce the amount of REM sleep by decreasing the number as well as the duration of REM episodes. Although the precise mechanism has not been fully elucidated, results of animal studies indicate that sertraline's effects on REM sleep are serotonergically mediated.

Effects on EEG Limited data currently are available regarding the effects of sertraline on the EEG. EEG changes in healthy individuals receiving single, 100-mg doses of sertraline resembled the EEG profiles of patients receiving desipramine-type antidepressants (increased alpha and decreased but accelerated delta activity) and suggest improved vigilance and psychometric performance. In individuals receiving higher single doses (200 and 400 mg) of the drug, sertraline produced EEG changes similar to imipramine-type antidepressants (reduced alpha and low beta activity and increased theta and fast beta activity), which reflect vigilance changes of the dissociative type and therefore possible sedative activity.

Effects on Psychomotor Function Sertraline does not appear to cause clinically important sedation and does not interfere with psychomotor performance. The drug did not appear to have any adverse effects on psychomotor performance when given to healthy women in single doses up to 100 mg. In healthy individuals over 50 years of age, single, 100-mg doses of sertraline increased the critical flicker fusion frequency slightly and the subjective perception of sedation; however, the drug had no depressant effect on objective tests of psychomotor performance. In addition, no adverse effects on psychomotor performance were observed in geriatric individuals who received the drug in a controlled study.

Cardiovascular Effects Sertraline appears to have little effect on the ECG. Data from controlled studies indicate sertraline does not produce clinically

important changes in heart rate, cardiac conduction, or other ECG parameters in depressed patients.

Effects on Appetite and Body Weight Like some other serotonergic agents (e.g., fenfluramine [no longer commercially available in the US], fluoxetine, zimelidine), sertraline possesses anorexigenic activity. Limited data from animal studies suggest that fenfluramine has been the most effective inhibitor of food intake followed by fluoxetine and then sertraline. Although the precise mechanism has not been clearly established, results from animal studies indicate that sertraline's appetite-inhibiting action may result at least in part from serotonin-reuptake blockade and the resultant increase in serotonin availability at the neuronal synapse. Because sertraline's anorexigenic activity was not antagonized by prior administration of serotonergic antagonists, other mechanisms also may be involved but require further study. Following administration of single doses of sertraline in meal-fed animals, food intake was reduced in a dose-dependent manner. At a dose of 3 mg/kg, the reduction in food intake was substantially reduced and higher doses of 10 or 30 mg/kg reduced food intake by 45 or 74%, respectively.

Sertraline therapy has resulted in dose-dependent decreases in body weight in animals receiving the drug for 3 days; the weight loss was not accompanied by any overt signs of behavioral abnormality. Sertraline therapy also has resulted in decreases in body weight in individuals receiving the drug. However, weight loss is usually minimal and averaged about 0.45–0.9 kg in individuals treated with the drug in controlled clinical trials. (See Cautions: Metabolic Effects and see also Cautions: Pediatric Precautions.) Rarely, weight loss has required discontinuance of therapy.

Effects on Alcohol Intake Like some other serotonergic agents, sertraline produces a substantial decrease in voluntary alcohol intake. In animals, because serotonin appears to be involved in the regulation of alcohol intake, it has been suggested that selective serotonin-reuptake inhibitors may attenuate alcohol consumption via enhanced serotonergic neurotransmission. (See Cautions.)

Neuroendocrine Effects Limited data currently are available regarding the effects of sertraline on the endocrine system. In one animal study, sertraline did not demonstrate substantial neuroendocrine effects at a dose that substantially reduced gross activity.

Although a causal relationship has not been established, hypothyroidism, decreased serum thyroxine concentrations, and/or increased serum thyrotropin (thyroid-stimulating hormone, TSH) concentrations have been reported in a limited number of sertraline patients, some of whom were receiving thyroxine concurrently. (See Cautions: Other Adverse Effects and also see Precautions and Contraindications.)

Other Effects Sertraline appears to have a weak uricosuric effect; mean decreases in serum uric acid of approximately 7% have been reported in patients receiving the drug. The clinical importance of these findings is unknown, and there have been no reports of acute renal failure associated with the drug. (See Cautions: Precautions and Contraindications.)

Pharmacokinetics

In all human studies described in the Pharmacokinetics section, sertraline was administered as the hydrochloride salt; dosages and concentrations are expressed in terms of sertraline.

Absorption Sertraline appears to be slowly but well absorbed from the GI tract following oral administration. The oral bioavailability of sertraline in humans has not been fully elucidated to date because a preparation for IV administration is not available. However, the relative proportion of an oral dose that reaches systemic circulation unchanged appears to be relatively small because sertraline undergoes extensive first-pass metabolism. In animals, the oral bioavailability of sertraline ranges from 22–36%. The manufacturers state that the bioavailability of a single dose of sertraline hydrochloride tablets is approximately equal to that of an equivalent dose of sertraline hydrochloride oral solution. In a study in healthy adults who received a single 100-mg dose of sertraline as a tablet or oral solution, the solution to tablet ratios of the mean geometric AUC and peak plasma concentration were 114.8 and 120.6%, respectively.

The effect of food on the absorption of sertraline hydrochloride given as tablets or the oral solution has been studied in single-dose studies. Administration of a sertraline hydrochloride tablet with food slightly increased the area under the concentration-time curve (AUC) of sertraline, increased peak plasma concentrations by approximately 25%, and decreased the time to achieve peak plasma concentrations from about 8 to 5.5 hours. Administration of sertraline hydrochloride oral solution with food increased the time to achieve peak plasma concentrations from 5.9 to 7.0 hours.

Peak plasma sertraline concentrations usually occur within 4.5–8.4 hours following oral administration of 50–200 mg once daily for 14 days. Peak plasma sertraline concentrations following administration of single oral doses of 50–200 mg are proportional and linearly related to dose. Peak plasma concentrations and bioavailability are increased in geriatric individuals.

Following multiple dosing, steady-state plasma sertraline concentrations should be achieved after approximately 1 week of once-daily dosing. When compared with a single dose, there is an approximate twofold accumulation of sertraline after multiple daily dosing in dosages ranging from 50–200 mg daily.

N-Desmethylsertraline, sertraline's principal metabolite, exhibits time-related, dose-dependent increases in AUC (0–24 hour), peak plasma concentrations, and trough plasma concentrations with about a 5- to 9-fold increase in these parameters between day 1 and 14.

As with other serotonin-reuptake inhibitors, the relationship between plasma sertraline and *N*-desmethylsertraline concentrations and the therapeutic and/or toxic effects of the drug has not been clearly established.

■ Distribution Distribution of sertraline and its metabolites into human body tissues and fluids has not been fully characterized. However, limited pharmacokinetic data suggest that the drug and some of its metabolites are widely distributed in body tissues. Although the apparent volume of distribution of sertraline has not been determined in humans, values exceeding 20 L/kg have been reported in rats and dogs. The drug crosses the blood-brain barrier in humans and animals.

At *in vitro* plasma concentrations ranging from 20–500 ng/mL, sertraline is approximately 98% bound to plasma proteins, principally to albumin and α_1 -acid glycoprotein. Protein binding is independent of plasma concentrations from 20–2000 mcg/mL. However, sertraline and *N*-desmethylsertraline did not alter the plasma protein binding of 2 other highly protein bound drugs, warfarin or propranolol, at concentrations of 300 and 200 ng/mL, respectively.

Sertraline and *N*-desmethylsertraline are distributed into milk. In a study involving 12 lactating women who received oral dosages of sertraline ranging from 25–200 mg daily, both sertraline and *N*-desmethylsertraline were present in all breast milk samples, with the highest concentrations observed in hind milk 7–10 hours after the maternal dose. Detectable concentrations of sertraline were found in 3 and *N*-desmethylsertraline in 6, respectively, out of 11 nursing infants.

■ Elimination The elimination half-life of sertraline averages approximately 25–26 hours and that of desmethylsertraline averages about 62–104 hours. In geriatric adults elimination half-life may be increased (e.g., to about 36 hours); however, such prolongation does not appear clinically important and does not warrant dosing alterations.

The exact metabolic fate of sertraline has not been fully elucidated. Sertraline appears to be extensively metabolized, probably in the liver, to *N*-desmethylsertraline and several other metabolites. Like some other serotonin-reuptake inhibitors, sertraline undergoes metabolism via *N*-demethylation to form *N*-desmethylsertraline, the principal metabolite. Unlike some other serotonin-reuptake inhibitors, the drug metabolizing isoenzyme CYP2D6 (a cytochrome P-450 isoenzyme implicated in the sparteine/debrisoquine polymorphism) does not appear to have a major role in the conversion of sertraline to *N*-desmethylsertraline. Nonetheless, sertraline has the potential for clinically important inhibition of this enzyme. (See Drug Interactions: Drugs Undergoing Hepatic Metabolism or Affecting Hepatic Microsomal Enzymes.) *In vitro*, the conversion of sertraline to *N*-desmethylsertraline correlates more with CYP3A3/4 activity than with CYP2D6 activity. Data from *in vivo* and *in vitro* studies have shown that *N*-desmethylsertraline is approximately 5–10 times less potent as an inhibitor of serotonin reuptake than sertraline; however, the metabolite retains selectivity for serotonin reuptake compared with either norepinephrine or dopamine reuptake. Both sertraline and desmethylsertraline undergo oxidative deamination and subsequent reduction, hydroxylation, and glucuronide conjugation. Desmethylsertraline has an elimination half-life approximately 2.5 times that of sertraline.

Following oral administration, sertraline and its metabolites are excreted in both urine and feces. Following oral administration of a single, radiolabeled dose in 2 healthy males, unchanged sertraline accounted for less than 5% of plasma radioactivity. Approximately 40–45% of the radiolabeled dose was excreted in urine within 9 days. Unchanged sertraline was not detectable in urine. During the same period, approximately 40–45% of the radiolabeled drug was eliminated in feces, including 12–14% of unchanged sertraline.

The effect of age on the elimination of sertraline has not been fully elucidated. Plasma clearance of sertraline was approximately 40% lower in a group of 16 geriatric patients (8 males and 8 females) who received 100 mg of the drug for 14 days than that reported in a similar study involving younger individuals (from 25–32 years of age). Based on these results, the manufacturers state that steady-state should be achieved in about 2–3 weeks in older individuals. In addition, decreased clearance of *N*-desmethylsertraline was noted in older males but not in older females. (See Dosage and Administration: Dosage in Geriatric Patients.)

Because sertraline is extensively metabolized by the liver, hepatic impairment can affect the elimination of the drug. In one study in patients with chronic mild hepatic impairment (Child-Pugh scores of 5–8) who received 50 mg of sertraline daily for 21 days, sertraline clearance was reduced resulting in a 2–3 times greater exposure to the drug and its metabolite (desmethylsertraline) than that reported for age-matched individuals without hepatic impairment. In a single-dose study in patients with mild, stable cirrhosis, the elimination half-life of sertraline was prolonged to a mean of 52 hours compared with 22 hours in individuals without hepatic disease. In addition, peak plasma concentrations and AUC values for sertraline were 1.7- and 4.4-fold higher, respectively, in patients with hepatic impairment when compared with healthy individuals without liver disease, reflecting decreased clearance of the drug. The pharmacokinetics of sertraline have not been studied to date in patients with moderate and severe hepatic impairment; therefore, the manufacturers recommend that sertraline be administered with caution and in reduced dosage or less frequently

in patients with hepatic impairment. (See Cautions: Precautions and Contraindications and see Dosage and Administration: Dosage in Renal and Hepatic Impairment.)

Because sertraline is extensively metabolized in the liver and renal clearance of the drug is negligible, the manufacturers state that clinically important decreases in sertraline clearance are not anticipated if the drug is used in patients with renal impairment. Results of a multiple-dose study indicate that the pharmacokinetics of sertraline are not affected by renal impairment. In this study, individuals with mild to moderate renal impairment (creatinine clearance: 30–60 mL/minute), moderate to severe renal impairment (creatinine clearance: 10–29 mL/minute), or severe renal impairment (undergoing hemodialysis) received 200 mg of sertraline daily for 21 days; the pharmacokinetics and protein binding of the drug in these patients were similar to those reported for age-matched individuals without renal impairment. (See Cautions: Precautions and Contraindications and see Dosage and Administration: Dosage in Renal and Hepatic Impairment.)

Limited data indicate that sertraline is not appreciably removed by hemodialysis. Because of the large volume of distribution of sertraline and its principal metabolite, peritoneal dialysis, forced diuresis, hemoperfusion, and/or exchange transfusion also are likely to be ineffective in removing substantial amounts of sertraline and *N*-desmethylsertraline from the body.

Chemistry and Stability

■ Chemistry Sertraline, a selective serotonin-reuptake inhibitor antidepressant agent, is a naphthalenamine (naphthylamine)-derivative. Sertraline differs structurally from other selective serotonin-reuptake inhibitor antidepressants (e.g., citalopram, fluoxetine, paroxetine) and also differs structurally and pharmacologically from other currently available antidepressants (e.g., tricyclic antidepressants, monoamine oxidase inhibitors). Like most other serotonin-reuptake inhibitors, sertraline contains an asymmetric carbon; therefore, there are 2 existing optical isomers of the drug. However, only one of the optical isomers is present in the commercially available form of the drug.

Sertraline is commercially available as the hydrochloride salt, which occurs as a white, crystalline powder that is slightly soluble in water and isopropyl alcohol and sparingly soluble in ethanol. Commercially available sertraline hydrochloride oral solution is a clear, colorless solution with a menthol scent containing 20 mg of sertraline per mL and 12% alcohol.

■ Stability Commercially available sertraline hydrochloride tablets and oral solution should be stored at 25°C, but may be exposed to temperatures ranging from 15–30°C. Sertraline hydrochloride oral solution should be diluted only in the liquids specified by the manufacturer, and should be used immediately after dilution.

Preparations

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

Sertraline Hydrochloride

Oral		
For solution, concentrate	20 mg (of sertraline) per mL*	Sertraline Hydrochloride Oral Solution Zoloft® (with calibrated dropper dispenser containing latex rubber), Pfizer
Tablets, film-coated	25 mg (of sertraline)*	Sertraline Hydrochloride Tablets Zoloft® (scored), Pfizer
	50 mg (of sertraline)*	Sertraline Hydrochloride Tablets Zoloft® (scored), Pfizer
	100 mg (of sertraline)*	Sertraline Hydrochloride Tablets Zoloft® (scored), Pfizer
	150 mg (of sertraline)*	Sertraline Hydrochloride Tablets, Ranbaxy
	200 mg (of sertraline)*	Sertraline Hydrochloride Tablets, Ranbaxy

*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. Selected Revisions December 2009. © Copyright, January, 1999, American Society of Health-System Pharmacists, Inc.

Olanzapine

28:16.08.04 Atypical Antipsychotics (AHFS primary)

Special Alerts:

[Posted 01/29/2010] Lilly and FDA notified healthcare professionals of changes to the Prescribing Information for olanzapine (Zyprexa) related to its indication for use in adolescents (ages 13-17) for treatment of schizophrenia and bipolar I disorder [manic or mixed episodes]. The revised labeling states that:

- Section 1, Indications and Usage: When deciding among the alternative treatments available for adolescents, clinicians should consider the increased potential (in adolescents as compared with adults) for weight gain and hyperlipidemia. Clinicians should consider the potential long-term risks when prescribing to adolescents, and in many cases this may lead them to consider prescribing other drugs first in adolescents.
- Section 17.14, Need for comprehensive Treatment Program in Pediatric Patients: Olanzapine is indicated as an integral part of a total treatment program for pediatric patients with schizophrenia and bipolar disorder that may include other measures (psychological, educational, social) for patients with the disorder. Effectiveness and safety of olanzapine have not been established in pediatric patients less than 13 years of age.

For more information visit the FDA website at: <http://www.fda.gov/Safety/MedWatch/SafetyInformation> and <http://www.fda.gov/Drugs/DrugSafety>.

- Olanzapine is considered an atypical or second-generation antipsychotic agent.

Uses

Pending revision, the material in this section should be considered in light of more recently available information in the MedWatch notification at the beginning of this monograph.

Olanzapine is used for the symptomatic management of psychotic disorders (e.g., schizophrenia). In addition, olanzapine is used alone or in conjunction with lithium or divalproex sodium for the management of acute mixed or manic episodes associated with bipolar I disorder; the drug also is used for longer-term maintenance monotherapy in patients with this disorder. Olanzapine also is used for the management of acute agitation in patients with bipolar disorder or schizophrenia.

■ Psychotic Disorders

Olanzapine is used for the symptomatic management of psychotic disorders (e.g., schizophrenia). Drug therapy is integral to the management of acute psychotic episodes and accompanying violent behavior in patients with schizophrenia and generally is required for long-term stabilization to sustain symptom remission or control and to minimize the risk of relapse. Antipsychotic agents are the principal class of drugs used for the management of all phases of schizophrenia. Patient response and tolerance to antipsychotic agents are variable, and patients who do not respond to or tolerate one drug may be successfully treated with an agent from a different class or with a different adverse effect profile.

Schizophrenia

Olanzapine is used orally for the management of schizophrenia. Schizophrenia is a major psychotic disorder that frequently has devastating effects on various aspects of the patient's life and carries a high risk of suicide and other life-threatening behaviors. Manifestations of schizophrenia involve multiple psychologic processes, including perception (e.g., hallucinations), ideation, reality testing (e.g., delusions), emotion (e.g., flatness, inappropriate affect), thought processes (e.g., loose associations), behavior (e.g., catatonia, disorganization), attention, concentration, motivation (e.g., avolition, impaired intention and planning), and judgment. The principal manifestations of this disorder usually are described in terms of positive and negative (deficit) symptoms, and more recently, disorganized symptoms. Positive symptoms include hallucinations, delusions, bizarre behavior, hostility, uncooperativeness, and paranoid ideation, while negative symptoms include restricted range and intensity of emotional expression (affective flattening), reduced thought and speech productivity (alogia), anhedonia, apathy, and decreased initiation of goal-directed behavior (avolition). Disorganized symptoms include disorganized speech (thought disorder) and behavior and poor attention.

The American Psychiatric Association (APA) considers certain atypical antipsychotic agents (i.e., olanzapine, aripiprazole, quetiapine, risperidone, ziprasidone) first-line drugs for the management of the acute phase of schizophrenia (including first psychotic episodes), principally because of the decreased risk of adverse extrapyramidal effects and tardive dyskinesia, with the understanding that the relative advantages, disadvantages, and cost-effectiveness of conventional (first-generation) and atypical antipsychotic agents remain controversial. The APA states that, with the possible exception of clozapine for the management of treatment-resistant symptoms, there currently is no definitive evidence that one atypical antipsychotic agent will have superior efficacy compared with another agent in the class, although meaningful differences in response may be observed in individual patients. Conventional antipsychotic agents may be considered first-line in patients who have been treated successfully in the past with or who prefer conventional agents. The choice of an antipsychotic agent should be individualized, considering past response to therapy,

adverse effect profile (including the patient's experience of subjective effects such as dysphoria), and the patient's preference for a specific drug, including route of administration.

To compare the long-term effectiveness and tolerability of older, first-generation antipsychotic agents (i.e., perphenazine) with those of newer, atypical antipsychotic agents (i.e., olanzapine, quetiapine, risperidone, ziprasidone), a double-blind, multicenter study (the first phase of Clinical Antipsychotic Trials of Intervention Effectiveness [CATIE]) was sponsored by the National Institute of Mental Health. More than 1400 patients with schizophrenia received one of the drugs for up to 18 months or until therapy was discontinued for any reason. Patients with tardive dyskinesia could enroll in this trial; however, the randomization scheme prevented their assignment to the perphenazine group. The primary outcome measure in this study was the discontinuance of treatment for any cause; this measure was selected because discontinuing or switching an antipsychotic agent occurs frequently and is an important problem in the management of schizophrenia. In addition, this measure integrates the patient's and clinician's judgments concerning efficacy, safety, and tolerability into a more comprehensive measure of effectiveness reflecting therapeutic benefits in relation to adverse effects. Overall, 74% of patients in this study discontinued their medication before receiving the full 18 months of therapy because of inadequate efficacy, intolerable adverse effects, or for other reasons, suggesting substantial limitations in the long-term clinical effectiveness of currently available antipsychotic agents. Olanzapine appeared to be more effective than the other drugs evaluated in this study with a lower (64%) discontinuance rate and a lower rate of hospitalization for exacerbation of schizophrenia, while no significant differences between the effectiveness of the conventional agent, perphenazine, and the other second-generation agents studied were observed (discontinuance rates were 75, 82, 74, and 79% for perphenazine, quetiapine, risperidone, and ziprasidone, respectively). The time to discontinuance of therapy for any cause was found to be longer in the olanzapine group than in the quetiapine, risperidone, perphenazine, and ziprasidone groups in this study; however, the differences between the olanzapine and perphenazine groups and between the olanzapine and ziprasidone groups did not achieve statistical significance. Although there were no significant differences in the time until discontinuance of therapy because of drug intolerance among the drugs studied, the incidences of discontinuance for certain adverse effects differed among the drugs with olanzapine discontinued more frequently because of weight gain or metabolic effects (e.g., increases in glycosylated hemoglobin [hemoglobin A_{1c}; HbA_{1c}], cholesterol, and triglycerides) and perphenazine discontinued more frequently because of adverse extrapyramidal effects.

An open, multicenter, randomized, controlled trial comparing the relative long-term effectiveness (over a 1-year period) of a group of first-generation antipsychotic agents (e.g., chlorpromazine, flupentixol [not commercially available in the US], flupentixol decanoate [not commercially available in the US], fluphenazine decanoate, haloperidol, haloperidol decanoate, loxapine, methotrimeprazine (no longer commercially available in the US), pipothiazine palmitate [not commercially available in the US], sulphiride [not commercially available in the US], trifluoperazine, zuclopenthixol [not commercially available in the US], zuclopenthixol decanoate [not commercially available in the US]) with a group of second-generation antipsychotic agents other than clozapine (e.g., olanzapine, amisulpride [not commercially available in the US], quetiapine, risperidone, zotepine [not commercially available in the US]) in patients with schizophrenia was conducted throughout the United Kingdom by the National Health Service. In the Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study (CUtLASS 1), the primary outcome measure was the Quality of Life Scale score, and secondary outcome measures included symptom improvement, adverse effects, patient satisfaction, and costs of health care. Patients in the first-generation antipsychotic group demonstrated a trend toward greater improvements in the Quality of Life Scale and symptom improvements scores in this study. In addition, the patients studied did not report a clear preference for either group of drugs and costs of health care in the 2 groups were found to be similar.

Emerging data from the first phase of the pivotal CATIE trial and the CUtLASS 1 trial suggest that newer, atypical antipsychotics may not provide clinically important advantages over older, first-generation antipsychotics in patients with chronic schizophrenia and that several factors, including adequacy of symptom relief, tolerability of adverse effects, and cost of therapy, may influence a patient's ability and willingness to remain on long-term antipsychotic medication. In addition, these results suggest that it may often be necessary to try 2 or more different antipsychotic agents in an individual patient in order to provide optimal therapeutic benefit with an acceptable adverse effect profile.

In a randomized, double-blind, second phase trial, patients with schizophrenia who had discontinued an atypical antipsychotic agent during the first phase of the CATIE trial were reassigned to treatment with a different atypical antipsychotic agent (olanzapine, quetiapine, risperidone, or ziprasidone). Similarly to the first phase of the CATIE trial, efficacy and tolerability in this second phase study were principally measured by time until drug discontinuance for any reason. The time until antipsychotic treatment was discontinued was longer for patients receiving risperidone and olanzapine than for those receiving quetiapine and ziprasidone (median: 7, 6.3, 4, and 2.8 months, respectively). Among patients who discontinued their prior antipsychotic agent because of lack of efficacy, olanzapine was found to be more effective than quetiapine and ziprasidone, while risperidone was more effective than quetiapine.

In another study that was part of the second phase of the CATIE investigation, schizophrenic patients who had discontinued treatment with olanzapine, quetiapine,

risperidone, or ziprasidone during the first phase of the CATIE investigation, principally because of inadequate efficacy, were randomized to receive open-label clozapine therapy or blinded treatment with another atypical antipsychotic agent not previously received in the trial. Clozapine was found to be more effective in this study than switching to another atypical antipsychotic agent. Patients receiving clozapine also were found to be less likely to discontinue treatment for any reason than patients receiving quetiapine or risperidone. In addition, the clozapine-treated patients were less likely to discontinue therapy because of an inadequate clinical response than were patients receiving the other atypical antipsychotic agents.

Pending further data clarifying the relative effectiveness and tolerability of first- and second-generation antipsychotics in the treatment of schizophrenia, many clinicians recommend that the choice of an antipsychotic agent be carefully individualized taking into consideration the clinical efficacy and adverse effect profile (including the risk for extrapyramidal effects, weight gain, and adverse metabolic effects) of the antipsychotic agent as well as the individual patient's risk factors; the patient's previous experience of subjective effects such as dysphoria; the patient's preference for and willingness to take (i.e., compliance) a specific drug, including route of administration; and the relative cost of therapy. Olanzapine and clozapine may be reasonable alternatives in any patient with schizophrenia who has not achieved a full clinical remission with other antipsychotic agents; however, the risk of adverse metabolic effects with both drugs necessitates dietary and exercise counseling before therapy is initiated, monitoring during drug therapy, and possible discontinuance of therapy if these effects become troublesome during therapy. Additional analyses from data generated by the CATIE trial addressing other schizophrenia treatment-related issues such as quality of life and predictors of response are ongoing.

For additional information on the symptomatic management of schizophrenia, see *Schizophrenia and Other Psychotic Disorders under Uses: Psychotic Disorders*, in the *Phenothiazines General Statement* 28:16.08.24.

Atypical antipsychotic agents, including olanzapine, generally appear less likely to induce adverse extrapyramidal effects and tardive dyskinesia than conventional, first-generation antipsychotic agents. In addition, stabilization of or improvement in tardive dyskinesia associated with conventional antipsychotic agents has been reported in some patients when they have been switched to second-generation antipsychotic therapy, including olanzapine. Therefore, the APA and some clinicians recommend that atypical antipsychotic agents be considered in patients with schizophrenia who have experienced tardive dyskinesia associated with conventional antipsychotic agents.

The efficacy of oral olanzapine for the management of psychotic disorders has been established in hospital settings by 2 placebo-controlled studies of 6 weeks' duration in patients who met the DSM-III-R criteria for schizophrenia. In these and several other studies, improvement in manifestations of schizophrenia was based principally on the results of various psychiatric rating scales, including the Brief Psychiatric Rating Scale (BPRS) that assesses factors such as anergy, thought disturbances, activation, hostility/suspiciousness, and anxiety/depression; the Scale for the Assessment of Negative Symptoms (SANS); the Positive and Negative Symptoms Scale (PANSS); and the Clinical Global Impression (CGI).

In the first 6-week, placebo-controlled study, olanzapine was given in a fixed dosage of 1 or 10 mg once daily. Results indicated that the 10-mg, but not the 1-mg, once-daily dosage was more effective than placebo in improving the scores on the PANSS total (also on the extracted BPRS total), the BPRS psychosis cluster, the PANSS Negative subscale, and the CGI Severity assessments. Results of the second 6-week, placebo-controlled study, which evaluated 3 fixed dosage ranges (5 ± 2.5 mg once daily, 10 ± 2.5 mg once daily, and 15 ± 2.5 mg once daily), found that the 2 highest dosages (actual mean dosages were 12 and 16 mg once daily, respectively) were more effective than placebo in reducing the BPRS total score, BPRS psychosis cluster, and CGI severity score; the highest dosage also was superior to placebo on the SANS. There appeared to be no therapeutic advantage for the higher dosage of olanzapine compared with the medium dosage in this study. No race- or gender-related differences in outcome were noted in either of these studies.

The efficacy of oral olanzapine for long-term use (i.e., longer than 6 weeks) in schizophrenia has been established in one controlled study, and the drug has been used in some other patients for prolonged periods (e.g., reportedly up to 1 year) without apparent loss of clinical effect. In the long-term clinical trial, adult outpatients who predominantly met DSM-IV criteria for schizophrenia and who remained stable on olanzapine therapy during an open-label treatment phase lasting at least 8 weeks were randomized to continue receiving their current olanzapine dosage (ranging from 10–20 mg daily) or to receive placebo. Although the follow-up period to observe patients for relapse, which was defined in terms of increases in BPRS positive symptoms or hospitalization, initially was planned for 12 months, criteria were met for stopping the trial early because of an excess of placebo relapses compared with olanzapine relapses. In addition, olanzapine was found to be superior to placebo on prolonging time to relapse, which was the primary outcome measure in this study. Therefore, olanzapine was more effective than placebo at maintaining efficacy in schizophrenic patients stabilized for approximately 8 weeks and followed for an observation period of up to 8 months. If olanzapine is used for extended periods, the need for continued therapy should be reassessed periodically.

Olanzapine has been shown to be an effective, relatively rapid-acting, broad-spectrum antipsychotic agent in both controlled and uncontrolled studies of patients with schizophrenia. Like other second-generation antipsychotic agents, olanzapine appears to improve both positive (florid symptomatology such as hallucinations,

conceptual disorganization, and suspiciousness) and negative ("deficit" symptomatology such as emotional withdrawal, motor retardation, blunted affect, and disorientation) manifestations of schizophrenia; conventional antipsychotic agents may have lesser effects on negative manifestations of the disorder. Some evidence also suggests that atypical antipsychotic agents may be more effective in treating cognitive and mood symptoms as well as global psychopathology than conventional antipsychotic agents, but this is controversial and remains to be fully established. In addition, some patients with schizophrenia who have been stabilized on long-term conventional antipsychotic therapy have demonstrated further improvement following a switch to an atypical antipsychotic agent.

Results from one comparative study suggest that oral olanzapine dosages of 7.5–17.5 mg daily may be as effective as oral haloperidol dosages of 10–20 mg daily in reducing positive symptoms of schizophrenia, while oral olanzapine dosages of 12.5–17.5 mg daily may be more effective than oral haloperidol dosages of 10–20 mg daily in reducing negative symptoms of schizophrenia. However, a randomized, controlled trial comparing the long-term (i.e., 1 year) effectiveness and cost of olanzapine and haloperidol therapy in patients with schizophrenia or schizoaffective disorder did not reveal any important advantage of olanzapine compared with haloperidol on measures of compliance, symptom improvement, adverse extrapyramidal effects, overall quality of life, and cost; olanzapine also was more frequently associated with weight gain. However, olanzapine therapy was associated with reduced akathisia, less tardive dyskinesia in a secondary analysis, and small but significant improvements in measures of memory and motor function compared with haloperidol. In other comparative studies, olanzapine usually was found to be at least as effective as or more effective than haloperidol and several other atypical antipsychotic agents, including quetiapine, risperidone, and ziprasidone. In a comparative, double-blind trial conducted in patients with schizophrenia or schizoaffective disorder, both olanzapine and risperidone were found to be effective and well tolerated, although greater reductions in the severity of positive and affective symptoms were noted in the risperidone-treated patients compared with those receiving olanzapine.

Olanzapine also has been studied in patients with treatment-refractory schizophrenia (i.e., patients who have demonstrated an inadequate response to prior antipsychotic therapy) in both open and comparative clinical trials. In an open trial of 6 weeks' duration, olanzapine (15–25 mg daily) was found to be effective and well tolerated in patients with treatment-refractory schizophrenia with 36% responding to the drug. In a double-blind trial of 8 weeks' duration, although olanzapine (25 mg daily) was found to be as effective as chlorpromazine (1.2 g daily with benztropine), the total amount of improvement with either drug was modest; olanzapine was better tolerated than chlorpromazine. In a double-blind trial of 14 weeks' duration comparing efficacy and safety of several atypical antipsychotics (olanzapine, clozapine, and risperidone) with each other and with haloperidol, olanzapine (mean dosage of approximately 30 mg daily) and clozapine produced greater clinical improvement in global psychopathology and negative symptoms than haloperidol (mean dosage of approximately 26 mg daily) in patients with chronic schizophrenia or schizoaffective disorder, but the effects of atypical antipsychotic agents were considered small and of limited clinical importance. In another study using the manufacturer's clinical trial database to retrospectively identify treatment-resistant schizophrenic patients, olanzapine (mean dosage of approximately 11 mg daily) was found to be more effective than haloperidol therapy (mean dosage of approximately 10 mg daily) in improving positive, negative, and mood symptoms and produced fewer extrapyramidal effects. The results of clinical trials to date suggest that olanzapine may be somewhat less effective than or similarly effective to clozapine in the management of resistant schizophrenia patients. Clozapine generally appears to be more effective in the management of treatment-refractory schizophrenia than most first-generation and other second-generation antipsychotic agents and may produce greater improvement in negative symptoms of schizophrenia than other antipsychotic agents; however, tolerability concerns (e.g., hematologic toxicity, hypotension, dizziness, sedation) limit its use in many patients. Although higher olanzapine dosages (i.e., up to 60 mg daily) have been used in some patients with treatment-resistant schizophrenia, it remains to be established whether higher dosages of the drug result in improved efficacy in such patients, and higher dosages may increase the risk of extrapyramidal and other adverse effects.

Like some other atypical antipsychotic agents (e.g., clozapine, risperidone), olanzapine therapy appears to reduce the risk of violent behavior in patients with schizophrenia. Although the precise mechanism(s) for the antiaggressive effects are not known, improved compliance with atypical antipsychotic agents may play a role.

Olanzapine also has been used with a variety of adjunctive agents, including other antipsychotic agents, antidepressants (including selective serotonin-reuptake inhibitors such as fluoxetine and fluvoxamine), valproate (e.g., divalproex sodium, valproic acid, valproate sodium), and topiramate, in some patients with treatment-refractory schizophrenia, inadequate response to antipsychotic therapy, or acute exacerbations of schizophrenia in both controlled and uncontrolled trials. Further controlled trials of olanzapine combined with these agents are necessary to more clearly determine the potential risks and benefits of such combined therapy.

Pediatric Considerations.

Pending revision, the material in this section should be considered in light of more recently available information in the MedWatch notification at the beginning of this monograph.

Although the manufacturer states that the safety and efficacy of olanzapine in children and adolescents with schizophrenia have not been established, the drug has

been successfully used for the management of childhood-onset schizophrenia in a limited number of children and adolescents†. In addition, a double-blind, placebo-controlled trial of 6 weeks' duration conducted in adolescents 13–17 years of age with schizophrenia has demonstrated that olanzapine is effective in the management of schizophrenia, but that the drug's adverse effects on weight and prolactin concentrations may be greater in adolescents.

Based on the observed efficacy and tolerability of atypical antipsychotics in adults and the available clinical experience in pediatric patients, the American Academy of Child and Adolescent Psychiatry (AACAP) currently states that the use of atypical antipsychotic agents in children and adolescents with schizophrenia is justified, and many clinicians consider atypical antipsychotic agents, with the exception of clozapine, the drugs of first choice in the management of childhood-onset schizophrenia.

However, well-controlled studies are necessary to more clearly establish the efficacy and safety of atypical antipsychotics in pediatric patients, particularly during long-term therapy. For additional information on the symptomatic management of childhood-onset schizophrenia, see Pediatric Considerations under Psychotic Disorders: Schizophrenia, in Uses in the Phenothiazines General Statement 28:16.08.24.

Acute Agitation.

Olanzapine is used IM for the management of acute agitation in patients with schizophrenia for whom treatment with olanzapine is appropriate and who require an IM antipsychotic agent for rapid control of behaviors that interfere with diagnosis and care (e.g., threatening behaviors, escalating or urgently distressing behavior, self-exhausting behavior). According to DSM-IV, psychomotor agitation is excessive motor activity associated with a feeling of inner tension. The efficacy of IM olanzapine for the management of acute agitation in patients with schizophrenia was established in 2 short-term (single-day), placebo-controlled trials in hospital settings; an active comparator treatment arm using haloperidol injection was included in both studies. The patients in this study exhibited a level of agitation that met or exceeded a threshold score of 14 on the 5 items comprising the Positive and Negative Syndrome Scale (PANSS) Excited Component (i.e., poor impulse control, tension, hostility, uncooperativeness, and excitement items) with at least one individual item score of 4 ("moderate") or greater using a 1–7 scoring system, where scores of 1 or 7 indicate absent or extreme agitation, respectively. The primary measure used for assessing efficacy in managing agitation in these trials was the change from baseline in the PANSS Excited Component at 2 hours post-injection. Patients could receive up to 3 injections of IM olanzapine; however, patients could not receive the second injection until after the initial 2-hour period when the primary efficacy measure was assessed.

In the first placebo-controlled trial, IM olanzapine was given in fixed single doses of 2.5, 5, 7.5, or 10 mg in agitated hospitalized patients with schizophrenia. All 4 IM olanzapine doses were found to be statistically superior to placebo in reducing the PANSS Excited Component score at 2 hours following injection; however, the effect was larger and more consistent for the 3 highest doses studied. There were no significant differences in efficacy noted for the 7.5- and 10-mg doses compared with the 5-mg dose in this study. In the second placebo-controlled trial in agitated patients with schizophrenia, a fixed, 10-mg dose of IM olanzapine was evaluated and found to be superior to placebo on the PANSS Excited Component at 2 hours following injection. An analysis of these 2 controlled studies as well as an additional controlled study conducted in agitated patients with bipolar mania for possible age-, race-, or gender-related effects on treatment outcome did not suggest any difference in efficacy based on these patient characteristics.

■ **Bipolar Disorder**

Oral olanzapine is used alone or in conjunction with lithium or divalproex sodium for the management of acute mixed or manic episodes associated with bipolar I disorder; the drug also is used orally for longer-term maintenance monotherapy in patients with this disorder. According to DSM-IV criteria, manic episodes are distinct periods lasting 1 week or longer (or less than 1 week if hospitalization is required) of abnormally and persistently elevated, expansive, or irritable mood accompanied by at least 3 (or 4 if the mood is only irritability) of the following 7 symptoms: grandiosity, reduced need for sleep, pressure of speech, flight of ideas, distractibility, increased goal-directed activity (either socially, at work or school, or sexually) or psychomotor agitation, and engaging in high-risk behavior (e.g., unrestrained buying sprees, sexual indiscretions, foolish business investments).

For the initial management of less severe manic or mixed episodes in patients with bipolar disorder, current APA recommendations state that monotherapy with lithium, valproate (e.g., valproate sodium, valproic acid, divalproex), or an antipsychotic such as olanzapine may be adequate. For more severe manic or mixed episodes, combination therapy with an antipsychotic and lithium or valproate is recommended as first-line therapy. For further information on the management of bipolar disorder, see Uses: Bipolar Disorder, in Lithium Salts 28:28.

Acute Manic Episodes

Efficacy of oral olanzapine monotherapy in the treatment of acute manic episodes has been demonstrated in 2 short-term (i.e., 3 or 4 weeks' duration), randomized, double-blind, placebo-controlled, parallel-group trials in patients who met the DSM-IV criteria for bipolar I disorder (with or without a rapid-cycling course) and who met diagnostic criteria for an acute manic or mixed episode (with or without psychotic features). Olanzapine was given in an initial dosage of 10 mg once daily in the 3-week trial and 15 mg once daily in the 4-week trial; the dosage was subsequently adjusted within the range of 5–20 mg once daily in both of these trials. The principal rating instrument used for assessing manic symptoms in these trials was the Y-MRS

score, an 11-item clinician-rated scale traditionally used to assess the degree of manic symptomatology (e.g., irritability, disruptive/aggressive behavior, sleep, elevated mood, speech, increased activity, sexual interest, language/thought disorder, thought content, appearance, insight) in a range from 0 (no manic features) to 60 (maximum score). All patients were hospitalized at the onset of these trials, but some patients were allowed to continue the studies on an outpatient basis after 1 week of hospitalization if their Clinical Global Impressions-Bipolar Version of severity of illness (CGI-BP) mania score was no greater than 3 (mild) and they had at least a 50% reduction in their Young Mania Rating Scale (Y-MRS) scores. In the 3- and 4-week placebo-controlled trials, approximately 49–65% of patients receiving 5–20 mg of olanzapine once daily achieved a 50% or greater improvement in Y-MRS total score from baseline compared with approximately 24–43% of those who received placebo. In addition, unlike therapy with typical antipsychotic agents, patients receiving olanzapine in these clinical studies did not experience a worsening in depressive symptoms (defined as an increase in the Hamilton Psychiatric Rating Scale for Depression-21 item [HAM-D-21] score of at least 3 points) compared with those receiving placebo. In another 3-week, placebo-controlled trial that was designed identically to the first 3-week trial and was conducted simultaneously, olanzapine demonstrated a similar treatment difference in reduction of the Y-MRS total score but was not found to be superior to placebo on this outcome measure, possibly due to sample size and site variability.

Data from one limited comparative study suggest that oral olanzapine dosages of 10 mg daily may be as effective as lithium carbonate dosages of 400 mg twice daily in the treatment of manic episodes in patients with bipolar disorder. In a randomized, double-blind trial of 3 weeks' duration comparing olanzapine (5–20 mg daily) and divalproex sodium therapy in hospitalized patients with bipolar disorder experiencing acute manic or mixed episodes, olanzapine therapy was found to produce greater improvement in Y-MRS total scores, which was the primary efficacy measure in this trial. In addition, a significantly greater proportion of patients in the olanzapine group achieved remission compared with the divalproex group. In a randomized, double-blind study of 12 weeks' duration comparing olanzapine and divalproex sodium in patients with bipolar I disorder hospitalized for acute mania, the drugs were found to be equally effective although divalproex sodium was somewhat better tolerated than olanzapine.

Combined Therapy

Efficacy of oral olanzapine when used in combination with lithium or divalproex sodium in the short-term treatment of acute manic episodes has been demonstrated in 2 randomized, double-blind, placebo-controlled studies of 6 weeks' duration in patients who met the DSM-IV criteria for bipolar I disorder (with or without a rapid-cycling course) and who met diagnostic criteria for an acute manic or mixed episode (with or without psychotic features). In these studies, patients with bipolar disorder experiencing manic or mixed episodes (Y-MRS scores of 16 or greater) who had not responded to at least 2 weeks of lithium or divalproex sodium monotherapy despite adequate plasma drug concentrations (in a therapeutic range of 0.6–1.2 mEq/L for lithium or 50–125 mcg/mL of valproate for divalproex sodium) were randomized to receive either olanzapine (initial dosage of 10 mg once daily; range: 5–20 mg once daily) or placebo, in combination with their original therapy. Addition of olanzapine to lithium or divalproex sodium was shown to be superior to continued monotherapy with lithium or divalproex sodium in the reduction of Y-MRS total score in both of these studies.

Maintenance Monotherapy of Bipolar Disorder

Oral olanzapine also is used for maintenance monotherapy in patients with bipolar disorder. The long-term efficacy of oral olanzapine as maintenance monotherapy in bipolar disorder has been demonstrated in a double-blind, placebo-controlled trial and in double-blind comparative trials. In the placebo-controlled study, patients who met DSM-IV criteria for bipolar I disorder and experienced manic or mixed episodes and who had responded during an initial open-label treatment phase to oral olanzapine therapy (5–20 mg daily) for an average of about 2 weeks were randomized either to continue olanzapine at the same dosage or to receive placebo for up to 48 weeks and were observed for relapse. Response during the open-label phase was defined as a reduction in the Y-MRS total score of 12 or more and in the 21-item Hamilton Depression Rating Scale (HAM-D 21) of 8 or more; relapse during the double-blind phase of the study was defined as an increase in the Y-MRS or HAM-D 21 total score to 15 or more or being hospitalized for either mania or depression. Approximately 50% of the patients in the olanzapine group had discontinued therapy by day 59, and approximately 50% of the patients in the placebo group had discontinued placebo by day 23 of the double-blind phase. A longer time until relapse was observed in the patients receiving olanzapine compared with those receiving placebo (median of 174 and 22 days, respectively, for relapse into any mood episode) during the randomized phase of this study. The relapse rate also was significantly lower in the olanzapine group (approximately 47%) than in the placebo group (approximately 80%). If olanzapine is used for extended periods, the need for continued therapy should be reassessed periodically.

In a double-blind, 52-week trial comparing olanzapine and lithium maintenance therapy in patients with bipolar disorder, olanzapine was found to be significantly more effective than lithium in preventing relapses and recurrences of manic and mixed episodes following initial stabilization with combined olanzapine and lithium therapy. Olanzapine and lithium demonstrated comparable efficacy in preventing relapses and recurrences of depression in this study. In a retrospective analysis from this trial, patients were subcategorized into illness stage (early, intermediate, or later) based on the number of prior manic or mixed episodes they had experienced. The rates of relapse or recurrence of manic or mixed episodes were approximately 2 and 26%, 13 and 24%,

and 24 and 33% for olanzapine and lithium in the early, intermediate, and later stage groups of bipolar patients, respectively; no substantial treatment effect for treatment or illness stage for depressive relapse or recurrence was observed. Because olanzapine was associated with a lower rate of relapse or recurrence of manic and mixed episodes in early-stage patients, it was suggested that the drug may be particularly effective early in the course of bipolar disorder.

In a double-blind, 47-week trial comparing monotherapy with olanzapine or divalproex sodium in patients with bipolar disorder experiencing manic or mixed episodes, mean improvement in Y-MRS scores was greater for olanzapine-treated patients. In addition, the median time to symptomatic mania remission was shorter for patients receiving olanzapine compared with those receiving divalproex sodium (14 days vs. 62 days, respectively). However, no significant differences in the rates of symptomatic mania remission and symptomatic relapse into mania or depression between the olanzapine- and divalproex-treated patients were observed in this study. In a double-blind, 18-month, relapse prevention trial comparing the efficacy of combined olanzapine plus lithium or valproate therapy with lithium or valproate therapy alone in patients with bipolar disorder, more sustained symptomatic remission (163 days vs 42 days, respectively) occurred in the group receiving combined olanzapine plus lithium or valproate therapy than in the group receiving lithium or valproate therapy alone.

Rapid-Cycling Bipolar Disorder

In an analysis of pooled data from several trials comparing the clinical response to olanzapine therapy in rapid-cycling and non-rapid-cycling patients with bipolar disorder, relative clinical response to olanzapine was found to be similar in the 2 groups, although earlier responses were observed in the rapid-cycling group of patients, and long-term outcomes were more favorable in the non-rapid-cycling group. Rapid-cycling patients were found to be less likely to achieve an initial symptomatic remission, more likely to experience recurrences, especially of depression, and had more hospitalizations and suicide attempts than non-rapid-cycling patients in this study.

Acute Depressive Episodes in Bipolar Disorder

In a secondary analysis of data from dysphoric manic patients participating in a placebo-controlled trial evaluating olanzapine combined with lithium or valproate therapy in patients with bipolar I disorder, the addition of olanzapine was found to improve symptoms of depression, mania, and suicidality compared with lithium or valproate therapy alone.

Olanzapine also is used in combination with fluoxetine for the treatment of acute depressive episodes in patients with bipolar disorder. In 2 randomized, double-blind studies of 8 weeks' duration comparing a fixed combination of olanzapine and fluoxetine hydrochloride (Symbyax[®]) with olanzapine monotherapy and placebo, the fixed combination (flexible daily dosages of 6 mg olanzapine with 25 or 50 mg of fluoxetine or 12 mg of olanzapine with 50 mg of fluoxetine) was more effective than olanzapine monotherapy (5–20 mg daily) or placebo in improvement in depressive symptoms as assessed by the Montgomery-Asberg Depression Rating Scale (MADRS). Although the manufacturer states that efficacy beyond 8 weeks' duration remains to be established, patients have received the fixed combination for up to 24 weeks in clinical trials. Clinicians who elect to extend therapy beyond 8 weeks should reevaluate the risks and benefits of continued therapy periodically.

Pediatric Considerations

Although the manufacturer states that the safety and efficacy of olanzapine in children and adolescents with bipolar disorder have not been established, the drug has been successfully used for the management of bipolar disorder in a limited number of children and adolescents[†]. In a double-blind, placebo-controlled, 3-week study in adolescents 13–17 years of age with bipolar disorder, olanzapine was found to be effective in the treatment of acute manic or mixed episodes; however, weight gain and hyperprolactinemia occurred more often in patients receiving olanzapine compared with those receiving placebo.

Based on the observed efficacy and tolerability of mood stabilizers and atypical antipsychotic agents in clinical trials in adults and the available clinical experience in pediatric patients, the American Academy of Child and Adolescent Psychiatry (AACAP) currently states that the mood stabilizers lithium, divalproex sodium, and carbamazepine and the atypical antipsychotics olanzapine, quetiapine, and risperidone are drugs of first choice in the acute management of pediatric patients with bipolar I disorder experiencing manic or mixed episodes without psychosis. The AACAP also currently recommends that a mood stabilizer such as lithium, divalproex sodium, or carbamazepine combined with an atypical antipsychotic be used as first line therapy in pediatric patients with bipolar I disorder experiencing manic or mixed episodes accompanied by psychosis. Additional controlled studies are necessary to more clearly establish the efficacy and safety of atypical antipsychotics in pediatric patients with bipolar disorder, particularly during long-term therapy.

Acute Agitation

Olanzapine is used IM for the management of acute agitation in patients with bipolar I disorder for whom treatment with olanzapine is appropriate and who require an IM antipsychotic agent for rapid control of behaviors that interfere with their diagnosis and care (e.g., threatening behaviors, escalating or urgently distressing behavior, self-exhausting behavior). According to DSM-IV, psychomotor agitation is excessive motor activity associated with a feeling of inner tension.

The efficacy of IM olanzapine for the management of acute agitation in patients with bipolar mania was established in a short-term (single-day), double-blind, placebo-controlled trial in agitated, hospitalized patients who met the DSM-IV criteria for

bipolar I disorder and who displayed an acute manic or mixed episode with or without psychotic features. The patients in this study exhibited a level of agitation that met or exceeded a threshold score of 14 on the 5 items comprising the Positive and Negative Syndrome Scale (PANSS) Excited Component (i.e., poor impulse control, tension, hostility, uncooperativeness, and excitement items) with at least one individual item score of 4 ("moderate") or greater using a 1–7 scoring system where scores of 1 or 7 indicate absent or extreme agitation, respectively. An active comparator treatment arm using IM lorazepam was included in this study. The primary measure used for assessing efficacy in managing agitation in this trial was the change from baseline in the PANSS Excited Component at 2 hours post-injection of a fixed, 10-mg IM dose of olanzapine. Patients in this study could receive up to 3 injections of IM olanzapine; however, patients could not receive the second injection until after the initial 2-hour period when the efficacy was assessed. IM olanzapine was found to be statistically superior to placebo in reducing the PANSS Excited Component score at 2 hours and at 24 hours following the initial injection. An analysis of this study as well as 2 additional controlled studies conducted in agitated patients with schizophrenia for possible age-, race-, or gender-related effects on treatment outcome did not suggest any difference in efficacy based on these patient characteristics.

Dosage and Administration

■ Reconstitution and Administration

Olanzapine is administered orally or by IM injection.

Oral Administration

Olanzapine conventional tablets and orally disintegrating tablets are administered orally. Since food does not appear to affect GI absorption of olanzapine, the drug generally can be administered as conventional tablets or orally disintegrating tablets without regard to meals. In patients who experience persistent or troublesome daytime sedation during oral olanzapine therapy, administration of the daily dosage in the evening at bedtime may be helpful.

Patients receiving olanzapine orally disintegrating tablets should be instructed not to remove a tablet from the blister until just prior to dosing. The tablet should not be pushed through the foil. With dry hands, the blister backing should be peeled completely off the blister. The tablet should then be gently removed and immediately placed on the tongue, where it rapidly disintegrates in saliva, and then subsequently swallowed with or without liquid.

The fixed combination capsules of olanzapine with fluoxetine hydrochloride are administered orally once daily in the evening. Although the manufacturer states that food has no appreciable effect on absorption of either drug when administered alone, absorption of the drugs when administered as the fixed combination has not been studied.

Dispensing and Administration Precautions

Because of similarities in spelling, dosage intervals (once daily), and tablet strengths (5 and 10 mg) of Zyprexa[®] (olanzapine) and Zyrtec[®] (cetirizine hydrochloride, an antihistamine), extra care should be exercised in ensuring the accuracy of prescriptions for these drugs. (See Cautions: Precautions and Contraindications.)

IM Administration

Commercially available olanzapine for injection must be reconstituted prior to administration by adding 2.1 mL of sterile water for injection to single-dose vials labeled as containing 10 mg of olanzapine to provide a solution containing approximately 5 mg/mL. Other solutions should not be used to reconstitute olanzapine for injection.

Following reconstitution, olanzapine for injection should be used immediately (within 1 hour). If necessary, the reconstituted solution may be stored for up to 1 hour at 20–25°C; after 1 hour, any unused portion should be discarded. Olanzapine for injection should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

Olanzapine for injection is administered only by IM injection and should *not* be administered IV or subcutaneously. The drug should be injected slowly, deep into the muscle mass.

■ Dosage

Pending revision, the material in this section should be considered in light of more recently available information in the MedWatch notification at the beginning of this monograph.

Conventional olanzapine tablets and orally disintegrating tablets of the drug are bioequivalent. However, IM administration of a 5-mg dose of the commercially available injection results in a maximum plasma olanzapine concentration that is about fivefold higher than that resulting from a 5-mg oral dose. Dosage of olanzapine must be adjusted carefully according to individual requirements and response, using the lowest possible effective dosage.

Oral Dosage

Schizophrenia.

For the management of schizophrenia, the recommended initial oral dosage of olanzapine is 5–10 mg daily, usually given as a single daily dose. Dosage may be increased by 5 mg daily within several days, to a target dosage of 10 mg daily. Because steady-state plasma concentrations of olanzapine may not be attained for 7 days at a given dosage, subsequent dosage adjustments generally should be made at intervals of not less than 7 days, usually in increments or decrements of 5 mg once daily. An initial

dosage of 5 mg daily is recommended in debilitated patients, in those predisposed to hypotension, in those who may be particularly sensitive to the effects of olanzapine, or in those who might metabolize olanzapine slowly (e.g., nonsmoking female patients who are 65 years of age or older).

While a relationship between dosage and antipsychotic effect has not been established, the effective oral dosage of olanzapine in clinical studies generally ranged from 10–15 mg daily. The manufacturer states that increasing olanzapine dosages beyond 10 mg daily usually does not result in additional therapeutic effect and recommends that such increases generally should occur only after the patient's clinical status has been assessed. In addition, the manufacturer states that safety of dosages exceeding 20 mg daily has not been established in clinical trials. However, olanzapine occasionally has been used in controlled and uncontrolled trials and in individual patients in dosages of up to 40 mg daily; dosages of up to 60 mg daily have been used in some patients with treatment-resistant schizophrenia. It remains to be established whether higher dosages of the drug are safe and result in improved efficacy in such patients. Some clinicians state that olanzapine dosages of up to 30 mg daily may produce further clinical improvement in schizophrenia patients who did not respond adequately to dosages of up to 20 mg daily; however, they recommend that caution be exercised when dosage of the drug exceeds 40 mg daily because of the potential for serious adverse effects (e.g., extrapyramidal reactions, excitement, metabolic changes, weight gain, cardiovascular complications).

Although clinical experience generally has not revealed age-related differences in tolerance of olanzapine in adults, dosage generally should be titrated carefully in geriatric patients 65 years of age or older, usually initiating therapy at the low end of the dosage range.

The optimum duration of olanzapine therapy currently is not known, but maintenance therapy with antipsychotic agents is well established. Patients responding to olanzapine therapy should continue to receive the drug as long as clinically necessary and tolerated, but at the lowest possible effective dosage, and the need for continued therapy with the drug should be reassessed periodically.

Bipolar Disorder.

As monotherapy for the management of acute mania associated with bipolar I disorder, the recommended initial oral dosage of olanzapine is 10 or 15 mg daily, usually given as a single dose. Dosage may be increased by 5 mg daily at intervals of not less than 24 hours, reflecting the procedures in the placebo-controlled trials. The effective dosage of olanzapine in clinical studies generally has ranged from 5–20 mg daily. Safety of dosages exceeding 20 mg daily has not been established.

When administered in conjunction with lithium or divalproex sodium for the management of acute manic episodes associated with bipolar I disorder, the recommended initial oral dosage of olanzapine is 10 mg once daily. The effective dosage of olanzapine as adjunctive therapy for up to 6 weeks in clinical studies generally ranged from 5–20 mg daily. Safety of dosages exceeding 20 mg daily has not been established.

When used in fixed combination with fluoxetine hydrochloride for acute depressive episodes in patients with bipolar disorder, olanzapine is administered once daily in the evening, usually initiating therapy with a dosage of 6 mg of olanzapine and 25 mg of fluoxetine (Symbyax® 6/25). This dosage generally should be used as initial and maintenance therapy in patients with a predisposition to hypotensive reactions, patients with hepatic impairment, or those with factors that may slow metabolism of the drug(s) (e.g., female gender, geriatric age, nonsmoking status); when indicated, dosage should be escalated with caution. In other patients, dosage can be increased according to patient response and tolerance as indicated. In clinical trials, antidepressant efficacy was demonstrated at olanzapine dosages ranging from 6–12 mg daily and fluoxetine dosages ranging from 25–50 mg daily. Dosages exceeding 18 mg of olanzapine and 75 mg of fluoxetine have not been evaluated in clinical studies.

The long-term efficacy of oral olanzapine (dosage range: 5–20 mg daily) for maintenance monotherapy in patients with bipolar disorder has been demonstrated in a double-blind, placebo-controlled trial of 52 weeks' duration and in comparative studies of 47–52 weeks' duration. The mean modal dosage of olanzapine in the placebo-controlled study was 12.5 mg daily. The manufacturer states that patients receiving oral olanzapine for extended periods should be reassessed periodically to determine the need for continued therapy.

Although the manufacturer states that efficacy of the fixed-combination of olanzapine and fluoxetine beyond 8 weeks' duration remains to be established, patients have received the fixed combination for up to 24 weeks in clinical trials. Clinicians who elect to use the fixed combination for extended periods should periodically reevaluate the long-term risks and benefits of the drug for the individual patient.

IM Dosage for Acute Agitation in Schizophrenia or Bipolar Mania

For the prompt control of acute agitation in patients with schizophrenia or bipolar mania, the recommended initial adult IM dose is 10 mg given as a single dose. A lower initial IM dose (2.5, 5, or 7.5 mg) may be considered when clinically warranted. In clinical trials, the efficacy of IM olanzapine for controlling agitation in patients with schizophrenia or bipolar mania has been demonstrated in a dosage range of 2.5–10 mg.

If agitation necessitating additional IM doses of olanzapine persists following the initial dose, subsequent single doses of up to 10 mg may be given. However, the manufacturer states that the efficacy of repeated doses of IM olanzapine in agitated patients has not been systematically evaluated in controlled clinical trials. In addition, the safety of IM dosages exceeding 30 mg daily or of 10-mg IM doses given more

frequently than 2 hours after the initial dose and 4 hours after the second dose has not been evaluated in clinical trials.

Maximal dosing of IM olanzapine (e.g., 3 doses of 10 mg administered 2–4 hours apart) may be associated with a substantial risk of clinically important orthostatic hypotension. Patients who experience drowsiness or dizziness after the IM injection should remain recumbent until an examination indicates that they are not experiencing orthostatic hypotension, bradycardia, and/or hypoventilation. (See Cardiovascular Effects under Precautions and Contraindications in Cautions.)

The manufacturer states that oral therapy should replace IM therapy as soon as possible. In one controlled study evaluating IM olanzapine in acutely agitated patients, patients initially received 1–3 IM injections of olanzapine 10 mg and were then switched to oral olanzapine therapy in dosages ranging from 5–20 mg daily for a period of 4 days.

A lower initial IM olanzapine dose of 5 mg may be considered for geriatric patients or when other clinical factors warrant. In addition, a lower IM dose of 2.5 mg per injection should be considered for patients who are debilitated, who may be predisposed to hypotensive reactions, or who may be more sensitive to the pharmacodynamic effects of olanzapine.

■ Dosage in Renal and Hepatic Impairment

The manufacturer states that because only minimal amounts of olanzapine (about 7%) are excreted in urine and because the pharmacokinetics of olanzapine appear not to be altered in patients with renal or hepatic impairment, dosage adjustment is not necessary in such patients.

Cautions

The adverse effect profile of olanzapine generally is similar to that of other atypical (second-generation) antipsychotic agents (e.g., aripiprazole, clozapine, quetiapine, risperidone, ziprasidone). Although olanzapine differs chemically from the phenothiazines, the drug also may be capable of producing many of the toxic manifestations of phenothiazine derivatives. (See Cautions in the Phenothiazines General Statement 28:16.08.24.) Not all adverse effects of the phenothiazines have been reported with olanzapine, but the possibility that they may occur should be considered. Adverse effects of olanzapine, other atypical antipsychotics, and the phenothiazines are numerous and may involve nearly all body organ systems.

In controlled studies, the most common adverse effects occurring more frequently in patients receiving oral olanzapine for schizophrenia or bipolar mania than in those receiving placebo included central and autonomic nervous system effects such as somnolence, asthenia, dry mouth, dizziness, tremor, personality disorder, and akathisia; cardiovascular system effects such as postural hypotension; GI effects such as constipation, dyspepsia, and increased appetite; and weight gain. There was no clear relationship between the incidence of adverse events and dosage in patients receiving oral olanzapine for schizophrenia in placebo-controlled trials except for certain extrapyramidal symptoms, asthenia, dry mouth, nausea, somnolence, and tremor. Discontinuance of olanzapine therapy was required in 5% of patients with schizophrenia compared with 6% for placebo in controlled trials; however, discontinuance because of increased serum ALT (SGPT) concentrations was required in 2% of the olanzapine-treated patients compared with none of those receiving placebo, and this adverse effect was considered to be drug related. Similar between olanzapine and placebo discontinuance rates were observed in the controlled trials for oral olanzapine for bipolar mania (2% for olanzapine and 2% for placebo) and IM olanzapine for acute agitation (0.4% for IM olanzapine and 0% for placebo).

Adverse effects occurring in 5% or more of patients with schizophrenia receiving oral olanzapine in short-term clinical studies and with an incidence of at least twice that of placebo included dizziness (11%), constipation (9%), personality disorder (i.e., nonaggressive objectionable behavior; 8%), weight gain (6%), postural hypotension (5%), and akathisia (5%).

Adverse effects occurring in 6% or more of patients with acute mania associated with bipolar disorder receiving oral olanzapine in clinical studies and with an incidence of at least twice that of placebo included somnolence (35%), dry mouth (22%), dizziness (18%), asthenia (15%), constipation (11%), dyspepsia (11%), increased appetite (6%), and tremor (6%).

When oral olanzapine was used in conjunction with lithium or divalproex sodium for treatment of acute mania associated with bipolar disorder, adverse effects occurring in 5% or more of patients in clinical studies and with an incidence of at least twice that of placebo included dry mouth (32%), weight gain (26%), increased appetite (24%), dizziness (14%), back pain (8%), constipation (8%), speech disorder (7%), increased salivation (6%), amnesia (5%), and paresthesia (5%).

When IM olanzapine was used for the management of acute agitation in short-term clinical studies, somnolence was the only adverse effect that occurred in 5% or more of patients with schizophrenia or bipolar mania and with an incidence of at least twice that of placebo (6% and 3%, respectively).

Nervous System Effects Seizures

Seizures occurred in about 0.9% of patients receiving oral olanzapine in controlled clinical trials during premarketing testing. Confounding factors that may have contributed to the occurrence of seizures were present in many of these cases. Myoclonic status reportedly occurred shortly after initiation of olanzapine in one patient with probable dementia of the Alzheimer's type (Alzheimer's disease) who was concurrently receiving citalopram and donepezil; the myoclonic jerks in this patient

coincided with EEG changes indicative of seizure activity (spikes and polyspike/wave complexes), and the seizures subsided following discontinuance of olanzapine. A new-onset seizure also reportedly occurred in an adult female patient upon the addition of quetiapine to maintenance therapy with olanzapine and following discontinuance of clonazepam therapy. In addition, an apparent lowering of seizure threshold occurred in at least 2 epileptic patients who experienced increased seizure activity following initiation of olanzapine therapy that resolved upon discontinuance of the drug. Fatal status epilepticus also has been reported in a patient who had been receiving olanzapine therapy for 5 months.

Olanzapine should be administered with caution to patients with a history of seizures, with conditions known to lower the seizure threshold (e.g., Alzheimer's disease, geriatric patients), and during concurrent therapy with drugs that may lower seizure threshold.

Extrapyramidal Reactions

Like other atypical antipsychotic agents, olanzapine has a low potential for causing certain adverse extrapyramidal effects (e.g., dystonias). Results from controlled clinical trials suggest that extrapyramidal reactions associated with olanzapine therapy are dose related.

Tremor was reported in about 4% of patients receiving oral olanzapine and in about 1% of patients receiving IM olanzapine in controlled clinical trials; the incidence of tremor appears to be dose related. In addition, akathisia occurred in about 3% of patients receiving oral olanzapine and in less than 1% of patients receiving IM olanzapine; hypertonia occurred in about 3% of patients receiving oral olanzapine in short-term controlled clinical trials. Akinesia and cogwheel rigidity have been reported in less than 1% of patients; these adverse effects have not been definitely attributed to the drug. Oculogyric crisis also has been reported in a patient receiving olanzapine, lithium, and paroxetine concurrently. (See Drug Interactions: Other CNS-Active Agents and Alcohol.)

Neuroleptic Malignant Syndrome

Neuroleptic malignant syndrome (NMS), a potentially fatal symptom complex, has been reported in patients receiving antipsychotic agents, including olanzapine. Clinical manifestations of NMS generally include hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac arrhythmias). Additional signs of NMS may include increased serum creatine kinase (CK, creatine phosphokinase, CPK), myoglobinuria (rhabdomyolysis), and acute renal failure. NMS attributable to olanzapine therapy alone has been reported in some patients, and there also have been reports of NMS in olanzapine-treated patients concomitantly receiving other drugs, including antipsychotic agents, antidepressants, lithium, or valproate. Extrapyramidal reactions were present in approximately two-thirds of the olanzapine-treated patients diagnosed with NMS. Atypical presentations of NMS (e.g., absence of or lessened rigidity, presenting as fever of unknown origin) and less severe presentations of NMS also have been reported in some patients receiving olanzapine or other atypical antipsychotic agents.

The diagnostic evaluation of patients with NMS is complicated. In arriving at a diagnosis, serious medical illnesses (e.g., pneumonia, systemic infection) and untreated or inadequately treated extrapyramidal signs and symptoms must be excluded. In addition, clinical features of NMS and serotonin syndrome sometimes overlap, and it has been suggested that these 2 syndromes may share certain underlying pathophysiological mechanisms. Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever, and primary CNS pathology.

The management of NMS should include immediate discontinuance of antipsychotic agents and other drugs not considered essential to concurrent therapy, intensive symptomatic treatment and medical monitoring, and treatment of any concomitant serious medical problems for which specific treatments are available. There currently is no specific drug therapy for NMS, although dantrolene, bromocriptine, amantadine, and benzodiazepines have been used in a limited number of patients. If a patient requires antipsychotic therapy following recovery from NMS, the potential reintroduction of drug therapy after several weeks should be carefully considered. If antipsychotic therapy is reintroduced, the dosage generally should be increased gradually and an antipsychotic agent other than the agent believed to have precipitated NMS generally is chosen. In addition, such patients should be carefully monitored since recurrences of NMS have been reported in some patients. For additional information on NMS, see Neuroleptic Malignant Syndrome under Cautions: Nervous System Effects, in the Phenothiazines General Statement 28:16.08.24.

Tardive Dyskinesia

Use of antipsychotic agents may be associated with tardive dyskinesia, a syndrome of potentially irreversible, involuntary, dyskinetic movements. Although the incidence of tardive dyskinesia appears to be highest among geriatric individuals, particularly geriatric females, it is not possible to reliably predict at the beginning of antipsychotic therapy which patients are likely to develop this syndrome. Tardive dyskinesia has been reported in less than 1% of patients receiving olanzapine therapy. Although the manufacturer states that it is not yet known whether antipsychotic agents differ in their potential to cause tardive dyskinesia, available evidence suggests that the risk appears to be substantially less with second-generation antipsychotic agents, including olanzapine, than with conventional, first-generation antipsychotic agents. Analyses from controlled, long-term trials have found an approximately 12-fold lower risk of tardive dyskinesia

with olanzapine therapy compared with haloperidol therapy. In addition, stabilization of or improvement in tardive dyskinesia associated with conventional antipsychotic agents has been reported in some patients when they have been switched to second-generation antipsychotic therapy, including olanzapine. However, a transient increase in dyskinetic movements (sometimes referred to as withdrawal-emergent dyskinesia) occasionally may occur when a patient is switched from a first-generation to a second-generation antipsychotic agent or upon dosage reduction of an antipsychotic agent.

The risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, following relatively brief treatment periods at low dosages. There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic therapy is discontinued. However, antipsychotic therapy itself may suppress or partially suppress the signs and symptoms of the syndrome and thereby may possibly mask the underlying process. The effect that such symptomatic suppression has upon the long-term course of tardive dyskinesia is unknown. There also is some evidence that vitamin E administration may reduce the risk of development of tardive dyskinesia; therefore, the American Psychiatric Association (APA) currently states that patients receiving antipsychotic agents may be advised to take 400-800 units of vitamin E daily for prophylaxis. (See Cautions in Vitamin E 88:20.)

Olanzapine should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment generally should be reserved for patients who suffer from a chronic illness that is known to respond to antipsychotic agents, and for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought, and the need for continued treatment should be reassessed periodically. The APA currently recommends that all patients receiving second-generation antipsychotic agents be assessed clinically for abnormal involuntary movements every 12 months and that patients considered to be at increased risk for tardive dyskinesia be assessed every 6 months. If signs and symptoms of tardive dyskinesia appear in a patient receiving olanzapine, drug discontinuance or a reduction in dosage should be considered. However, some patients may require treatment with olanzapine or another antipsychotic agent despite the presence of the syndrome. For additional information on tardive dyskinesia, see Tardive Dyskinesia under Cautions: Nervous System Effects, in the Phenothiazines General Statement 28:16.08.24.

Other Nervous System Effects

Somnolence or sedation, which usually appears to be moderate in severity compared with other antipsychotic agents and dose related, is among the most common adverse effects of olanzapine, occurring in approximately 29% of patients receiving oral olanzapine in controlled clinical trials. Somnolence associated with olanzapine and other antipsychotic agents generally is most pronounced during early therapy, since most patients develop some tolerance to the sedating effects with continued administration. Although sedation can have therapeutic benefits in some cases, persistent daytime drowsiness and increased sleep time can become troublesome in some patients and necessitate a lower dosage or evening administration of the drug. (See Administration under Dosage and Administration and see also Effects on Sleep under Pharmacology: Nervous System Effects.)

Insomnia occurred in about 12%, dizziness in about 11%, asthenia in about 10%, and abnormal gait in about 6% of patients receiving oral olanzapine in short-term controlled clinical trials. The incidence of asthenia appears to be dose related. In addition, articulation impairment was reported in about 2% of patients receiving oral olanzapine in short-term, controlled clinical trials.

Abnormal dreams, amnesia, delusions, emotional lability, euphoria, manic reaction, paresthesia, and schizophrenic reaction each has been reported in at least 1% of patients receiving oral olanzapine; however, a causal relationship to the drug has not been established. Alcohol misuse, antisocial reaction, ataxia, CNS stimulation, delirium, dementia, and depersonalization have been reported in less than 1% of patients; these adverse effects have not been definitely attributed to the drug.

Dysarthria, facial paralysis, hypesthesia, hypokinesia, hypotonia, incoordination, increased or decreased libido, migraine, obsessive-compulsive symptoms, phobias, somatization, and stimulant misuse have been reported in less than 1% of patients receiving oral olanzapine; these adverse effects have not been definitely attributed to the drug. Although a causal relationship has not been established, stupor, stuttering, vertigo, and withdrawal syndrome also have been reported in up to 1% of patients receiving oral olanzapine. Circumoral paresthesia, coma, encephalopathy, neuralgia, neuropathy, nystagmus, paralysis, suicide attempt, subarachnoid hemorrhage, and tobacco misuse have been reported in less than 0.1% of patients receiving oral olanzapine; however, a causal relationship to the drug has not been clearly established.

In short-term (i.e., 24-hour), controlled clinical trials of IM olanzapine for acute agitation, somnolence occurred in approximately 6%, dizziness in approximately 4%, and asthenia in about 2% of the patients. Abnormal gait, articulation impairment, confusion, and emotional lability have been reported in less than 1% of patients; these adverse effects have not been definitely attributed to the drug.

Cardiovascular Effects Hemodynamic Effects

Oral olanzapine may produce orthostatic hypotension that may be associated with dizziness, tachycardia, and, in some patients, syncope, particularly during the initial

period of dosage titration. In short-term, controlled clinical trials for oral olanzapine, postural hypotension and tachycardia occurred in approximately 3% and hypertension occurred in approximately 2% of patients. In addition, hypotension has been reported in at least 1% of patients receiving oral olanzapine in the short-term controlled clinical trials. Bradycardia, congestive heart failure, and vasodilatation have been reported in less than 1% of patients; these adverse effects have not been definitely attributed to the drug. These effects probably are due to the drug's α_1 -adrenergic blocking activity.

Hypotension, bradycardia with or without hypotension, tachycardia, and syncope also were reported during the clinical trials with IM olanzapine. In an open trial in nonagitated patients with schizophrenia designed to evaluate the safety and tolerability of a dosage regimen of three 10-mg IM doses of olanzapine administered 4 hours apart, approximately one-third of the patients experienced a substantial orthostatic decrease in systolic blood pressure (i.e., decrease of 30 mm Hg or more).

Syncope was reported in 0.6% of olanzapine-treated patients in phase 2 and 3 clinical trials of oral olanzapine and in 0.3% of patients receiving IM olanzapine in the acute agitation clinical trials. In phase 1 trials of olanzapine, 3 healthy volunteers experienced hypotension, bradycardia, and sinus pauses of up to 6 seconds that spontaneously resolved; 2 of these cases occurred in association with IM olanzapine and one case involved oral olanzapine. In short-term, controlled clinical trials for IM olanzapine for acute agitation, hypotension occurred in approximately 2% and postural hypotension occurred in approximately 1% of the patients. Syncope has been reported in less than 1% of the patients receiving IM olanzapine in clinical trials. The manufacturer states that the risk for this sequence of hypotension, bradycardia, and sinus pause may be greater in nonpsychiatric patients compared with psychiatric patients, who may be more adapted to certain pharmacologic effects of psychotropic agents. (See Dosage and Administration and see also Cardiovascular Effects, under Cautions: Precautions and Contraindications.)

ECG Effects

Pooled analyses from controlled clinical trials did not reveal statistically significant differences in the proportions of olanzapine-treated patients experiencing potentially important ECG changes, including QT, QT_c, and PR intervals. Olanzapine was associated with a mean increase in heart rate of 2.4 beats per minute compared with no change among placebo patients in controlled trials. The manufacturer states that the slight tendency to cause tachycardia may be related to olanzapine's potential for inducing orthostatic changes in blood pressure. Like some other antipsychotic agents, olanzapine has been associated with prolongation of the QT_c interval in some patients and there is some evidence that higher dosages of the drug may increase the risk of QT_c interval prolongation; however, the clinical relevance of these findings remains to be established.

Other Cardiovascular Effects

In short-term, controlled clinical trials for oral olanzapine, chest pain occurred in approximately 3% of patients. Atrial fibrillation, cerebrovascular accident, cardiac arrest, hemorrhage, pallor, palpitation, and ventricular extrasystoles have been reported in less than 1% of patients; these adverse effects have not been definitely attributed to the drug.

Although a causal relationship has not been established, arteritis and heart failure have been reported in less than 0.1% of patients receiving oral olanzapine. In addition, venous thromboembolic effects, including pulmonary embolism and deep venous thrombosis, have been reported in patients receiving olanzapine during postmarketing surveillance.

In controlled clinical trials for IM olanzapine for acute agitation, AV block and heart block have been reported in less than 1% of the patients receiving IM olanzapine.

Hepatic Effects

During premarketing clinical trials, olanzapine therapy was associated with asymptomatic elevations in serum aminotransferase (transaminase) concentrations, including elevations in serum concentrations of ALT (SGPT), AST (SGOT), and γ -glutamyltransferase (GGT). Clinically important ALT elevations (3 or more times the upper limit of the normal range) were observed in 2% (6 of 243) of patients exposed to olanzapine in placebo-controlled clinical studies; none of these patients experienced jaundice. In 2 of these patients, the transaminases decreased toward normal values despite continued therapy, and in 2 other patients, the transaminases decreased upon discontinuance of olanzapine therapy. In the 2 remaining patients, one patient, who was seropositive for hepatitis C, had persistent transaminase elevations for 4 months after discontinuance of therapy, and the other patient had insufficient follow-up to determine whether the transaminase elevation normalized. Within the larger premarketing database of about 2400 patients with baseline ALT values of 90 IU/L or less, the incidence of SGPT elevation exceeding 200 IU/L was 2% (50 of 2381 patients). None of these patients experienced jaundice or other symptoms attributable to hepatic impairment, and most had transient changes that tended to normalize while olanzapine therapy was continued. Among 2500 patients receiving oral olanzapine in clinical trials, about 9% of the patients experienced transient elevations in serum transaminase levels, usually within 1–2 weeks following initiation of therapy, and the median time to maximal levels in these patients was about 4 weeks; olanzapine therapy was discontinued in about 1% (23 of 2500) of the patients because of transaminase elevations. (See Cautions: Precautions and Contraindications.)

Hepatitis has rarely been reported in postmarketing experience, as well as very rare cases of cholestatic or mixed hepatic injury. In addition, fatty deposit in the liver

has been reported in less than 0.1% of patients receiving oral olanzapine in short-term clinical trials, although a causal relationship to the drug remains to be established.

Endocrine and Metabolic Effects Weight Gain

Like some conventional (first-generation) and atypical (second-generation) antipsychotic agents, olanzapine therapy may result in weight gain. In placebo-controlled studies of 6 weeks' duration, weight gain occurred in approximately 6% of patients receiving oral olanzapine, and increased appetite occurred in 3% of patients receiving oral olanzapine in short-term controlled trials. Patients receiving olanzapine in the 6-week, placebo-controlled studies gained an average of 2.8 kg compared with an average loss of 0.4 kg in those receiving placebo; 29% of the olanzapine-treated patients gained greater than 7% of their baseline weight compared with 3% of placebo recipients. Patients with a low body mass index (BMI) in these studies appeared to be more susceptible to olanzapine-induced weight gain than normal or overweight patients, although weight gain was substantially greater in all 3 groups compared with placebo. During long-term continuation therapy with olanzapine, 56% of olanzapine-treated patients gained greater than 7% of their baseline weight; the average weight gain observed during long-term therapy was 5.4 kg.

Although the precise mechanism(s) remains to be clearly established, weight gain may result at least in part from the drug's serotonergic-, histaminergic-, and adrenergic-blocking properties. Weight gain has been reported to be troublesome for some patients during long-term therapy with atypical antipsychotics, particularly olanzapine and clozapine, and may be an important cause of outpatient noncompliance. Some clinicians suggest regular physical exercise and nutritional counseling in the prevention and treatment of weight gain associated with these drugs. There currently are no well established pharmacologic treatments for antipsychotic agent-induced weight gain; however, a number of drugs, including amantadine, bupropion, histamine H₂-receptor antagonists (e.g., nizatidine) orlistat, metformin, sibutramine, and topiramate, have been used with limited success to date. Because the potential risk of adverse effects in patients receiving these drugs may outweigh their possible weight-reducing effects in some cases, routine use of pharmacologic therapy currently is not recommended by most clinicians, although individual patients may benefit. Additional controlled studies are needed to more clearly determine the optimum management of antipsychotic-associated weight gain during long-term therapy with these drugs.

Hyperglycemia and Diabetes Mellitus

Severe hyperglycemia, sometimes associated with ketoacidosis, hyperosmolar coma, or death, has been reported in patients receiving certain atypical antipsychotic agents, including olanzapine. While confounding factors such as an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population make it difficult to establish with certainty the relationship between use of agents in this drug class and glucose abnormalities, epidemiologic studies suggest an increased risk of treatment-emergent hyperglycemia-related adverse events in patients treated with the atypical antipsychotic agents included in the studies (e.g., olanzapine, clozapine, quetiapine, risperidone). (See Cautions: Precautions and Contraindications.)

Precise risk estimates for hyperglycemia-related adverse events in patients treated with atypical antipsychotics currently are not available. While some evidence suggests that the risk for diabetes may be greater with some atypical antipsychotics (e.g., olanzapine, clozapine) than with others (e.g., quetiapine, risperidone) in the class, available data are conflicting and insufficient to provide reliable estimates of relative risk associated with use of the various atypical antipsychotics.

Diabetes mellitus has been reported in less than 1% of patients and diabetic acidosis has been reported in less than 0.1% of patients receiving oral olanzapine in short-term, controlled clinical trials.

Hyperlipidemia

Like some other antipsychotic agents, particularly clozapine, olanzapine therapy has been associated with hyperlipidemia, including elevations in serum triglyceride and cholesterol concentrations.

In clinical trials in olanzapine-treated patients with random triglyceride concentrations of less than 150 mg/dL at baseline, 0.5% of patients experienced elevated triglyceride concentrations of 500 mg/dL or higher at any time, and severely elevated triglyceride concentrations of 1000 mg/dL or more have been reported rarely during postmarketing surveillance. During the same trials, olanzapine-treated patients experienced a mean increase of 20 mg/dL in triglyceride concentrations from a mean baseline value of 175 mg/dL.

In placebo-controlled trials, olanzapine-treated patients who had random cholesterol concentrations of less than 200 mg/dL at baseline experienced elevated cholesterol concentrations of 240 mg/dL or higher at any time during the trials more frequently than those receiving placebo (approximately 4% and 2% of patients, respectively). In these trials, olanzapine-treated patients had a mean increase of 0.4 mg/dL in serum cholesterol concentrations while those receiving placebo had a mean decrease of 4.6 mg/dL, both from a mean baseline value of 203 mg/dL.

Hypercholesterolemia and hyperlipidemia have been reported in less than 1% of patients receiving oral olanzapine in short-term trials. In addition, cholesterol concentration of 240 mg/dL or higher have been reported rarely during postmarketing surveillance.

Although the manufacturer currently does not recommend routine monitoring of lipid parameters in patients receiving olanzapine, the APA recommends a baseline

lipid panel in all patients with schizophrenia and recommends that this be repeated at least every 5 years. In addition, some clinicians recommend that lipid profiles be monitored at baseline and periodically (e.g., every 3–6 months) in all patients receiving long-term therapy with atypical antipsychotic agents. There is some evidence from a study in individuals with developmental disabilities that the risk of hyperlipidemia in patients receiving atypical antipsychotic agents may be minimized or avoided by careful monitoring, dietary management, and suitable physical activity. In patients who develop persistent and clinically important hyperlipidemia during olanzapine therapy, nondrug therapies and measures (e.g., dietary management, weight control, an appropriate program of physical activity) and drug therapy (e.g., antilipemic agents) may be helpful. Consideration also may be given to switching to an alternative antipsychotic agent that is less frequently associated with hyperlipidemia (such as aripiprazole, risperidone, or ziprasidone).

Hyperprolactinemia

As with other drugs that antagonize dopamine D₂ receptors, olanzapine can elevate serum prolactin concentrations, and a modest elevation may persist during chronic administration of the drug. However, in contrast to conventional (first-generation) antipsychotic agents and similar to many other atypical antipsychotic agents, olanzapine therapy in usual dosages generally produces relatively modest and transient elevations in serum prolactin concentrations in humans. It has been suggested that the more transient effect of atypical antipsychotic agents on prolactin may be because these drugs appear to dissociate from dopamine receptors more rapidly than conventional antipsychotic agents.

Olanzapine is considered by many experts to be low in its potential for inducing hyperprolactinemia, and it has been recommended along with other prolactin-sparing atypical antipsychotics (e.g., aripiprazole, clozapine, quetiapine, ziprasidone) in patients with schizophrenia who are at risk of hyperprolactinemia. Although clinical disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been associated with prolactin-elevating drugs, the clinical importance of elevated prolactin concentrations is unknown for most patients.

Like other drugs that increase prolactin, an increase in mammary gland neoplasia was observed in olanzapine carcinogenicity studies conducted in mice and rats. However, neither clinical studies nor epidemiologic studies have demonstrated an association between chronic administration of dopamine antagonists and tumorigenesis in humans; the available evidence is considered too limited to be conclusive. (See Cautions: Precautions and Contraindications and see also Cautions: Mutagenicity and Carcinogenicity.) In patients who develop elevated prolactin concentrations during antipsychotic therapy, some clinicians recommend reducing the dosage of the current antipsychotic agent or switching to a prolactin-sparing antipsychotic agent. Dopamine receptor agonists (e.g., bromocriptine) also may be helpful, and estrogen replacement therapy may be considered in hypoestrogenic female patients.

Other Endocrine and Metabolic Effects

Peripheral edema has been reported in approximately 3% of patients receiving oral olanzapine in short-term clinical trials. Acidosis, increased serum alkaline phosphatase concentrations, bilirubinemia, dehydration, hypoglycemia, hypokalemia, hyponatremia, lower extremity edema, and upper extremity edema have been reported in less than 1% of patients receiving oral olanzapine in short-term trials; however, a causal relationship remains to be established. Goiter, gout, hyperkalemia, hypernatremia, hypoproteinemia, ketosis, and water intoxication have been reported in less than 0.1% of patients receiving oral olanzapine; these adverse effects have not been definitely attributed to the drug.

Adverse metabolic effects that have been reported in less than 1% of patients receiving IM olanzapine in short-term clinical trials include increased serum creatine phosphokinase concentrations, dehydration, and hyperkalemia; however, a causal relationship remains to be established.

GI Effects

Dryness of the mouth and constipation both occurred in about 9%, dyspepsia in about 7%, vomiting in about 4%, and increased appetite in about 3% of patients receiving oral olanzapine in short-term controlled clinical trials.

Flatulence, increased salivation, and thirst have been reported in at least 1% of patients receiving oral olanzapine in short-term clinical trials. Dysphagia, esophagitis, fecal impaction, fecal incontinence, gastritis, gastroenteritis, gingivitis, melena, mouth ulceration, nausea and vomiting, oral moniliasis, periodontal abscess, rectal hemorrhage, stomatitis, tongue edema, and tooth caries have been reported in less than 1% of olanzapine-treated patients; these adverse effects have not been definitely attributed to the drug.

Abdominal pain, diarrhea, and nausea have been reported in less than 1% of patients receiving IM olanzapine in clinical trials; these adverse effects have not been definitely attributed to the drug.

Aphthous stomatitis, enteritis, eructation, esophageal ulcer, glossitis, ileus, intestinal obstruction, and tongue discoloration have been reported in less than 0.1% of patients receiving oral olanzapine in short-term clinical trials, although a causal relationship to the drug remains to be established.

Respiratory Effects

Rhinitis occurred in about 7%, increased cough in about 6%, and pharyngitis in about 4% of patients receiving oral olanzapine in short-term controlled clinical trials. Dyspnea has been reported in at least 1% of patients receiving oral olanzapine in short-

term clinical trials. Apnea, asthma, epistaxis, hemoptysis, hyperventilation, hypoxia, laryngitis, and voice alteration have been reported in less than 1% of olanzapine-treated patients; these adverse effects have not been definitely attributed to the drug. In addition, dyspnea and hyperventilation, which appeared to be dose related, have been reported together in a patient treated with oral olanzapine.

Atelectasis, hiccup, hypoventilation, lung edema, and stridor have been reported in less than 0.1% of patients receiving oral olanzapine; however, a causal relationship to the drug has not been clearly established. Respiratory failure developed in a geriatric individual with chronic lung disease who was receiving olanzapine therapy; although not clearly established, it was suggested that the respiratory failure was due at least in part to the sedative effect of the drug.

Dermatologic and Sensitivity Reactions

Sweating has been reported in at least 1% of patients receiving oral olanzapine and in less than 1% of patients receiving IM olanzapine in short-term clinical trials. Alopecia, contact dermatitis, dry skin, eczema, maculopapular rash, photosensitivity reaction, pruritus, seborrhea, skin discoloration (e.g., hyperpigmentation), skin ulcer, urticaria, and vesiculobullous rash have been reported in less than 1% of olanzapine-treated patients; these adverse effects have not been definitely attributed to the drug. Hirsutism and pustular rash have been reported in less than 0.1% of patients receiving oral olanzapine; however, a causal relationship to the drug has not been clearly established.

Allergic reactions (e.g., anaphylactoid reaction, angioedema, pruritus, urticaria) have been reported during postmarketing surveillance of olanzapine. In addition, a hypersensitivity syndrome consisting of a severe and generalized pruritic eruption, fever, eosinophilia, and toxic hepatitis has been reported in at least one olanzapine-treated patient; the manifestations improved following discontinuance of the drug, and skin and liver biopsy results suggested that the hypersensitivity syndrome was caused by olanzapine. Eruptive xanthomas, which are associated with hyperlipidemia, have occurred in several patients receiving olanzapine therapy. Leukocytoclastic vasculitis also has been reported in a geriatric patient receiving olanzapine and warfarin concurrently; the vasculitis improved following discontinuance of olanzapine in this patient but recurred when the drug was subsequently reintroduced.

Local Effects

Pain at the injection site also has been reported in at least 1% of patients receiving IM olanzapine in controlled clinical trials.

Genitourinary Effects

Urinary incontinence and urinary tract infection both have been reported in approximately 2% and vaginitis has been reported in at least 1% of patients receiving oral olanzapine in short-term controlled clinical trials, although a causal relationship to the drug remains to be established. Abnormal ejaculation, amenorrhea, breast pain, cystitis, decreased menstruation, dysuria, female lactation, glycosuria, gynecomastia, and hematuria have been reported in less than 1% of olanzapine-treated patients; these adverse effects have not been definitely attributed to the drug.

Impotence, increased menstruation, menorrhagia, metrorrhagia, polyuria, premenstrual syndrome, pyuria, urinary frequency, urinary retention, urinary urgency, impaired urination, enlarged uterine fibroids, and vaginal hemorrhage have been reported in less than 1% of patients receiving oral olanzapine in short-term clinical trials; however, a causal relationship to the drug remains to be established. Albuminuria, breast enlargement, mastitis, and oliguria have been reported in less than 0.1% of patients receiving oral olanzapine; however, these adverse effects have not been definitely attributed to the drug.

Priapism also has been reported in several male patients and at least one case of clitoral priapism has been reported in a female patient. The α -adrenergic blocking effect of olanzapine appears to be responsible for this rare but potentially serious adverse effect requiring immediate medical attention to prevent long-term consequences such as erectile dysfunction.

Musculoskeletal Effects

Joint pain, back pain, and extremity (other than joint) pain have been reported in 5% and joint stiffness and muscle twitching in more than 1% of patients receiving oral olanzapine; muscle twitching also has been reported in less than 1% of patients receiving IM olanzapine in short-term controlled clinical trials. Arthritis, arthrosis, leg cramps, and myasthenia have been reported in less than 1% of olanzapine-treated patients; these adverse effects have not been definitely attributed to the drug. Bone pain, bursitis, myopathy, osteoporosis, and rheumatoid arthritis have been reported in less than 0.1% of patients receiving oral olanzapine; however, a causal relationship to the drug has not been clearly established. Rhabdomyolysis also has been reported rarely in olanzapine-treated patients and may be seen as one of the clinical features of NMS. (See Neuroleptic Malignant Syndrome in Cautions: Nervous System Effects.)

Ocular and Otic Effects

Amblyopia has been reported in 3% of patients, and conjunctivitis has been reported in at least 1% of patients receiving oral olanzapine in short-term clinical trials; however, a causal relationship to the drug for these effects remains to be established. Accommodation abnormality, blepharitis, cataract, deafness, diplopia, dry eyes, ear pain, eye hemorrhage, eye inflammation, eye pain, ocular muscle abnormality, and tinnitus have been reported in less than 1% of olanzapine-treated patients; these adverse effects have not been definitely attributed to the drug. In addition, corneal lesion, glaucoma, keratoconjunctivitis, macular hypopigmentation, myopia, mydriasis, and pigment

deposits in the eye lens have been reported in less than 0.1% of patients receiving oral olanzapine; however, a causal relationship to the drug has not been clearly established.

Hematologic Effects

Because of concern about neutropenia associated with other psychotropic agents (e.g., clozapine) and the finding of leukopenia associated with the administration of olanzapine in several animal models, hematologic parameters were carefully evaluated during premarketing clinical trials with olanzapine. There was no indication of a risk of clinically important neutropenia in olanzapine-treated patients in the premarketing database for the drug.

Ecchymosis has been reported in 5% of patients receiving oral olanzapine in short-term clinical trials; however, a causal relationship to the drug remains to be established. Anemia has been reported in less than 1% of patients receiving oral or IM olanzapine; this adverse effect has not been definitely attributed to the drug. Cyanosis, leukocytosis, leukopenia, lymphadenopathy, and thrombocytopenia have been reported in less than 1% of patients receiving oral olanzapine; however, a causal relationship to the drug remains to be established.

During premarketing clinical trials, asymptomatic elevation of the eosinophil count was reported in approximately 0.3% of patients receiving oral olanzapine. In addition, normocytic anemia and thrombocytopenia have been reported in less than 0.1% of patients receiving oral olanzapine; however, a causal relationship to the drug has not been clearly established.

Other Adverse Effects

Accidental injury has been reported in approximately 12% of patients receiving oral olanzapine in short-term controlled trials. Fever has been reported in approximately 6% of patients receiving oral olanzapine and in less than 1% of patients receiving IM olanzapine in short-term clinical trials. Dental pain and flu syndrome have been reported in at least 1% of patients receiving oral olanzapine in short-term clinical trials; however, a causal relationship to the drug remains to be established. Enlarged abdomen, chills, facial edema, intentional injury, malaise, moniliasis, neck pain, neck rigidity, pelvic pain, and taste perversion have been reported in less than 1% of oral olanzapine-treated patients; these adverse effects have not been definitely attributed to the drug. In addition, chills accompanied by fever, hangover effect, and sudden death have been reported in less than 0.1% of patients receiving oral olanzapine; however, a causal relationship to the drug has not been clearly established.

Pancreatitis, which has been fatal in some cases, has occurred rarely in patients receiving atypical antipsychotic agents, including olanzapine, clozapine, and risperidone. In most of these cases, pancreatitis developed within 6 months of initiation of atypical antipsychotic therapy. Although the precise mechanism for this effect remains to be established, it has been suggested that it may be due at least in part to the adverse metabolic effects associated with these drugs.

■ Precautions and Contraindications

Pending revision, the material in this section should be considered in light of more recently available information in the MedWatch notification at the beginning of this monograph.

Olanzapine shares many of the toxic potentials of other antipsychotic agents (e.g., other atypical antipsychotic agents, phenothiazines), and the usual precautions associated with therapy with these agents should be observed. (See Cautions, in the Phenothiazines General Statement 28:16.08.24.)

When olanzapine is used in fixed combination with fluoxetine, the usual cautions, precautions, and contraindications associated with fluoxetine must be considered in addition to those associated with olanzapine.

Somnolence

Dose-related somnolence occurred in 26% of patients receiving oral olanzapine compared with 15% of those receiving placebo, and resulted in discontinuance of the drug in 0.4% of the patients in the premarketing database. Because of sedative effects of the drug and because it potentially may impair judgment, thinking, and motor skills, patients should be cautioned that olanzapine may impair their ability to perform activities requiring mental alertness or physical coordination (e.g., operating machinery, driving a motor vehicle) until they are reasonably certain that olanzapine does not adversely affect them.

Seizures

Although seizures occurred in about 0.9% of patients receiving oral olanzapine in controlled clinical trials during premarketing testing, it should be noted that confounding factors that may have contributed to the occurrence of seizures were present in many of these cases. Olanzapine should be administered with caution to patients with a history of seizures, patients with conditions known to lower the seizure threshold (e.g., Alzheimer's disease, geriatric patients), and during concurrent therapy with drugs that may lower the seizure threshold.

Body Temperature Regulation

Because disruption of the body's ability to reduce core body temperature has been associated with the use of antipsychotic agents, caution is advised when olanzapine is administered in patients exposed to conditions that may contribute to an elevation in core body temperature. Such conditions include strenuous exercise, exposure to extreme heat, concomitant use of drugs with anticholinergic activity, or dehydration. Patients receiving olanzapine should be advised to avoid overheating and dehydration.

Hepatic Effects

Because clinically important serum ALT elevations (3 or more times the upper limit of the normal range) were observed in about 2% of patients exposed to oral olanzapine in placebo-controlled clinical studies, the manufacturer states that olanzapine should be used with caution in patients with signs and symptoms of hepatic impairment, in patients with preexisting conditions associated with limited hepatic functional reserve, and in patients who are being treated concurrently with potentially hepatotoxic drugs. In addition, periodic assessment of transaminases is recommended in patients with clinically important hepatic disease.

Individuals with Phenylketonuria

Individuals with phenylketonuria (i.e., homozygous genetic deficiency of phenylalanine hydroxylase) and other individuals who must restrict their intake of phenylalanine should be warned that olanzapine 5, 10, 15, or 20 mg orally disintegrating tablets contain aspartame (e.g., NutraSweet®), which is metabolized in the GI tract to provide about 0.34, 0.45, 0.67, or 0.9 mg of phenylalanine, respectively, following oral administration.

Dysphagia

Because esophageal dysmotility and aspiration sometimes resulting in death have been associated with the use of antipsychotic agents, olanzapine and other antipsychotic agents should be used with caution in patients at risk for aspiration pneumonia.

Aspiration pneumonia is a common cause of morbidity and mortality in patients with advanced Alzheimer's disease.

Suicide

Because the possibility of a suicide attempt is inherent in patients with schizophrenia and bipolar disorder, close supervision of high-risk patients is recommended during olanzapine therapy. The manufacturer recommends that the drug be prescribed in the smallest quantity consistent with good patient management to reduce the risk of overdose.

Patients with Concomitant Illness

Clinical experience with olanzapine in patients with certain concurrent systemic diseases is limited. Olanzapine has demonstrated anticholinergic activity in vitro and constipation, dryness of the mouth, and tachycardia, possibly related to the drug's anticholinergic effects, have occurred in premarketing clinical trials. Although these adverse effects did not often result in drug discontinuance, the manufacturer states that olanzapine should be used with caution in patients with clinically important prostatic hypertrophy, angle-closure glaucoma, or a history of paralytic ileus.

Olanzapine has not been adequately evaluated in patients with a recent history of myocardial infarction or unstable cardiovascular disease to date and patients with these conditions were excluded from premarketing clinical trials. Because of the risk of orthostatic hypotension associated with olanzapine, the manufacturer states that the drug should be used with caution in patients with cardiovascular disease. (See Cautions: Cardiovascular Effects.)

Concomitant Medication or Alcohol Use

Because of the potential for adverse drug interactions, the manufacturer recommends that patients receiving olanzapine be advised to notify their clinician if they are taking or plan to take any prescription or nonprescription (over-the-counter) medications. The manufacturer also recommends that patients be advised to avoid alcohol while receiving the drug. (See Drug Interactions.)

Neuroleptic Malignant Syndrome

Neuroleptic malignant syndrome (NMS), a potentially fatal syndrome requiring immediate discontinuance of the drug and intensive symptomatic treatment, has been reported in patients receiving antipsychotic agents, including olanzapine. If a patient requires antipsychotic therapy following recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. If antipsychotic therapy is reintroduced, the dosage generally should be increased gradually, and an antipsychotic agent other than the agent believed to have precipitated NMS generally should be chosen. In addition, such patients should be carefully monitored since recurrences of NMS have been reported in some patients. (See Neuroleptic Malignant Syndrome in Cautions: Nervous System Effects.)

Tardive Dyskinesia

Because use of antipsychotic agents may be associated with tardive dyskinesia, a syndrome of potentially irreversible, involuntary, dyskinetic movements, olanzapine should be prescribed in a manner that is most likely to minimize the occurrence of this syndrome. Chronic antipsychotic treatment generally should be reserved for patients who suffer from a chronic illness that is known to respond to antipsychotic agents, and for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought, and the need for continued treatment should be reassessed periodically.

The APA currently recommends that patients receiving second-generation antipsychotic agents be assessed clinically for abnormal involuntary movements every 12 months and that patients considered to be at increased risk for tardive dyskinesia be assessed every 6 months. (See Tardive Dyskinesia in Cautions: Nervous System Effects.)

Dispensing and Administration Precautions

Because of similarities in spelling, dosage intervals (once daily), and tablet strengths (5 and 10 mg) of Zyprexa® (the trade name for olanzapine) and Zyrtec® (the trade name for cetirizine hydrochloride, an antihistamine), special dispensing or prescribing errors

have been reported to the manufacturer of Zyprexa[®]. These medication errors may result in unnecessary adverse events or a potential relapse in patients with schizophrenia or bipolar disorder. Therefore, the manufacturer of Zyprexa[®] cautions that extra care should be exercised in ensuring the accuracy of written prescriptions for Zyprexa[®] and Zyrtec[®] such as printing both the proprietary (brand) and nonproprietary (generic) names on all prescriptions for these drugs. The manufacturer also recommends that pharmacists assess various measures of avoiding dispensing errors and implement them as appropriate (e.g., placing drugs with similar names apart from one another on pharmacy shelves, patient counseling).

Cardiovascular Effects

Orthostatic hypotension associated with dizziness, tachycardia, and/or syncope, particularly during the initial dosage titration period, has been reported in patients receiving oral olanzapine therapy. The risk of orthostatic hypotension and syncope may be minimized by initiating therapy with a dosage of 5 mg orally once daily. A more gradual titration to the target dose should be considered if hypotension occurs. Patients should be cautioned about the risk of orthostatic hypotension, particularly during the initial dosage titration period and if the drug is given concurrently with drugs that may potentiate the orthostatic effect of olanzapine, including diazepam, or alcohol.

Hypotension, bradycardia with or without hypotension, tachycardia, and syncope have been reported in patients receiving IM olanzapine. The use of maximum recommended dosages of IM olanzapine (i.e., 3 doses of 10 mg each given IM 2–4 hours apart) may be associated with a substantial risk of clinically important orthostatic hypotension. Patients who experience drowsiness or dizziness after the IM injection should remain recumbent until an examination indicates that they are not experiencing orthostatic hypotension, bradycardia, and/or hypoventilation. Patients requiring additional IM injections of olanzapine should be assessed for orthostatic hypotension prior to administration of any subsequent doses. Administration of additional IM doses to patients with clinically important postural change in blood pressure is not recommended.

The manufacturer states that olanzapine should be used with caution in patients with known cardiovascular disease (e.g., history of myocardial infarction or ischemia, heart failure, conduction abnormalities), cerebrovascular disease, and/or other conditions that would predispose patients to hypotension (e.g., dehydration, hypovolemia, concomitant antihypertensive therapy) where the occurrence of syncope, hypotension, and/or bradycardia might put the patient at increased risk. The manufacturer also states that the drug should be used with caution in patients receiving other drugs that can induce hypotension, bradycardia, or respiratory and CNS depression. (See Drug Interactions.) Concurrent administration of IM olanzapine and parenteral benzodiazepines has not been well studied; therefore, combined use of these drugs is not recommended. If use of IM olanzapine in combination with parenteral benzodiazepine therapy is considered, careful evaluation of the patient's clinical status for excessive sedation and cardiorespiratory depression is recommended.

Hyperglycemia and Diabetes Mellitus

Because severe hyperglycemia, sometimes associated with ketoacidosis, hyperosmolar coma, or death, has been reported in patients receiving certain atypical antipsychotic agents, including olanzapine, the manufacturers state that patients with preexisting diabetes mellitus in whom therapy with an atypical antipsychotic is initiated should be closely monitored for worsening of glucose control; those with risk factors for diabetes (e.g., obesity, family history of diabetes) should undergo fasting blood glucose testing upon therapy initiation and periodically throughout treatment. Any patient who develops manifestations of hyperglycemia (e.g., polydipsia, polyphagia, polyuria, weakness) during treatment with an atypical antipsychotic should undergo fasting blood glucose testing. In some cases, patients who developed hyperglycemia while receiving an atypical antipsychotic have required continuance of antidiabetic treatment despite discontinuance of the suspect drug; in other cases, hyperglycemia resolved with discontinuance of the antipsychotic or with continuance of both the suspect drug and initiation of antidiabetic treatment.

Various experts have developed additional recommendations for the management of diabetes risks in patients receiving atypical antipsychotics; these include initial screening measures and regular monitoring (e.g., determination of diabetes risk factors; BMI determination using weight and height; waist circumference; blood pressure; fasting blood glucose; hemoglobin A_{1c} [HbA_{1c}]; fasting lipid profile), as well as provision of patient education and referral to clinicians experienced in the treatment of diabetes, when appropriate. Although some clinicians state that a switch from one atypical antipsychotic agent to another that has not been associated with substantial weight gain or diabetes should be considered in patients who experience weight gain (equal to or exceeding 5% of baseline body weight) or develop worsening glycemia or dyslipidemia at any time during therapy, such recommendations are controversial because differences in risk of developing diabetes associated with use of the different atypical antipsychotics remain to be fully established. Many clinicians consider antipsychotic efficacy the most important factor when making treatment decisions and suggest that detrimental effects of switching from a beneficial treatment regimen also should be considered in addition to any potential for exacerbation or development of medical conditions (e.g., diabetes). Decisions to alter drug therapy should be made on an individual basis, weighing the potential risks and benefits of the particular drug in each patient.

Contraindications

Olanzapine is contraindicated in patients with a known hypersensitivity to the drug. (See Cautions: Dermatologic and Sensitivity Reactions.)

Pediatric Precautions

Pending revision, the material in this section should be considered in light of more recently available information in the MedWatch notification at the beginning of this monograph.

The manufacturer states that safety and efficacy of olanzapine in children and adolescents younger than 18 years of age have not been established. However, the drug has been used in a limited number of children and adolescents with childhood-onset schizophrenia (see Pediatric Considerations under Psychotic Disorders: Schizophrenia, in Uses). In a double-blind, placebo-controlled trial of 6 weeks' duration conducted in 107 adolescents 13–17 years of age with schizophrenia, olanzapine was effective in the management of schizophrenia, but results indicated that the drug's effects on weight and prolactin concentrations may be greater in adolescents.

Olanzapine also has been effective and well tolerated in a limited number of children and adolescents with bipolar disorder (see Pediatric Considerations under Bipolar Disorder, in Uses) and pervasive developmental disorder, including autistic disorder. In a double-blind, placebo-controlled, 3-week study in 107 adolescents 13–17 years of age with bipolar disorder, olanzapine was found to be effective in the treatment of acute manic or mixed episodes; however, weight gain and hyperprolactinemia occurred more often in patients receiving olanzapine compared with those receiving placebo. Additional controlled and longer-term studies are needed to confirm these initial findings and to evaluate the relative benefits and risks of olanzapine therapy in pediatric patients.

As in adults, olanzapine therapy may be associated with weight gain in pediatric patients (see Cautions: Endocrine and Metabolic Effects). The American Academy of Child and Adolescent Psychiatry (AACAP) currently recommends that pediatric patients who experience weight gain associated with olanzapine or other agents be monitored closely for potential medical consequences associated with weight gain (e.g., diabetes mellitus, hyperlipidemia, elevations in serum transaminase concentrations) and be referred for exercise and nutritional counseling. (See Hyperglycemia and Diabetes Mellitus under Cautions: Precautions and Contraindications.)

Geriatric Precautions

Although clinical experience in patients with schizophrenia generally has not revealed age-related differences in safety of olanzapine, lower initial dosages and slower titration during the initial dosing period may be advisable in some geriatric patients.

The first phase of the large-scale Clinical Antipsychotic Trials of Intervention Effectiveness—Alzheimer's Disease (CATIE-AD) trial was designed to evaluate the overall effectiveness of atypical antipsychotic agents in the treatment of psychosis, aggression, and agitation associated with Alzheimer's disease. Patients in this multicenter, double-blind, placebo-controlled trial were randomized to receive either olanzapine, quetiapine, risperidone, or placebo for up to 36 weeks; the principal outcomes were the time from initial treatment until discontinuance of treatment for any reason and the number of patients with at least minimum improvement on the Clinical Global Impression of Change (CGIC) Scale at 12 weeks. No statistically significant differences were found among the 4 groups with regard to the time until discontinuation of treatment for any reason; patients remained on olanzapine, quetiapine, risperidone, and placebo for median times of approximately 8, 5, 7, and 8 weeks, respectively. In addition, no significant differences in CGIC Scale improvements were noted. However, patients receiving atypical antipsychotic therapy reportedly experienced more frequent adverse effects (e.g., drowsiness, weight gain, adverse extrapyramidal effects, confusion, and psychotic symptoms) compared with those receiving placebo. The authors stated that these results indicate that the overall therapeutic benefit of atypical antipsychotics in patients with Alzheimer's disease may be offset by the potential risk of adverse effects.

Studies in patients with dementia-related psychosis have suggested that there may be a different tolerability profile in patients 65 years of age or older with this condition compared with younger patients with schizophrenia. Geriatric patients with dementia-related psychosis receiving atypical antipsychotics including olanzapine appear to be at an increased risk of death compared with that among patients receiving placebo. Analyses of 17 placebo-controlled trials (average duration of 10 weeks) revealed an approximate 1.6- to 1.7-fold increase in mortality among geriatric patients receiving atypical antipsychotic drugs (i.e., olanzapine, aripiprazole, quetiapine, risperidone) compared with that in patients receiving placebo. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5% compared with a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature.

In placebo-controlled trials with olanzapine in geriatric individuals with dementia-related psychosis, an increased incidence of death also was observed; the incidence of death in olanzapine-treated patients was significantly higher than in patients receiving placebo (3.5% and 1.5%, respectively). In addition, a significantly higher incidence of adverse cerebrovascular effects (e.g., stroke, transient ischemic attack), including fatalities, was observed in patients receiving olanzapine compared with those receiving placebo in these trials. In 5 placebo-controlled studies of olanzapine in geriatric individuals with dementia-related psychosis, certain treatment-emergent adverse effects, including falls, somnolence, peripheral edema, abnormal gait, urinary incontinence, lethargy, increased weight, asthenia, pyrexia, pneumonia, dry mouth, and visual hallucinations, occurred in at least 2% of the patients, and the incidence was significantly

higher than in patients receiving placebo. Discontinuance of therapy because of adverse effects occurred in a significantly higher number of olanzapine-treated patients than in those receiving placebo (13% and 7%, respectively) in these studies.

The manufacturer states that olanzapine is *not* approved for the treatment of patients with dementia-related psychosis. Some clinicians recommend that the potential risks, therapeutic benefits, and individual needs of patients be carefully considered prior to prescribing olanzapine and other atypical antipsychotic agents for the management of behavioral problems associated with Alzheimer's disease. If a clinician decides to treat geriatric patients with dementia-related psychosis with olanzapine, the manufacturer recommends that caution be exercised. For additional information on the use of antipsychotic agents in the management of dementia-related psychosis, see Geriatric Considerations under Uses: Psychotic Disorders, in the Phenothiazines General Statement 28:16.08.24.

■ Mutagenicity and Carcinogenicity

Olanzapine did not exhibit mutagenic potential in the Ames reverse mutation test, in vivo micronucleus mutation test in mice, the chromosomal aberration test in Chinese hamster ovary cells, unscheduled DNA synthesis test in rat hepatocytes, induction of forward mutation test in mouse lymphoma cells, or in vivo sister chromatid exchange test in bone marrow of Chinese hamsters.

In oral carcinogenicity studies conducted in mice, olanzapine was administered in 2 studies of 78-weeks' duration at dosages of 3, 10, and 30 mg/kg (later reduced to 20 mg/kg) initially then reduced to 20 mg/kg daily (equivalent to 0.8–5 times the maximum recommended human daily oral dosage on a mg/m² basis) and 0.25, 2, and 8 mg/kg daily (equivalent to 0.06–2 times the maximum recommended human daily oral dosage on a mg/m² basis). In oral carcinogenicity studies conducted in rats, olanzapine was administered for 2 years at dosages of 0.25, 1, 2.5, and 4 mg/kg daily in males (equivalent to 0.13–2 times the maximum recommended human daily oral dosage on a mg/m² basis) and 0.25, 1, 4, and 8 mg/kg daily in females (equivalent to 0.13–4 times the maximum recommended human daily oral dosage on a mg/m² basis). An increased incidence of liver hemangiomas and hemangiosarcomas was observed in one mouse study in female mice receiving 8 mg/kg of the drug daily (equivalent to 2 times the maximum recommended human daily oral dosage on a mg/m² basis). The incidence of these tumors was not increased in another study in female mice receiving 10 or 30 mg/kg (later reduced to 20 mg/kg) of olanzapine daily (equivalent to 2–5 times the maximum recommended human daily oral dosage on a mg/m² basis); in this study, there was a high incidence of early mortalities in males in the 30 mg/kg (later reduced to 20 mg/kg) daily group. The incidence of mammary gland adenomas and adenocarcinomas was increased in female mice receiving 2 mg/kg or more of olanzapine daily and in female rats receiving 4 mg/kg or more of the drug daily (equivalent to 0.5 and 2 times the maximum recommended human daily oral dosage on a mg/m² basis, respectively).

Antipsychotic agents have been shown to chronically elevate prolactin concentrations in rodents. Serum prolactin concentrations were not measured during the olanzapine carcinogenicity studies; however, measurements during subchronic toxicity studies demonstrated that olanzapine administration produced up to a fourfold increase in serum prolactin concentrations in rats receiving the same dosages used in the carcinogenicity study. In addition, an increase in mammary gland neoplasms has been observed in rodents following chronic administration of other antipsychotic agents and generally is considered to be prolactin-mediated. However, the clinical importance in humans of this finding of prolactin-mediated endocrine tumors in rodents is unknown.

■ Pregnancy, Fertility, and Lactation

Pregnancy

Limited experience to date with olanzapine administration during pregnancy has been encouraging and has not revealed evidence of any obvious teratogenic risks; however, additional cases of olanzapine exposure during pregnancy need to be evaluated to more fully determine the relative safety of olanzapine and other antipsychotic agents when administered during pregnancy. The manufacturer states that there have been 7 pregnancies reported during clinical trials with olanzapine, including 2 resulting in normal births, one resulting in neonatal death due to a cardiovascular defect, 3 therapeutic abortions, and one spontaneous abortion. In a separate compilation of pregnancy exposures to olanzapine reported to the manufacturer during clinical trials and from spontaneous reports worldwide, outcomes were available from 23 prospectively-collected olanzapine-exposed pregnancies. Spontaneous abortion occurred in 13% of these pregnancies, stillbirth in 5%, major malformations in 0%, and prematurity in 5%; these rates were all within the range of normal historical control rates. In 11 retrospectively collected, olanzapine-exposed pregnancies, there was one case of dysplastic kidney, one case of Down's syndrome, and one case of heart murmur and sudden infant death syndrome at 2 months of age. In another study, the majority of women with schizophrenia receiving atypical antipsychotic agents were found to be overweight and to have reduced folate intake and low serum folate concentrations, which may increase the potential risk of neural tube defects. In a prospective, comparative trial assessing pregnancy outcome in women receiving atypical antipsychotic agents (olanzapine, clozapine, risperidone, and quetiapine) during pregnancy, atypical antipsychotics did not appear to be associated with an increased risk of major congenital malformations. In addition, several case reports have described healthy infants born to women without complications despite prenatal exposure to olanzapine.

The manufacturer and some clinicians state that there are no adequate and well-controlled studies to date using olanzapine in pregnant women, and the drug should be used during pregnancy only when the potential benefits justify the potential risks to the fetus. Women should be advised to notify their clinician if they become pregnant or plan to become pregnant during therapy with the drug.

Parturition in rats was not affected by olanzapine. The effect of olanzapine on labor and delivery is unknown.

In oral reproduction studies in rats receiving dosages of up to 18 mg/kg daily and in rabbits at dosages of up to 30 mg/kg daily (equivalent to 9 and 30 times the maximum recommended human daily oral dosage on a mg/m² basis, respectively), no evidence of teratogenicity was observed. In an oral rat teratology study, early resorptions and increased numbers of nonviable fetuses were observed at a dosage of 18 mg/kg daily (9 times the maximum recommended human daily oral dosage on a mg/m² basis), and gestation was prolonged at a dosage of 10 mg/kg daily (equivalent to 5 times the maximum recommended human daily oral dosage on a mg/m² basis). In an oral rabbit teratology study, fetal toxicity, which was manifested as increased resorptions and decreased fetal weight, occurred at a maternally toxic dosage of 30 mg/kg daily (equivalent to 30 times the maximum recommended human daily oral dosage on a mg/m² basis).

Fertility

In an oral fertility and reproductive performance study in rats, male mating performance, but not fertility, was impaired at an olanzapine dosage of 22.4 mg/kg daily, and female fertility was decreased at a dosage of 3 mg/kg daily (equivalent to 11 and 1.5 times the maximum recommended human daily oral dosage on a mg/m² basis, respectively). Discontinuance of olanzapine administration reversed the effects on male mating performance. In a female rat fertility study, the precoital period was increased, and the mating index reduced at a dosage of 5 mg/kg daily (equivalent to 2.5 times the maximum recommended human daily oral dosage on a mg/m² basis). Diestrus was prolonged and estrus was delayed at a dosage of 1.1 mg/kg daily (equivalent to 0.6 times the maximum recommended human daily oral dosage on a mg/m² basis).

Lactation

Olanzapine is distributed into milk. The mean dosage received by an infant at steady state is estimated to be about 1.8% of the maternal dosage. The manufacturer recommends that women receiving olanzapine not breast-feed.

Drug Interactions

■ Drugs Affecting Hepatic Microsomal Enzymes

Olanzapine is a substrate for cytochrome P-450 (CYP) isoenzyme 1A2 and concomitant administration of drugs that induce CYP1A2 or glucuronyl transferase enzymes (e.g., carbamazepine, omeprazole, rifampin) may cause an increase in olanzapine clearance. Inhibitors of CYP1A2 (e.g., fluvoxamine) could potentially inhibit olanzapine clearance. Although olanzapine is metabolized by multiple enzyme systems, induction or inhibition of a single enzyme may appreciably alter olanzapine clearance. Therefore, an increase or decrease in olanzapine dosage may be necessary during concomitant administration of olanzapine with specific drugs that induce or inhibit olanzapine metabolism, respectively.

Carbamazepine

Carbamazepine therapy (200 mg twice daily for 2 weeks) causes an approximately 50% increase in the clearance of a single, 10-mg dose of olanzapine. The manufacturer of olanzapine states that higher dosages of carbamazepine may cause an even greater increase in olanzapine clearance. Increased clearance of olanzapine probably is caused by carbamazepine-induced induction of CYP1A2 activity.

Selective Serotonin-reuptake Inhibitors

Concomitant administration of fluoxetine (60 mg as a single dose or 60 mg daily for 8 days) with a single 5-mg dose of oral olanzapine caused a small increase in peak plasma olanzapine concentrations (averaging 16%) and a small decrease (averaging 16%) in olanzapine clearance; the elimination half-life was not substantially affected. Fluoxetine is an inhibitor of CYP2D6, and thereby may affect a minor metabolic pathway for olanzapine. Although the changes in pharmacokinetics are statistically significant when olanzapine and fluoxetine are given concurrently, the changes are unlikely to be clinically important in comparison to the overall variability observed between individuals; therefore, routine dosage adjustment is not recommended.

Fluvoxamine, a CYP1A2 inhibitor, has been shown to decrease the clearance of olanzapine, which is metabolized by CYP1A2; there is some evidence that fluvoxamine-induced CYP1A2 inhibition is dose dependent. In one pharmacokinetic study, peak plasma olanzapine concentrations increased by an average of 54 and 77% and area under the plasma concentration-time curve (AUC) increased by an average of 52 and 108% in female nonsmokers and male smokers, respectively, when fluvoxamine and olanzapine were administered concomitantly. Symptoms of olanzapine toxicity also have been reported in at least one patient during combined therapy. The manufacturer and some clinicians state that a lower olanzapine dosage should therefore be considered in patients receiving concomitant treatment with fluvoxamine. Preliminary data indicate that concurrent fluvoxamine administration may potentially be used to therapeutic advantage by reducing the daily dosage of olanzapine and thereby the cost of therapy; further controlled studies are needed to more fully evaluate this approach. Although

combined therapy with olanzapine and fluvoxamine generally has been well tolerated and may be associated with clinical benefit, some clinicians recommend that caution be exercised and monitoring of plasma olanzapine concentrations be considered in patients receiving these drugs concurrently.

Preliminary results from a therapeutic drug monitoring service suggest that concurrent administration of sertraline and olanzapine does not substantially affect the pharmacokinetics of olanzapine.

Warfarin

Concomitant administration of a single 20-mg dose of warfarin (which has a potential CYP2C9 interaction) and a single oral 10-mg dose of olanzapine did not substantially alter the pharmacokinetics of olanzapine.

■ **Drugs Metabolized by Hepatic Microsomal Enzymes**

In vitro studies utilizing human liver microsomes suggest that olanzapine has little potential to inhibit metabolism of CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A substrates. Therefore, clinically important drug interactions between olanzapine and drugs metabolized by these isoenzymes are considered unlikely.

■ **Levodopa and Dopamine Agonists**

Olanzapine may antagonize the effects of levodopa and dopamine agonists.

■ **Lamotrigine**

In a multiple-dose study in healthy individuals, the pharmacokinetics of olanzapine and lamotrigine were not substantially affected when the drugs were administered concomitantly. In another multiple-dose study conducted in healthy volunteers, olanzapine did not substantially alter lamotrigine pharmacokinetics when the drugs were administered concurrently. However, the time to reach maximal plasma concentrations of lamotrigine was substantially prolonged in this study, possibly because of olanzapine's anticholinergic activity. The tolerability of this combination was found to be similar to that of olanzapine alone, with mild sedative effects reported in some patients receiving the drugs concurrently. Although routine dosage adjustment does not appear to be necessary when olanzapine and lamotrigine are given concurrently, adjustment in lamotrigine dosage may be necessary in some patients for therapeutic reasons when olanzapine therapy is initiated or discontinued. In addition, careful monitoring of patients receiving high dosages of olanzapine and lamotrigine has been recommended by some clinicians.

■ **Other CNS-Active Agents and Alcohol**

Because of the prominent CNS actions of olanzapine, the manufacturer states that caution should be exercised when olanzapine is administered concomitantly with other centrally acting drugs and alcohol. The manufacturer also states that concomitant use of olanzapine with CNS agents that are associated with hypotension (e.g., diazepam) may potentiate the orthostatic hypotension associated with olanzapine.

Benzodiazepines

Because of the prominent CNS actions of olanzapine, the manufacturer states that caution should be exercised when olanzapine is administered concomitantly with benzodiazepines. The manufacturer also states that concomitant use of olanzapine and diazepam or other benzodiazepines that are associated with hypotension may potentiate the orthostatic hypotension associated with olanzapine. However, administration of multiple doses of olanzapine did not substantially alter the pharmacokinetics of diazepam or its active metabolite *N*-desmethyldiazepam.

The pharmacokinetics of olanzapine, unconjugated lorazepam, and total lorazepam were not substantially affected when IM lorazepam (2 mg) was administered 1 hour after IM olanzapine (5 mg); however, increased somnolence was observed with this combination. Hypotension also has been reported when IM olanzapine and IM lorazepam have been administered concurrently. The manufacturer of olanzapine states that concurrent use of IM olanzapine in conjunction with parenteral benzodiazepines has not been adequately studied to date and therefore is not recommended. If therapy with IM olanzapine in conjunction with a parenteral benzodiazepine is considered, the clinical status of the patient should be carefully evaluated for excessive sedation and cardiorespiratory depression.

Tricyclic Antidepressants

Administration of single doses of olanzapine did not substantially affect the pharmacokinetics of imipramine or its active metabolite desipramine.

Lithium

Multiple doses of olanzapine (10 mg for 8 days) did not affect the pharmacokinetics of a single dose of lithium. Although combined olanzapine and lithium therapy generally has been well tolerated in controlled clinical studies, rare cases of apparent lithium toxicity and adverse extrapyramidal effects, including oculogyric crisis, have been reported in patients receiving these drugs concurrently; the mechanism(s) for this potential drug interaction remains to be established. The manufacturer of olanzapine states that lithium dosage adjustment is not necessary during concurrent olanzapine administration.

Valproic Acid

In vitro studies using human liver microsomes indicated that olanzapine has little potential to inhibit the major metabolic pathway (glucuronidation) of valproic acid. In addition, valproic acid has little potential effect on the metabolism of olanzapine in vitro. In a pharmacokinetic study, olanzapine administration (10 mg daily for 2 weeks) did not affect the steady-state plasma concentrations of valproic acid. However, substantially decreased plasma olanzapine concentrations have been reported in several patients following initiation of valproate in patients already receiving olanzapine; it was

suggested that induction of the hepatic enzymes responsible for olanzapine's metabolism by valproate may have been responsible for these findings. Further studies are needed to determine whether a pharmacokinetic interaction exists between olanzapine and valproic acid since these drugs are frequently used in combination in clinical practice. The manufacturer of olanzapine currently states that routine dosage adjustment of valproic acid is not necessary during concurrent olanzapine administration.

Alcohol

In a pharmacokinetic study, concomitant administration of a single dose of alcohol did not substantially alter the steady-state pharmacokinetics of olanzapine (given in dosages of up to 10 mg daily). However, the manufacturer states that concomitant use of olanzapine with alcohol could potentiate the orthostatic hypotension associated with olanzapine and that alcohol should be avoided during olanzapine therapy.

■ **Hypotensive Agents**

Olanzapine therapy potentially may enhance the effects of certain hypotensive agents during concurrent use. In addition, the administration of dopamine, epinephrine, and/or other sympathomimetic agents with β -agonist activity should be avoided in the treatment of olanzapine-induced hypotension, since such stimulation may worsen hypotension in the presence of olanzapine-induced α -blockade. (See Acute Toxicity: Treatment.)

■ **Antacids or Cimetidine**

In pharmacokinetic studies, single doses of cimetidine (800 mg) or aluminum- and magnesium-containing antacids (30 mL) did not substantially affect the oral bioavailability of a single, 7.5-mg dose of olanzapine.

■ **Activated Charcoal**

Concurrent administration of activated charcoal (1 g) reduced peak plasma concentrations and the AUC of a single, 7.5-mg dose of olanzapine by approximately 60%. Since peak plasma concentrations are not usually obtained until about 6 hours after oral administration, activated charcoal may be useful in the management of olanzapine intoxication. (See Acute Toxicity: Treatment.)

■ **Smoking**

The manufacturer states that the clearance of olanzapine in smokers is approximately 40% higher than in nonsmokers. Therefore, plasma olanzapine concentrations generally are lower in smokers than in nonsmokers receiving the drug. Adverse extrapyramidal effects have been reported in one olanzapine-treated patient after a reduction in cigarette smoking, while worsened delusions, hostility, and aggressive behavior have been reported in another olanzapine-treated patient following a marked increase in smoking (i.e., an increase from 12 up to 80 cigarettes per day). Although the precise mechanism(s) for this interaction has not been clearly established, it has been suggested that induction of the CYP isoenzymes, particularly 1A2, by smoke constituents may be responsible at least in part for the reduced plasma olanzapine concentrations observed in smokers compared with nonsmokers.

Although the manufacturer states that routine dosage adjustment is not recommended in patients who smoke while receiving olanzapine, some clinicians recommend that patients treated with olanzapine should be monitored with regard to their smoking consumption and that dosage adjustment be considered in patients who have reduced or increased their smoking and/or who are not responding adequately or who are experiencing dose-related adverse reactions to the drug. In addition, monitoring of plasma olanzapine concentrations may be helpful in patients who smoke and have other factors associated with substantial alterations in metabolism of olanzapine (e.g., geriatric patients, women, concurrent fluvoxamine administration).

■ **Other Drugs**

Multiple doses of olanzapine did not substantially alter the pharmacokinetics of theophylline or its metabolites.

Multiple doses of olanzapine did not substantially affect the pharmacokinetics of biperiden.

Acute Toxicity

■ **Pathogenesis**

The acute lethal dose of olanzapine in humans remains to be established. However, the toxic and lethal doses of olanzapine and other atypical antipsychotic agents appear to be highly variable and depend on concurrent administration of other drugs or toxic substances, patient age and habituation, and the time from exposure until treatment is initiated; pediatric and/or nonhabituated patients appear to be more sensitive to the toxic effects of these drugs. During premarketing clinical trials involving more than 3100 patients and/or healthy individuals, accidental or intentional acute overdosage of olanzapine was identified in 67 patients. In one adult patient who took 300 mg of the drug, the only symptoms reported were drowsiness and slurred speech. In a limited number of patients who were evaluated in hospitals following olanzapine overdosage, no adverse changes in laboratory values or ECG findings were observed. In addition, vital signs usually were within normal limits following these overdosages.

Fatalities have been reported following overdosage of olanzapine alone. In one of these deaths, the amount of olanzapine acutely ingested was possibly as low as 450 mg, while it was estimated to be up to 600 mg in another case; however, in 2 other cases, patients reportedly survived acute ingestions of 1.1 and 1.5 g. The cases of olanzapine intoxication reported to date suggest that overdosages of less than 200 mg of the drug alone in adults generally result in moderate and self-limiting toxicity; however, olanzapine overdosages exceeding 200 mg and/or when taken in combination with

other psychoactive agents or alcohol often were associated with more severe toxicity, including profound CNS depression, mental status changes, and miotic pupils.

■ Manifestations

In postmarketing reports of overdosages with olanzapine alone, manifestations have been reported in the majority of cases. Following acute overdosage of olanzapine or other atypical antipsychotic agents, toxic effects usually begin within 1–2 hours and maximal toxic effects usually are seen 4–6 hours following acute ingestion. In general, overdosage of olanzapine may be expected to produce effects that are extensions of its pharmacologic and adverse effects. The most commonly reported manifestations of olanzapine overdosage and those that have occurred in 10% or more of symptomatic patients following postmarketing overdosage reports of olanzapine alone are agitation and/or aggressiveness, dysarthria, tachycardia, anticholinergic syndrome, miosis, various extrapyramidal symptoms, jerking and myoclonus, hypersalivation, and reduced level of consciousness ranging in severity from sedation to coma. Less commonly reported but potentially medically serious events included aspiration, cardiopulmonary arrest, cardiac arrhythmias (e.g., supraventricular tachycardia), delirium, possible neuroleptic malignant syndrome, respiratory depression and/or arrest, convulsions, hypertension, and hypotension (including orthostatic hypotension); one patient experienced sinus pause with spontaneous resumption of normal rhythm.

In some cases of acute olanzapine intoxication, rapid fluctuation in mental status (i.e., between sedation and agitation or agitation despite sedation) has been reported. In addition, olanzapine overdosage may resemble opiate overdosage because CNS depression and miosis sometimes are observed. Increased creatine kinase (CK, creatine phosphokinase, CPK) concentrations also have occurred following acute olanzapine overdosage. Cardiac arrhythmias, persistent choreoathetosis, nonconvulsive status epilepticus, hypersalivation, and coma occurred in an adult following an intentional ingestion estimated to be 750 mg of olanzapine; both coma and choreoathetosis persisted until the patient's death 8 weeks later.

The toxic effects of olanzapine and other atypical antipsychotic agents in children appear to be similar to those seen in adults. In young children, marked CNS depression and anticholinergic delirium have occurred following ingestion of 7.5–15 mg of olanzapine (equivalent to 0.5–1 mg/kg). In an adolescent who ingested 275 mg of olanzapine and had an extremely high serum olanzapine concentration (1503 ng/mL), somnolence, agitation, and extrapyramidal symptoms developed initially, but the patient recovered without complications. A 400-mg olanzapine overdosage in another adolescent reportedly produced severe respiratory depression requiring intubation and mechanical ventilation; the patient recovered after 3 days. In addition, polyuria and other signs suggesting possible diabetes insipidus, including hypo-osmolar urine, normo-osmolar plasma, and increased serum sodium concentrations, have been reported in one adolescent following an overdosage of olanzapine and prazepam (a benzodiazepine; not commercially available in the US).

■ Treatment

Management of olanzapine overdosage generally involves symptomatic and supportive care, including continuous cardiovascular and respiratory monitoring and ensuring IV access. Cardiovascular monitoring should be initiated immediately and should include continuous ECG monitoring to detect possible arrhythmias. There is no specific antidote for olanzapine intoxication. In managing olanzapine overdosage, the clinician should consider the possibility of multiple drug intoxication.

The manufacturer and many clinicians recommend establishing and maintaining an airway and ensuring adequate ventilation and oxygenation, which may include intubation. Gastric lavage (following intubation, if the patient is unconscious) and/or activated charcoal, which may be used with sorbitol, should be considered. (See Drug Interactions: Activated Charcoal.) The possibility that obtundation, seizures, or dystonic reaction of the head and neck following olanzapine overdosage may create a risk of aspiration with induction of emesis should be considered.

Hypotension and circulatory collapse, if present, should be treated with appropriate measures, such as Trendelenburg's position, IV fluids, and/or sympathomimetic agents (e.g., norepinephrine, phenylephrine). However, dopamine, epinephrine, and/or other sympathomimetic agents with β -adrenergic agonist activity should be avoided, since such stimulation may worsen hypotension in the presence of olanzapine-induced α -adrenergic blockade. Tachycardia associated with olanzapine intoxication usually does not require specific therapy. Atrial and ventricular arrhythmias and conduction disturbances should be treated with appropriate measures; sodium bicarbonate may be helpful if QRS interval prolongation is present. Seizures following olanzapine overdosage may be treated initially with a benzodiazepine followed by barbiturates, if necessary. Acute extrapyramidal reactions should be treated with anticholinergic agents (e.g., diphenhydramine, benztropine).

Physostigmine salicylate or benzodiazepine therapy may be useful in the management of severe agitation and delirium in patients with severe anticholinergic toxicity and a narrow QRS complex on their ECG. Physostigmine has been used successfully in the treatment of anticholinergic toxicity associated with overdosages of olanzapine or clozapine, another atypical antipsychotic agent. However, experience with physostigmine in the management of atypical antipsychotic overdosage is limited, and some clinicians recommend that the drug be used only by experienced clinicians and in cases in which the potential therapeutic benefit outweighs the potential risks.

Resolution of toxic effects following atypical antipsychotic intoxication generally occurs within 12–48 hours following acute overdosage, although it has taken up to 6 days. Patients should remain under close medical supervision and monitoring until fully recovered.

Hemodialysis has not been shown to be useful for enhancing elimination of olanzapine in acute overdosage. Clinical experience with other enhanced elimination techniques, including multiple-dose activated charcoal, hemoperfusion, forced diuresis, and urinary alkalization, is lacking; however, these treatments also are unlikely to be beneficial following olanzapine overdosage because of the drug's large volume of distribution and extensive protein binding.

Chronic Toxicity

In animal studies prospectively designed to assess abuse and dependence potential, olanzapine was shown to produce acute CNS depressive effects but little or no potential for abuse or physical dependence in rats administered oral doses up to 15 times the maximum recommended human daily oral dosage (20 mg) and rhesus monkeys administered oral doses up to 8 times the maximum recommended human daily oral dosage on a mg/m² basis. Olanzapine has not been systematically evaluated in humans to date for its potential for abuse, tolerance, or physical dependence. While clinical trials did not reveal any tendency for drug-seeking behavior, these observations were not systematic, and it is not possible to predict on the basis of this limited experience the extent to which a CNS-active drug will be misused, diverted, and/or abused once marketed. Consequently, patients should be evaluated carefully for a history of drug abuse, and such patients should be observed closely for signs of misuse or abuse of olanzapine (e.g., development of tolerance, increases in dose, drug-seeking behavior).

Pharmacology

Olanzapine is a thienobenzodiazepine-derivative antipsychotic agent. The drug shares some of the pharmacologic actions of other antipsychotic agents and has been described as an atypical or second-generation antipsychotic agent. Like other atypical or second-generation antipsychotics (e.g., aripiprazole, clozapine, quetiapine, risperidone, ziprasidone), olanzapine produces minimal adverse extrapyramidal effects, is unlikely to cause tardive dyskinesia with chronic treatment, and is effective in the treatment of positive, negative, and depressive manifestations of schizophrenia.

■ Nervous System Effects

The exact mechanism of antipsychotic action of olanzapine and other atypical antipsychotic agents has not been fully elucidated but appears to be more complex than that of conventional, first-generation antipsychotic agents and may involve central antagonism at serotonin type 2 (5-hydroxytryptamine [5-HT_{2A}, 5-HT_{2C}]), type 3 (5-HT₃), and type 6 (5-HT₆) and dopamine receptors.

The exact mechanism(s) of antimanic action of olanzapine is not fully known. However, it has been suggested that the ability of olanzapine to block and downregulate 5-HT_{2A} receptors may play a role in its antimanic activity. In addition, olanzapine's mood-stabilizing action may be caused at least in part by antagonism of D₂ receptors. Further studies are needed to more clearly elucidate the potential mechanism(s) of the drug's antimanic activity.

Although not clearly established, the efficacy of IM olanzapine in the treatment of acute agitation appears to be due at least in part to its distinct calming effects rather than solely to nonspecific sedation.

Antidopaminergic Effects

The therapeutic effects of antipsychotic drugs are thought to be mediated by dopaminergic blockade in the mesolimbic and mesocortical areas of the CNS, while antidopaminergic effects in the neostriatum appear to be associated with extrapyramidal effects. The relatively low incidence of extrapyramidal effects associated with olanzapine therapy suggests that the drug is more active in the mesolimbic than the neostriatal dopaminergic system.

Several (at least 5) different types or subtypes of dopamine receptors have been identified in animals or humans. The relative densities of these receptors and their distribution and function vary for different neuroanatomical regions, and olanzapine's effects may be secondary to regionally specific receptor interactions and/or other effects on dopaminergic neurons. Current evidence suggests that the clinical potency and antipsychotic efficacy of both typical and atypical antipsychotic drugs generally are related at least in part to their affinity for and blockade of central dopamine D₂ receptors. Some studies suggest that clinically effective dosages of most antipsychotic agents result in occupation of between 60 and 80% of central dopamine D₂ receptors. However, antagonism at D₂ receptors does not appear to account fully for the antipsychotic effects of olanzapine. In vivo and in vitro studies have demonstrated that olanzapine is a comparatively weak antagonist at D₂ receptors. Although their role in eliciting the pharmacologic effects of antipsychotic agents remains to be fully elucidated, dopamine D₃, D₄, and D₅ receptors also have been identified. Olanzapine may have a higher affinity for D₄ receptors than for D₂ or D₃ receptors. K_i values of olanzapine for dopamine D_{1,4} receptors range from 11–31 nM.

Atypical antipsychotic agents generally have demonstrated relatively loose binding to dopamine D₂ receptors. Compared with typical antipsychotic agents, atypical antipsychotics appear to have faster dissociation rates from and lower affinity for dopamine D₂ receptors, which may result in fewer adverse extrapyramidal effects and less risk of elevated prolactin concentrations; however, further studies are needed to confirm these initial findings.

Serotonergic Effects

It has been suggested that schizophrenia may involve a dysregulation of serotonin- and/or dopamine-mediated neurotransmission, and olanzapine may at least partially restore a normal balance of neurotransmitter function, possibly through serotonergic modulation of dopaminergic tone. Olanzapine blocks serotonin type 2 (5-hydroxytryptamine [5-HT_{2A} and 5-HT_{2C}; K_i of 4 and 11 nM, respectively]), type 3 (5-HT₃; K_i of 57 nM), and type 6 (5-HT₆; K_i of 5 nM) receptors.

Anticholinergic Effects

Olanzapine blocks muscarinic cholinergic receptors and has demonstrated moderate affinity for all 5 muscarinic receptor subtypes (K_i values for M₁₋₅ were 73, 96, 132, 32, and 48 nM, respectively). Anticholinergic activity in antipsychotic agents may contribute to certain adverse anticholinergic events associated with these drugs but also may help reduce the risk of adverse extrapyramidal reactions.

Effects on Other Central Neurotransmitters

Antagonism at receptors other than dopamine and 5-HT₂ receptors may produce some of the therapeutic and adverse effects associated with olanzapine. Olanzapine exhibits α_1 -adrenergic blocking activity (K_i of 19 nM), which may explain the occasional orthostatic hypotension associated with the drug. In addition, olanzapine blocks histamine H₁ receptors (K_i of 7 nM), which may explain the sedative effects associated with the drug; affinity for H₂ and H₃ receptors appears to be low.

Olanzapine demonstrated weak binding affinity (K_i exceeding 10 μ M) for β -adrenergic, γ -aminobutyric acid (GABA), and benzodiazepine receptors; the drug also has little or no affinity for opiate receptors.

Neurophysiologic Effects

In vivo electrophysiologic studies demonstrate different sensitivities of various brain areas to antipsychotic-mediated postsynaptic receptor blockade. While conventional antipsychotics generally reduce spontaneous firing activity in both the mesolimbic (A10) and nigrostriatal regions (A9), chronic administration of atypical antipsychotics generally reduces the number of spontaneously active dopaminergic neurons in the mesolimbic region but not in the nigrostriatal region. Although not clearly established, it has been suggested that the ability to decrease A10 but not A9 neurons is associated clinically with a low potential to cause adverse extrapyramidal reactions and tardive dyskinesia. Olanzapine has demonstrated such mesolimbic selectivity in the in vivo studies conducted to date.

Cognitive Effects in Humans

Clinical experience suggests that second-generation antipsychotics, including olanzapine, improve cognition in patients with schizophrenia and that there may be differences between these drugs in their effects on neurocognitive functioning. In an initial clinical trial evaluating the short-term effects of atypical antipsychotic agents on cognitive function, olanzapine-treated schizophrenic patients demonstrated improved learning and memory, verbal fluency, and executive function. In a controlled clinical trial evaluating the neurocognitive effects of olanzapine, clozapine, risperidone, and haloperidol in patients with treatment-resistant schizophrenia or schizoaffective disorder, global neurocognitive function improved with olanzapine and risperidone treatment, and these improvements were found to be superior to those seen with haloperidol. Patients treated with olanzapine exhibited improvement in the general and attention domains but not more than that observed with the other antipsychotic agents. In another controlled trial, patients with schizophrenia receiving long-term (1 year) therapy with olanzapine demonstrated improved results on a general cognition index compared with those receiving haloperidol and risperidone. Neurocognition also improved in olanzapine- and risperidone-treated schizophrenic and schizoaffective patients receiving the drug for 1 year in another controlled study; improvements in executive function, learning and memory, processing speed, attention and vigilance, verbal working memory, and motor function were reported. The clinical relevance of these cognitive findings in the management of schizophrenia remains to be determined and requires further study.

EEG Effects

Olanzapine may cause EEG changes. In one study, olanzapine-induced EEG slowing to a lesser extent than clozapine in patients with schizophrenia and did not appear to substantially alter epileptiform activity in most of the patients studied; further studies are needed to determine whether olanzapine can affect the seizure threshold. Similarly, a comparative study found that epileptiform activity did not increase during olanzapine therapy; however, EEG slowing and other nonspecific EEG changes did occur more frequently in olanzapine-treated patients than in those receiving certain other antipsychotic agents. In another study that was retrospective in design, EEG changes occurred more frequently in patients receiving olanzapine or clozapine than in those receiving typical antipsychotic agents, quetiapine, or risperidone. In a study in patients with schizophrenia, olanzapine therapy was associated with increased rates of slow waves, sharp waves, and paroxysmal slow wave discharges on EEG recordings in the patients evaluated; however, spike- and sharp-slow-wave complexes that indicate seizure risk were not observed in this study.

Seizures have been reported rarely (0.9% in premarketing clinical trials) in olanzapine-treated patients but confounding factors were present in most of these cases. Further studies and postmarketing surveillance are needed to determine whether olanzapine can affect the seizure threshold and to evaluate the clinical relevance of the observed EEG findings in patients receiving the drug.

Effects on Sleep

The available evidence suggests that atypical antipsychotics, including olanzapine, clozapine, and risperidone, substantially increase total sleep time and stage 2 sleep; both olanzapine and risperidone also have been shown to enhance slow-wave sleep. Olanzapine's beneficial effects on sleep quality are thought to be mediated principally via type 2 serotonergic (5-HT₂) receptors.

In a controlled study, administration of single evening doses of olanzapine (5 or 10 mg orally) in healthy individuals significantly increased slow-wave sleep in a dose-related manner; sleep continuity measures and subjective sleep quality also increased significantly. Single 10-mg doses of the drug also suppressed rapid eye movement (REM) sleep and increased REM sleep latency in this study. In another study in healthy males and females, single 10-mg oral doses of olanzapine also were found to increase slow-wave sleep but preserved the normal structure of sleep; these effects were more prominent in females than in males.

During subchronic administration of olanzapine (15–20 mg) in patients with schizophrenia with predominantly negative symptoms in an uncontrolled study, parameters of sleep efficiency improved and delta sleep and REM sleep increased. Acute olanzapine administration (10 mg orally) in schizophrenic patients improved sleep continuity variables and total sleep time in another study; the principal changes observed in sleep architecture were a reduction in stage 1 sleep, a significant enhancement in stage 2 and delta sleep, and an increase in REM density. In a study comparing the effect of aging on the improvement of subjective sleep quality in patients with schizophrenia receiving atypical antipsychotic agents, including olanzapine, the proportion of patients experiencing improved subjective sleep quality was significantly higher in geriatric patients than in middle-aged patients.

Neuroendocrine Effects

In contrast to conventional (first-generation) antipsychotic agents and similar to many other atypical antipsychotic agents, olanzapine therapy in usual dosages generally produces relatively modest and transient elevations in serum prolactin concentrations in humans. This prolactin-elevating effect appears to be mediated by dopamine blockade. The effect of atypical antipsychotic agents on prolactin generally appears to be transient, possibly because the drugs appear to dissociate from dopamine receptors more rapidly than conventional antipsychotic agents.

Pharmacokinetics

Absorption

Olanzapine is well absorbed following oral administration. However, because of extensive first-pass metabolism, only about 60% of an orally administered dose reaches systemic circulation unchanged. Olanzapine exhibits linear and dose-proportional pharmacokinetics when given orally within the clinical dosage range. Food does not appear to affect the rate or the extent of GI absorption of the drug. The relative oral bioavailability of olanzapine has been shown to be equivalent following administration of the conventional and orally disintegrating tablets of the drug. When olanzapine and fluoxetine hydrochloride are administered as the fixed-combination oral capsules, the pharmacokinetic characteristics of the drugs are expected to resemble those of the individual components; olanzapine pharmacokinetics are slightly altered when administered with fluoxetine, but the effects were not deemed to be clinically important. (See Selective Serotonin-reuptake Inhibitors under Drug Interactions: Drugs Affecting Hepatic Microsomal Enzymes.)

Following oral administration, peak plasma olanzapine concentrations occur in approximately 6 hours (range: 5–8 hours). Steady-state plasma concentrations of olanzapine are achieved after approximately 7 days of continuous dosing and are approximately twice those observed following single-dose administration.

Following IM administration, olanzapine is rapidly absorbed with peak plasma olanzapine concentrations occurring within 15–45 minutes. In one pharmacokinetic study performed in healthy individuals, a single 5-mg IM dose of olanzapine produced peak plasma concentrations that were an average of fivefold higher than the peak plasma concentrations produced following a single 5-mg oral dose of the drug. In this study, the areas under the plasma concentration-time curve (AUCs) achieved following IM and oral administration of the same dose of the drug were similar. Olanzapine exhibits linear pharmacokinetics when given IM within the clinical dosage range. Preliminary evidence suggests that the onset of antipsychotic action following IM administration of the drug is evident within 24 hours but may be observed as early as 2 hours after IM administration.

Plasma olanzapine concentrations may vary between individuals according to gender, smoking status, and age. There is limited evidence that gender may affect plasma olanzapine concentrations, with concentrations being somewhat higher, perhaps by as much as 30–40%, in females compared with males. Plasma concentrations of olanzapine also may be increased in geriatric individuals compared with younger individuals, possibly as a result of age-related decreases in hepatic elimination of the drug. Data from one limited study in children and adolescents 10–18 years of age with schizophrenia found that plasma olanzapine concentrations among adolescents were within the range reported in nonsmoking adult patients with schizophrenia. In vivo studies have shown that exposures to olanzapine are similar among Japanese, Chinese, and Caucasian individuals, particularly after normalization for body weight differences.

The therapeutic range for plasma olanzapine concentrations and the relationship of plasma concentration to clinical response and toxicity have not been clearly established; however, acutely ill schizophrenic patients with 24-hour post-dose plasma olanzapine concentrations of 9.3 ng/mL or higher in one study or 12-hour post-dose concentrations

of 23.2 ng/mL or higher in another study appeared to have a better clinical response to therapy than patients with lower plasma concentrations.

■ Distribution

Distribution of olanzapine, a highly lipophilic drug, into human body tissues is extensive.

The manufacturer states that the volume of distribution of olanzapine has been reported to be approximately 1000 L. In pharmacokinetic studies in healthy individuals, the apparent volume of distribution of the drug averaged 1150 L and ranged from 660 to 1790 L for the fifth to 95th percentiles. Olanzapine is 93% bound to plasma proteins over the concentration range of 7–1100 ng/mL, principally to albumin and α_1 -acid glycoprotein.

Olanzapine and its glucuronide metabolite have been shown to cross the placenta in humans. Placental transfer of olanzapine also has been shown to occur in rat pups.

Olanzapine is distributed into milk. The manufacturer states that in a study in lactating, healthy women, the average infant dose of olanzapine at steady-state was estimated to be approximately 1.8% of the maternal olanzapine dose. In a separate study that evaluated the extent of infant exposure to olanzapine in 7 breastfeeding women who had been receiving 5–20 mg of olanzapine daily for periods ranging from 19–395 days, median and maximum relative infant doses of 1 and 1.2%, respectively, were observed. Olanzapine was not detected in the plasma of the breastfed infants, and adverse effects possibly related to olanzapine exposure were not reported in the infants in this study. In addition, peak milk concentrations were achieved a median of 5.2 hours later than the corresponding maximal maternal plasma concentrations. In a case report, a relative infant dose of approximately 4% was estimated in one woman after 4 and 10 days (estimated to be at steady state) of olanzapine therapy at a dosage of 20 mg daily based on measurements of drug concentration in serum and in expressed breast milk. (See Cautions: Pregnancy, Fertility, and Lactation.)

■ Elimination

Although the exact metabolic fate has not been clearly established, it appears that olanzapine is extensively metabolized. Following a single oral dose of radiolabeled olanzapine, 7% of the dose was recovered in urine as unchanged drug. Approximately 57 and 30% of the dose was recovered in the urine and feces, respectively. In plasma, olanzapine accounted for only 12% of the AUC for total radioactivity, suggesting substantial exposure to metabolites. After multiple doses of olanzapine, the principal circulating metabolites are the 10-*N*-glucuronide, which is present at steady state at 44% of the plasma concentration of the parent drug, and 4'-*N*-desmethyl olanzapine, which is present at steady state at 31% of the plasma concentration of olanzapine. Both of these metabolites lack pharmacologic activity at the concentrations observed.

Direct glucuronidation and cytochrome P-450 (CYP)-mediated oxidation are the principal pathways for olanzapine metabolism. In vitro studies suggest that the CYP isoenzymes 1A2 and 2D6 and the flavin-containing monooxygenase system are involved in the oxidation of olanzapine. However, CYP2D6-mediated oxidation appears to be a minor metabolic pathway for olanzapine in vivo since the clearance of the drug is not reduced in individuals deficient in this enzyme.

Following oral administration, olanzapine has an elimination half-life ranging from 21 to 54 hours for the fifth to 95th percentiles of individual values with a mean of 30 hours. Following IM administration, the half-life and metabolic profile of olanzapine were similar to those observed with oral administration. The apparent plasma clearance of olanzapine ranges from 12 to 47 L/hr (mean: 25 L/hour).

The clearance of olanzapine in smokers is approximately 40% higher than in nonsmokers. (See Drug Interactions: Smoking.)

The clearance of olanzapine in females may be reduced by approximately 30% compared with males.

In a single-dose pharmacokinetic study, the elimination half-life of olanzapine was 1.5 times longer in healthy geriatric individuals 65 years of age or older than in healthy younger adults. (See Dosage and Administration: Dosage and see also Cautions: Geriatric Precautions.)

In one pharmacokinetic study conducted in a limited number of children and adolescents 10–18 years of age with schizophrenia who were treated with oral olanzapine, the apparent plasma clearance at steady-state averaged 9.6 L/hr, which was approximately half of the clearance values reported in adult studies but similar to clearance values reported in nonsmoking male and female schizophrenic patients. The elimination half-life averaged 37.2 hours in this same study. (See Dosage and Administration: Dosage and see also Cautions: Pediatric Precautions.)

The combined effects of age, smoking, and gender could result in substantial pharmacokinetic differences in populations. The clearance in younger, smoking adult male patients may be 3 times higher than that in geriatric, nonsmoking females. Dosage adjustment may be necessary in patients who exhibit a combination of factors that may result in slower metabolism of olanzapine. (See Dosage and Administration: Dosage.)

Because olanzapine is extensively metabolized before excretion and only 7% of the drug is excreted unchanged, renal impairment alone is unlikely to substantially alter the pharmacokinetics of olanzapine. The pharmacokinetics of olanzapine were similar in patients with severe renal impairment and healthy individuals, suggesting that dosage adjustment based upon the degree of renal impairment is not necessary. The effect of renal impairment on the elimination of olanzapine's metabolites has not been evaluated to date.

Although the presence of hepatic impairment would be expected to reduce the clearance of olanzapine, a pharmacokinetic study evaluating the effect of impaired

hepatic function in individuals with clinically important cirrhosis (Childs Pugh Classification A and B) revealed little effect on the pharmacokinetics of olanzapine.

Olanzapine is not appreciably removed by hemodialysis, probably due to its large volume of distribution and extensive protein binding. Clinical experience with other enhanced elimination techniques, including multiple-dose activated charcoal, hemoperfusion, forced diuresis, and urinary alkalization, is lacking; however, these treatments are unlikely to be beneficial following olanzapine overdose because of the drug's large volume of distribution and extensive protein binding.

Chemistry and Stability

■ Chemistry

Olanzapine is a thienobenzodiazepine-derivative antipsychotic agent. The drug is structurally similar to clozapine.

Olanzapine occurs as a yellow crystalline solid that is practically insoluble in water.

Olanzapine for injection contains lactose monohydrate and tartaric acid; hydrochloric acid and/or sodium hydroxide may have been added to adjust pH. When olanzapine for injection is reconstituted as directed, the resulting solution should appear clear and yellow.

■ Stability

Commercially available olanzapine conventional tablets, orally disintegrating tablets, and olanzapine for IM injection should be stored at a controlled room temperature of 20–25°C but may be exposed to temperatures ranging from 15–30°C. Olanzapine orally disintegrating tablets should be stored in their original sealed blister. The conventional and orally disintegrating tablets should be protected from light and moisture and olanzapine for injection should be protected from light and freezing.

Following reconstitution, olanzapine for injection may be stored at a controlled room temperature of 20–25°C for up to 1 hour if necessary, but immediate use is preferred. Lorazepam injection should not be used to reconstitute olanzapine for injection since this delays reconstitution time.

Olanzapine orally disintegrating tablets contain aspartame (e.g., NutraSweet®). (See Individuals with Phenylketonuria, under Cautions: Precautions and Contraindications.)

Olanzapine for IM injection should not be combined with diazepam injection in a syringe because precipitation occurs when these drugs are mixed. Olanzapine for injection should not be combined in a syringe with haloperidol injection because the resulting pH has been shown to degrade olanzapine over time. Specialized references should be consulted for additional specific compatibility information.

Preparations

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

Olanzapine

Oral

Tablets, film-coated

2.5 mg

Zyprexa®, Lilly

5 mg

Zyprexa®, Lilly

7.5 mg

Zyprexa®, Lilly

10 mg

Zyprexa®, Lilly

15 mg

Zyprexa®, Lilly

20 mg

Zyprexa®, Lilly

Tablets, orally disintegrating

5 mg

Zyprexa® Zydys®, Lilly

10 mg

Zyprexa® Zydys®, Lilly

15 mg

Zyprexa® Zydys®, Lilly

20 mg

Zyprexa® Zydys®, Lilly

**Parenteral
For injection**

10 mg

Zyprexa® IntraMuscular, Lilly

Olanzapine Combinations

**Oral
Capsules**

6 mg with Fluoxetine
Hydrochloride 25 mg (of
fluoxetine)

Symbyax®, Lilly

6 mg with Fluoxetine
Hydrochloride 50 mg (of
fluoxetine)

Symbyax®, Lilly

12 mg with Fluoxetine
Hydrochloride 25 mg (of
fluoxetine)

Symbyax®, Lilly

12 mg with Fluoxetine
Hydrochloride 50 mg (of
fluoxetine)

Symbyax®, Lilly

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